Lung Cancer Following Chemotherapy and Radiotherapy for Hodgkin's Disease

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Background: **Lung cancer is a frequent cause of death in patients cured of Hodgkin's disease, but the contributions of chemotherapy, radiotherapy, and smoking are not well described. We quantified the risk of treatment-associated lung cancer, taking into account tobacco use.** ***Methods:*** **Within a population-based cohort of 19 046 Hodgkin's disease patients (diagnosed from 1965 through 1994), a case–control study of lung cancer was conducted. The cumulative amount of cytotoxic drugs, the radiation dose to the specific location in the lung where cancer developed, and tobacco use were compared for 222 patients who developed lung cancer and for 444 matched control patients. All statistical tests were two-sided.** ***Results:*** **Treatment with alkylating agents without radiotherapy was associated with increased lung cancer risk (relative risk [RR] = 4.2; 95% confidence interval [CI] = 2.1 to 8.8), as was radiation dose of 5 Gy or more without alkylating agents (RR = 5.9; 95% CI = 2.7 to 13.5). Risk increased with both increasing number of cycles of alkylating agents and increasing radiation dose (*P* for trend <.001). Among patients treated with mechlorethamine, vincristine, procarbazine, and prednisone (MOPP), risk increased with cumulative amounts of mechlorethamine and procarbazine (*P*<.001) when evaluated separately. Statistically significantly elevated risks of lung cancer were apparent within 1–4 years after treatment with alkylating agents, whereas excess risk after radiotherapy began 5 years after treatment and persisted for more than 20 years. Risk after treatment with alkylating agents and radiotherapy together was as expected if individual excess risks were summed. Tobacco use increased lung cancer risk more than 20-fold; risks from smoking appeared to multiply risks from treatment.** ***Conclusions:*** **Past treatments with alkylating agents and radiation therapy for Hodgkin's disease were associated with an increased risk of lung cancer in a dose-dependent and additive fashion. The precise risk estimates, however, should be interpreted cautiously, given the possible residual and enhancing effects of tobacco. [J Natl Cancer Inst 2002;94:182–92]**

Second malignant neoplasms constitute the number one cause of mortality in patients cured of Hodgkin's disease, with lung cancer representing the most frequent solid tumor *(1–3).* Although leukemia was the first malignancy reported to be increased following Hodgkin's disease treatments, the absolute risk of solid cancers now far exceeds that of leukemia, with estimates of 48.8 and 18.4 excess cases per 10 000 patients per year, respectively *(3).* Leukemia is generally characterized by a short latency, whereas solid tumor risks increase with time and affect long-term survival *(3).* Despite the second cancer burden following Hodgkin's disease, analytic data that describe the relative importance of chemotherapy and radiotherapy in the development of one of the most frequent tumors—lung cancer—are conflicting, sparse, and inadequately controlled for smoking *(4–6).* On the basis of small numbers (30 case patients), van Leeuwen et al. *(5)* reported a statistically significant dose–response relation between radiation therapy for Hodgkin's disease and lung cancer risk in The Netherlands; radiation dose, however, was averaged across entire lung lobes, and only six case patients received mean doses of 9 Gy or more. In two larger studies *(4,6),* a quantitative association between radiation dose and lung cancer risk was not found. A relation between cumulative number of cycles of chemotherapy for Hodgkin's disease and subsequent lung cancer risk was not demonstrated in the largest investigation to date (n = 98 case patients) *(4)* or with cytotoxic drugs in The Netherlands study *(5).* Swerdlow et al. *(6)* recently reported a relative risk (RR) of 1.66 (95% confidence interval [CI] = 0.99 to 2.82) for lung cancer among British patients with Hodgkin's disease treated with the combination of mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) (n = 45 case patients), although risks following one to six cycles and seven or more cycles were similar and data on cumulative dose were not available. Of the three analytic investigations *(4–6)* to date, only the Dutch study *(5)* contained detailed information on tobacco use. Data on smoking habits were collected for only 39% of the patients in the British investigation *(6)* and 59% of the subjects in the study by Kaldor et al. *(4).* No analytic investigation has attempted to address the interaction between radiotherapy and chemotherapy on lung cancer risk or assessed long-term temporal patterns. Accordingly, our purpose was to analyze the risk of lung cancer in relation to amount of chemotherapy and radiation dose among more than 19 000 patients with Hodgkin's disease, taking into account tobacco use.

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See "Notes" following "References."

Patients and Methods

Study Subjects

A nested case–control study was conducted within a cohort of 19 046 one-year survivors of Hodgkin's disease diagnosed during the period from January 1, 1965, through December 31, 1994, and reported to one of seven population-based cancer registries in Connecticut, Iowa, Denmark, Finland, The Netherlands, Sweden, and Ontario, Canada *(7).* For each patient, registry files were searched to identify all subsequent diagnoses of lung cancer *(8).* Strict criteria for multiple primary cancers were applied by each center; i.e., the subsequent lung tumor had to present a definite picture of malignancy, be distinct, and not represent a metastatic lesion or recurrence. Because increased risks of lung cancer have been reported as early as 1–4 years after diagnosis of Hodgkin's disease *(2,9,10),* case patients in this time period were included to explore treatment effects. Previous case–control investigations of secondary lung cancer *(4–6)* have similarly included these early tumors, although analyses of treatment effects were not stratified by latency. Pathology reports (n = 217), results of radiologic studies (e.g., chest radiographs and computed tomography) (n = 5), and clinical information were independently reviewed (L. B. Travis and M. Gospodarowicz) to confirm the diagnosis of each reported case. For each of the 222 subjects with documented lung cancer, two control patients were selected by stratified random sampling from the cohort. Matching factors were registry, sex, calendar year, age at diagnosis of Hodgkin's disease, and survival without a second cancer at least as long as the period from Hodgkin's disease to lung cancer in the case patient. This type of case–control design has been used successfully in previous analytic investigations of second cancers *(4–6,8,11,12).* Nineteen case patients from Ontario, Denmark, and Sweden had been included in a previous study *(4).*

Data Collection

Medical records were abstracted for demographic information, all therapy for Hodgkin's disease, and smoking history during the matched time interval. Data sources included hospitals, medical centers, radiotherapy departments, and offices of private physicians. Smoking data included type, amount, and status (current or time of quitting). Since subjects could have smoking data derived from several sources at different times, rules were developed for the assignment of each patient to a category (never smoker, current cigarette smoker, former cigarette smoker, cigar and pipe smoker only, or not stated) based on all data recorded up to 1 year before diagnosis of lung cancer and the comparable date in control subjects. Subjects were classified as former smokers only if there was reasonable evidence that termination of smoking had occurred at least 5 years before lung cancer diagnosis (or a comparable date for control patients). The 1-year cutoff date for data collection was chosen to minimize bias arising from the potential availability of more thorough information on smoking habits for case patients than for control subjects. An alternative categorization of smoking status at Hodgkin's disease diagnosis was also developed based only on information recorded up to 1 year after that time. Analyses utilizing each approach yielded comparable results; thus, the former, more complete schema was used when adjusting for smoking and examining relations with treatment. Current cigarette smokers were further subdivided into smokers of less than one pack per day, one to two packs per day, and two or more packs per day. To explore interactions between smoking and treatment, we divided the patients into two groups: moderate (one to two packs per day) and heavy (two or more packs per day) cigarette smokers compared with all other categories taken together.

Information on dose and duration of administration of chemotherapy was abstracted for alkylating and intercalating agents and DNA topoisomerase II inhibitors, as recorded for each cycle of treatment. For other cytotoxic drugs, information was restricted to dates and duration of administration. Cumulative dose was calculated by summing each cyclic dose for each subject. Data on cumulative dose of alkylating agents were available for 293 of 330 patients (108 [86.4%] of 125 case patients and 185 [90.2%] of 205 control patients). One control patient for whom chemotherapy type was unknown was excluded from the analysis.

Radiotherapy and Dosimetry

For 535 patients (179 case patients and 356 control patients) treated with radiation, fields included mantle (34% of case patients and 30% of control patients), mantle and inverted-Y (32% of case patients and 30% of control patients), abdomen or inverted-Y (9% of case patients and 16% of control patients), mediastinum (9% of case patients and 8% of control patients), and other sites (16% of case patients and 16% of control patients). Radiotherapy fields were large and covered extensive areas of the chest and abdomen. The average and median treatment doses (36 Gy and 37 Gy, respectively) for mantle radiotherapy were identical for case patients and control patients. Daily radiotherapy logs for each patient were used to calculate the dose to the area of the lung in which the subsequent cancer developed and a comparable location in matched control patients. The specific location of the lung cancer was determined by a review of diagnostic pathology reports, surgical/bronchoscopy notes, hospital records, and radiologic studies, including copies of chest x-rays, computed tomography scans, and tomograms. Blocks to reduce lung exposure during treatment and radiotherapy simulation films were used in the estimation of doses. The dose to the blocked fields was estimated as a percentage of the in-beam full dose to several centimeters under the block. Based on tumor distance from block edge, correction factors were applied, with the use of a curve generated by the Pinnacle-3 Treatment Planning System (ADAC Laboratories, Milpitas, CA). For the unblocked fields (defined by machine collimators), the doses were derived by measurements in a water phantom to 60 cm outside the field *(13,14).* For some patients, information on either radiotherapy or lung tumor location was inadequate to estimate tissue dose: Excluded from the analyses were 23 case patients and 50 control patients who had doses that could not be estimated (or who were matched to case patients with inestimable doses). Repeat analyses including a yes/no indicator for chest radiotherapy for these excluded subjects showed comparable results. The mean dose of radiation to the specific location in the lung where cancer developed or a comparable location in matched control patients was 27.2 Gy (median: 33.8 Gy) and 21.8 Gy (median: 29.4 Gy), respectively; doses were similar for patients treated with radiation alone or with radiation and alkylating agents (mean: 24.4 Gy and 22.8 Gy, respectively). Among case patients who received radiotherapy, 26.3% of the lung cancers occurred in the unblocked

treatment field, 19.2% were diagnosed in areas that received lower dose radiation (1.9% beneath the lung blocks and 17.3% out of the beam), and 53.2% occurred on the beam edge. For 1.3% of the case patients, the relative location could not be determined.

Statistical Analysis

Conditional regression analysis was conducted to obtain maximum likelihood estimates of the RR of lung cancer associated with specific treatments by comparing the exposure histories of the case patients with those of individually matched control patients *(15)*. Analyses were implemented with the PECAN module of the software package EPICURE *(16)*. Most analyses were based on a model in which the odds ratio, which closely approximates the RR, is given by the expression

$$\exp(\lambda_j)\left[1 + \sum_k \beta_k z_k\right],$$

where j indexes four smoking categories (never smoker, current cigarette smoker, former cigarette smoker or cigar and pipe smoker only, and not stated), and the z_k are variables indicating treatments. This model, in which the effects of radiation therapy and chemotherapy are assumed to add rather than to multiply, was chosen because it gave a much better fit than the more commonly used multiplicative model. To test the adequacy of the additive model for a radiation variable z_1 and a chemotherapy variable z_2, we compared the fits of the two models

$$\exp(\lambda_j)[1 + \beta_1 z_1 + \beta_2 z_2] \text{ and } \exp(\lambda_j)[1 + \beta_1 z_1 + \beta_2 z_2 + \beta_3 z_1 z_2].$$

To test the adequacy of the multiplicative model, we compared the fits of the two models

$$\exp[\lambda_j + \alpha_1 z_1 + \alpha_2 z_2] \text{ and } \exp[\lambda_j + \alpha_1 z_1 + \alpha_2 z_2 + \alpha_3 z_1 z_2].$$

A similar approach was used to evaluate the interaction between smoking and treatment. Two-sided *P* values and 95% CIs were based on the likelihood ratio statistic. Trend *P* values test the hypothesis that $\beta_k = 0$ for continuous or ordered variables z_k.

Because nearly all of the patients had been treated with radiotherapy or alkylating agents, it was not possible to construct a reference group of subjects managed without these modalities. Thus, for categorical analyses (*see* Table 2, A; Table 3; and Table 5), patients who received an average radiation dose of less than 5 Gy to the lung without alkylating agents were combined with those treated only with nonalkylating agents to provide a larger reference group for the calculation of RRs. Analyses that addressed chemotherapy effects were adjusted for radiotherapy by including radiation dose as a continuous variable, whereas analyses evaluating radiotherapy were adjusted for chemotherapy by including the number of cycles with alkylating agents and yes/no variables for patients for whom either number of cycles was unknown or who received continuous therapy. Except for analyses addressing time since exposure, radiation dose received less than 5 years before lung cancer diagnosis (and a comparable date in control subjects) was excluded because other studies have shown a minimum 5-year latent period for radiation-induced lung cancer *(17)*.

Patients were grouped according to all chemotherapy received (initial and salvage), with categories based on animal studies of alkylating agents reported to induce lung cancer, i.e., mechlorethamine, chlorambucil, nitrosoureas, and dacarbazine *(18)*. Mutually exclusive treatment groups were defined, and various combinations were arranged hierarchically *(19)* for further evaluation. The large number (n = 244) of patients who received mechlorethamine (usually with vincristine, procarbazine, and prednisone in the MOPP regimen) *(20)* permitted further evaluation of this group. The correlation coefficient for cumulative doses of mechlorethamine and procarbazine was .63. Thus, to evaluate the relation between amount of each drug and lung cancer risk, we divided patients into quartiles, and we calculated the RR for each category compared with the referent group, after adjusting for tobacco use and radiation dose.

Results

The average age at diagnosis of Hodgkin's disease was 48.5 years (median: 50 years; range: 9–81 years) (Table 1) *(21)*. Case patients developed lung cancer an average of 10.8 years (median: 10.0 years) after diagnosis of Hodgkin's disease, with almost 80% occurring after 5 years (range: 1–28 years). Two hundred four (91.9%) of 222 patients were in clinical remission at the time of lung cancer diagnosis. Subsequent survival was poor for all 222 lung cancer patients (median: 4.0 months; 212 deaths).

Tobacco use, chemotherapy with alkylating agents, and radiation dose of 5 Gy or more were reported in 96%, 63%, and 53% of case patients and in 70%, 52%, and 41% of control patients, respectively (Table 2). Treatment of Hodgkin's disease with either radiotherapy alone (dose of $\geqslant$5 Gy) or chemotherapy with alkylating agents alone was associated with statistically significant increased risks of lung cancer compared with the reference group in analyses that adjusted for smoking (Table 2, A). Lung cancer risk following treatment with both alkylating agents and radiotherapy together was as expected if individual excess risks were summed, i.e., for combined therapy, 1 + (5.9 – 1) + (4.2 – 1) = 9.1, and were close to the observed value of 8.0. A multiplicative relationship between treatment with alkylating agents and radiation therapy (where the combined risk would be 5.9 × 4.2 = 24.8) was rejected ($P = .01$). Among patients with radiation doses exceeding 5 Gy and treated with alkylating agents, the RR of lung cancer after combined modality therapy was lower than that after radiotherapy and subsequent salvage chemotherapy, which was largely a result of the higher cumulative doses of radiation and chemotherapy received by those given salvage therapies.

Elevated lung cancer risks were found in all radiation categories with doses of 5 Gy or more, and the risk increased with increasing dose to the lung (*P* for trend <.001) (Table 2, B). Among patients treated with alkylating agents, risks increased with increasing number of cycles (*P* for trend <.001) (Table 2, C). A 13-fold risk of lung cancer followed nine or more cycles of alkylating agents. Patients classified as current cigarette smokers, whether with the use of data collected in follow-up (Table 2, D) or at diagnosis of Hodgkin's disease (Table 2, E), had more than 20-fold elevated risks of lung cancer.

Temporal trends of lung cancer risk following treatment are shown in Table 3. Statistically significant increased risks of lung cancer occurred 1–4 years and 5–9 years after the first treatment with alkylating agents. Analyses using only patients whose primary treatment included alkylating agents without radiotherapy yielded a similar pattern. In contrast, the RR of lung cancer did not increase until 5–9 years after radiotherapy and persisted for more than 20 years, although the twofold to threefold risks were not statistically significant.

Table 1. Characteristics of all patients with secondary lung cancer and of matched control patients among 19 046 individuals treated for Hodgkin's disease*

Characteristic	Patients with lung cancer (n = 222)		Matched control‡ patients (n = 444)	
	No.	%†	No.	%†
Cancer registry				
Connecticut	31	14.0	62	14.0
Denmark	41	18.5	82	18.5
Finland	24	10.8	48	10.8
Iowa	18	8.1	36	8.1
The Netherlands	10	4.5	20	4.5
Ontario	65	29.3	130	29.3
Sweden	33	14.9	66	14.9
Sex				
Male	167	75.2	334	75.2
Female	55	24.8	110	24.8
Age at diagnosis of Hodgkin's disease, y				
<30	25	11.3	48	10.8
30–39	33	14.9	73	16.4
40–49	51	23.0	101	22.8
50–59	68	30.6	127	28.6
⩾60	45	20.3	95	21.4
Year of diagnosis of Hodgkin's disease§				
1965–1969	41	18.5	76	17.1
1970–1974	67	30.2	139	31.3
1975–1979	49	22.1	100	22.5
1980–1984	39	17.6	80	18.0
1985–1994	26	11.7	49	11.0
Stage of Hodgkin's disease‖				
I or II	143	64.4	290	65.3
III or IV	79	35.6	151	34.0
Interval to second lung cancer, y¶				
1–4	46	20.7	93	20.9
5–9	70	31.5	139	31.3
10–14	45	20.3	90	20.3
15–19	33	14.9	67	15.1
⩾20	28	12.6	55	12.4
Histologic type of lung cancer#				
Squamous cell carcinoma	87	39.2	N/A	
Adenocarcinoma	48	21.6		
Small-cell carcinoma	36	16.2		
Large-cell carcinoma	20	9.0		
Other carcinoma or NOS	31	14.0		
Location of lung cancer**				
Main bronchus	13	5.9	N/A	
Upper lobe	114	51.4		
Middle lobe	8	3.6		
Lower lobe	39	17.6		
Overlapping lobes	11	5.0		
Other or NOS	37	16.7		
Stage of lung cancer				
I or II	81	36.5	N/A	
III or IV	126	56.8		
Not staged	15	6.8		

*N/A = not applicable; NOS = not otherwise specified.

†Percentages may not sum to 100 because of rounding.

‡Matching variables were registry, age, sex, calendar year of diagnosis of Hodgkin's disease, and period of latency. *See* the "Patients and Methods" section.

§Patients were diagnosed through December 31, 1991, in Connecticut; through December 31, 1992, in Ontario, Denmark, and Sweden; and through December 31, 1994, in Finland, Iowa, and The Netherlands.

‖Stage was not designated for three (0.7%) control patients.

¶Represents the interval between diagnosis of Hodgkin's disease and lung cancer for case patients and the comparable interval for matched control patients.

#Histologic codes (International Classification of Diseases for Oncology) *(21)* are 8051–52 and 8070–76 for squamous cell carcinoma; 8050, 8140–43, 8200, 8250–51, 8260, 8290, 8300, 8310, 8320, 8430, 8470–71, 8480–81, 8490, 8550, 8560, and 8571 for adenocarcinoma; 8041–45 and 8246 for small-cell carcinoma; 8012 for large-cell carcinoma; and 8010 for other carcinoma or NOS. The histologic distribution of first primary lung carcinomas (n = 223 924) in the Surveillance, Epidemiology, and End Results (SEER) Program (1973–1994) is squamous cell carcinoma (28.0%), adenocarcinoma (26.6%), small-cell carcinoma (17.0%), large-cell carcinoma (8.4%), and other carcinoma or NOS (20.0%).

**The location of first primary lung carcinomas (n = 223 924) in the SEER Program (1973–1994) is main bronchus (5.0%), upper lobe (46.3%), middle lobe (3.9%), lower lobe (19.1%), overlapping lobes (1.9%), and other or NOS (23.8%).

Table 2. Relative risk (RR) of lung cancer in patients with Hodgkin's disease according to type of treatment, radiation dose, number of cycles of alkylating agents, and smoking status*

	Parients with lung cancer	Matched control patients	RR	95% CI	P†
A) Treatment for Hodgkin's disease‡					
Radiation ⩾5 Gy / Alkylating agents					
No / No	21	98	1.0§	—	—
Yes / No	53	90	5.9	2.7 to 13.5	<.001
No / Yes	73	135	4.2	2.1 to 8.8	<.001
Yes / Yes	52	70	8.0	3.6 to 18.5	<.001
Combined modality therapy	21	41	5.4	2.1 to 14.1	<.001
Initial RT; salvage alkylating agents‖	31	29	11.1	4.6 to 29	<.001
B) Radiation dose to specific location in lung, Gy¶					
0	72	158	1.0#	—	—
>0–4.9	22	75	1.3	0.3 to 4.9	.69
5.0–14.9	14	18	4.1	0.7 to 22	.12
15.0–29.9	14	22	2.5	0.1 to 16.1	.46
30.0–39.9	51	87	8.6	2.9 to 30	<.001
⩾40.0	26	33	7.2	2.2 to 28	.001
C) No. of cycles with alkylating agent chemotherapy**					
0	74	188	1.0	—	—
1–4	22	44	4.0	1.3 to 12.5	.013
5–8	58	89	6.2	2.6 to 17.1	<.001
⩾9	28	29	13.0	4.3 to 45	<.001
Unknown No.	11	17	5.3	1.6 to 17.7	.005
Any noncyclic chemotherapy	6	26	1.3	0.2 to 6.7	.75
D) Smoking habit 5 y before lung cancer††					
Never smoker	7	92	1.0	—	—
Current cigarette smoker	135	143	22.6	9.5 to 65	<.001
Former cigarette smoker	23	56	5.7	2.2 to 16.6	<.001
Cigar or pipe smoker only	10	20	8.9	2.6 to 32	<.001
Not stated	24	82	5.0	1.9 to 15.3	.001
E) Smoking habit at diagnosis of Hodgkin's disease‡‡					
Never smoker	7	83	1.0	—	—
Current cigarette smoker	138	146	21.2	8.6 to 62	<.001
Former cigarette smoker	13	34	4.0	1.4 to 12.5	.009
Cigar or pipe smoker only	10	17	9.0	2.5 to 35	<.001
Not stated	31	113	4.0	1.5 to 12.3	.005

*Table is limited to 199 case patients and 393 control patients with adequate data for reliable radiation dose estimation. *See* the "Patients and Methods" section for details. CI = confidence interval; RT = radiotherapy.

†Two-sided *P* value based on likelihood ratio test of the null hypothesis that RR = 1.

‡Exposure was defined as treatment with alkylating agents for more than 1 month or radiotherapy that resulted in a dose of 5 Gy or more to the specific location in the lung where the cancer was diagnosed and the corresponding region in the control patients. All RRs were adjusted for smoking status. *See* the "Patients and Methods" section for details.

§The reference group consisted of 21 patients with lung cancer and 98 control patients who received a radiation dose of less than 5 Gy to the specific location in the lung where the cancer was diagosed (or the corresponding region in matched control patients) and/or treatment with nonalkylating agent chemotherapy. For 12 case patients and 46 control patients, the time since diagnosis of Hodgkin's disease was less than 5 years so that these patients were uninformative for radiotherapy comparisons. *See* the "Patients and Methods" section for details.

‖The median time between radiotherapy and salvage alkylating agents was 3.3 years.

¶Dose of radiation to the specific location in the lung where the cancer was diagnosed and the corresponding location in matched control patients. All RRs were adjusted for smoking status and number of cycles of alkylating agents. *P* for trend for radiation dose <.001.

#For 46 case patients and 91 control patients in this category, the time since diagnosis of Hodgkin's disease was less than 5 years so that these patients were uninformative for radiotherapy comparisons. *See* the "Patients and Methods" section for details.

**All RRs were adjusted for smoking status and radiation dose to the specific location in the lung where the cancer was diagnosed and the corresponding location in matched control patients. *P* for trend for number of cycles with alkylating agents <.001.

††Represents estimated tobacco habit 5 years before date of diagnosis of lung cancer and corresponding date in control patients, with the use of information recorded up to 1 year before these dates. All RRs were adjusted for radiation dose and number of cycles of alkylating agents. For current smokers, the risk of lung cancer at less than one pack per day (PPD), one to two PPD, and two or more PPD was 17, 25, and 70, respectively.

‡‡Represents estimated tobacco habit at diagnosis of Hodgkin's disease, using only information recorded up to 1 year after that date. All RRs were adjusted for radiation dose and number of cycles of alkylating agents.

Risk of lung cancer rose with increasing age at diagnosis of Hodgkin's disease, although differences between age groups of less than 40 years, 40–54 years, and 55 years or older were not statistically significant ($P = .36$ for alkylating agents; $P = .43$ for radiation dose ⩾5 Gy); the mean latency between treatment and lung cancer diagnosis for the three age groups was 17.0 years, 10.6 years, and 6.7 years, respectively. Risks due to treatment with alkylating agents or radiation therapy were higher among men than among women but were not statistically significant ($P = .23$ and $P = .20$, respectively). The stage of

Table 3. Risk of lung cancer according to time since first treatment of Hodgkin's disease, age at exposure, sex, stage of Hodgkin's disease, splenectomy status, and histopathologic type of lung cancer*

	Alkylating agents				Radiation ⩾5 Gy			
	Patients with lung cancer	Matched control patients	RR (95% CI)	P†	Patients with lung cancer	Matched control patients	RR (95% CI)	P†
A) Time since first treatment, y								
1–4	42	47	6.4 (2.1 to 21)	<.001	18	44	1.2 (0.3 to 4.5)	.76
5–9	39	69	5.7 (1.8 to 21)	.003	42	56	9.2 (2.9 to 34)	<.001
10–14	26	43	3.0 (1.0 to 11.4)	.058	25	47	1.9 (0.5 to 7.7)	.34
15–19	10	23	1.4 (0.3 to 8.0)	.70	19	31	2.4 (0.6 to 12.9)	.27
⩾20	6	19	1.1 (0.1 to 7.8)	.95	18	29	3.0 (0.7 to 18.9)	.24
B) Age at exposure, y								
<40	27	51	1.5 (0.4 to 8.8)	.58	42	73	3.8 (1.2 to 21)	.026
40–54	44	72	3.9 (1.4 to 12.5)	.007	37	56	3.5 (1.2 to 11.8)	.025
⩾55	54	82	6.5 (2.3 to 22)	<.001	26	31	10.2 (2.9 to 43)	<.001
C) Sex								
Male	96	149	4.8 (2.3 to 11.3)	<.001	72	110	7.2 (3.0 to 18.6)	<.001
Female	29	56	1.8 (0.6 to 7.1)	.35	33	50	2.1 (0.6 to 11.5)	.27
D) Stage of Hodgkin's disease‡								
I or II	60	98	3.2 (1.5 to 7.3)	.003	82	125	5.9 (2.8 to 13.2)	<.001
III or IV	65	106	4.7 (2.3 to 10.2)	<.001	23	34	5.1 (1.6 to 15.7)	.009
E) Staging splenectomy§								
No	93	163	4.3 (2.1 to 9.7)	<.001	71	113	6.4 (2.8 to 15.7)	<.001
Yes	31	34	6.8 (2.5 to 20)	<.001	31	41	6.1 (2.2 to 17.6)	<.001
F) Histopathologic type of lung cancer								
Squamous cell carcinoma	52	88	5.5 (1.3 to 39)	.017	41	70	7.3 (1.6 to 52)	.008
Small-cell carcinoma	21	28	8.8 (1.4 to 175)	.017	19	24	7.8 (1.2 to 156)	.031
Adenocarcinoma	25	44	2.5 (0.7 to 9.5)	.14	22	30	8.8 (2.2 to 43)	.002
Large-cell carcinoma	11	20	3.8 (0.7 to 23)	.12	9	12	13.5 (1.4 to 200)	.024
Other	16	25	3.5 (0.9 to 21)	.065	14	24	1.4 (0.2 to 12.0)	.75

*All analyses were adjusted for smoking status and other variables shown in the table. RR = relative risk; CI = confidence interval.

†Two-sided *P* value based on likelihood ratio test of the null hypothesis that RR = 1.

‡Three control patients for whom stage was not designated were excluded from the analyses.

§Five case patients and 15 control patients for whom data on staging splenectomy were not available were excluded from the analysis.

Hodgkin's disease ($P = .28$ and $P = .77$, respectively) and staging splenectomy ($P = .92$ and $P = .31$, respectively) also did not vary by alkylating agent or radiation treatment. Following alkylating agent therapy, risks of squamous cell lung cancer and small-cell lung cancer (SCLC) were statistically significantly elevated, although excesses were observed for all histopathologic categories. Statistically significantly increased risks for all designated morphologic groups of lung cancer occurred after radiotherapy.

Lung cancer risks according to type of alkylating agent are shown in Table 4. Overall risk for all MOPP-containing regimens was 5.0 (95% CI = 2.3 to 12.3) compared with 6.3 (95% CI = 2.5 to 17.7) for all other alkylating agents taken together. For patients whose therapy included MOPP, risk of lung cancer following one through four, five through eight, or nine or more cycles of treatment was 2.3, 4.5, and 14.4, respectively (*P* for trend <.001). The trend for increasing risk of lung cancer with increasing number of cycles of all other alkylating agents taken together was also highly significant (*P*<.001). Among patients treated with mechlorethamine (Table 4, B), risk of lung cancer increased with increasing cumulative dose of either mechlorethamine (*P* for trend <.001) or procarbazine (*P* for trend <.001) evaluated separately. No evidence was found for increasing risk of lung cancer with increasing cumulative dose of other alkylating agents, but the number of patients in most other categories was small.

Risks of lung cancer according to treatment of Hodgkin's disease and smoking category are shown in Table 5. All risks are relative to patients who were not moderate-to-heavy smokers, did not receive radiation dose to lung of more than 5 Gy, and were not treated with alkylating agents; thus, the RRs in the last column of Table 5 include the effects of both smoking and treatment. Regardless of treatment category, risks for moderate-to-heavy smokers were much higher than risks for other smoking categories combined. The data were compatible with a multiplicative relation ($P = .46$) of smoking and treatment category, and an additive relation was rejected ($P = .03$). The largest risks (RR = 49.1) for lung cancer were observed among moderate-to-heavy smokers given both radiotherapy and alkylating agents. For patients given alkylating agents only, the risk of lung cancer in moderate-to-heavy smokers was 17-fold compared with four-fold in other categories.

Discussion

To our knowledge, this is the first study of lung cancer following Hodgkin's disease to include quantitative measures of radiation dose to the precise location where the lung tumor was diagnosed, cumulative amounts of chemotherapeutic agents, and data on tobacco use. Human lung cancer was clearly linked to alkylating agents in a dose-dependent fashion and was distinguished from the effects of radiotherapy and smoking. In addition, on the basis of dosimetry that accounts for tumor location, we report a strong relation between increasing radiation dose of up to 40 Gy or more and statistically significant excesses of lung cancer and an additive relation between radiation and chemo-

Table 4. Risk of lung cancer according to type of alkylating agent and cumulative dose of mechlorethamine and procarbazine among 330 patients treated for Hodgkin's disease*

	Patients with lung cancer	Matched control patients	RR	95% CI	P†
A) Alkylating agent					
Mechlorethamine‡	92	152	5.0	2.3 to 12.3	<.001
MOPP§	55	92	5.0	2.1 to 13.6	<.001
MOPP-ABVD‖	16	28	3.8	1.1 to 13.2	.034
MOPP + other¶	21	32	6.1	2.1 to 18.8	<.001
Chlorambucil#	8	7	14.9	3.4 to 70	<.001
Nitrosourea**	7	10	5.4	1.2 to 26	.032
Dacarbazine††	2	4	5.4	0.5 to 47	.14
Other alkylating agents‡‡	16	32	5.1	1.7 to 16.7	.004
B) Mechlorethamine group‡					
Cumulative dose of mechlorethamine, mg/m^2§§					
<33	13	37	3.3	0.96 to 11.5	.059
33–51	19	37	2.9	0.94 to 9.5	.063
52–66	25	30	8.6	2.9 to 28	<.001
⩾67	22	28	6.6	2.3 to 21	<.001
Unknown	13	20	4.7	1.3 to 16.8	.021
Cumulative dose of procarbazine, mg/m^2§§					
<3700	13	38	1.4	0.3 to 5.6	.62
3700–5399	16	33	3.2	0.9 to 11.5	.077
5400–7599	21	34	6.2	2.0 to 21	.001
⩾7600	25	27	10.5	3.5 to 36	<.001
Unknown	17	20	6.7	2.2 to 22	.001

*Treatment categories are mutually exclusive. Alkylating drugs were usually given in combination with other drugs. All relative risks were adjusted for radiation dose and smoking status. RR = relative risk; CI = confidence interval; MOPP = mechlorethamine, vincristine, procarbazine, and prednisone; MOPP-ABVD = MOPP, doxorubicin, bleomycin, vinblastine, and dacarbazine.

†Two-sided *P* value based on likelihood ratio test of the null hypothesis that RR = 1.

‡Patients in this category received therapy with mechlorethamine as the principal alkylating agent, typically with procarbazine (87 case patients and 150 control patients) as part of the MOPP regimen. The median cumulative dose of mechlorethamine for case patients and control patients was 56 mg/m^2 and 48 mg/m^2, respectively. The median cumulative dose of procarbazine was 6700 mg/m^2 and 4800 mg/m^2, respectively.

§Cytotoxic drugs administered to patients in this category included mechlorethamine (55 case patients and 92 control patients), procarbazine (53 case patients and 91 control patients), vincristine (52 case patients and 78 control patients), and/or vinblastine (13 case patients and 29 control patients).

‖Cytotoxic drugs administered to patients in this category included mechlorethamine (16 case patients and 28 control patients), vincristine (12 case patients and 25 control patients), procarbazine (14 case patients and 28 control patients), doxorubicin (16 case patients and 28 control patients), bleomycin (16 case patients and 28 control patients), vinblastine (14 case patients and 26 control patients), and dacarbazine (15 case patients and 22 control patients).

¶Cytotoxic drugs administered to patients in this category included mechlorethamine (21 case patients and 32 control patients), procarbazine (20 case patients and 31 control patients), vincristine (18 case patients and 31 control patients), doxorubicin (four case patients and 11 control patients), bleomycin (five case patients and 12 control patients), vinblastine (11 case patients and 18 control patients), dacarbazine (three case patients and seven control patients), chlorambucil (four case patients and seven control patients), nitrosoureas (six case patients and nine control patients), and cyclophosphamide (12 case patients and 17 control patients).

#Patients received a variant of the MOPP regimen in which orally administered chlorambucil was substituted for mechlorethamine and vinblastine was used instead of vincristine. Other cytotoxic drugs administered included nitrosoureas (four case patients and four control patients), procarbazine (eight case patients and seven control patients), and cyclophosphamide (two case patients and two control patients).

**Patients in this category received therapy with carmustine (two case patients and two control patients) or lomustine (five case patients and eight control patients) as the principal alkylating agent. Other cytotoxic drugs administered included procarbazine (seven case patients and 10 control patients), cyclophosphamide (three case patients and five control patients), and dacarbazine (one case patient).

††Patients in this category received therapy with dacarbazine as the principal alkylating agent. Other cytotoxic drugs administered included procarbazine (one case patient and two control patients) and cyclophosphamide (two control patients).

‡‡This category included patients who did not receive mechlorethamine, chlorambucil, a nitrosourea, or dacarbazine. Cytotoxic drugs included cyclophosphamide (16 case patients and 30 control patients) and procarbazine (13 case patients and 25 control patients). Other administered cytotoxic drugs included vinblastine (nine case patients and 14 control patients), vincristine (six case patients and 15 control patients), doxorubicin (two case patients and one control patient), bleomycin (one case patient and two control patients), and thiotepa (one control patient).

§§ *P* for trend <.001.

therapy. Our investigation includes the largest number of patients studied to date, and the long-term follow-up permits for the first time an analysis of temporal trends of lung cancer risk in Hodgkin's disease survivors according to treatment; we also consider all major histopathologic groups of lung cancer.

Our findings are consistent with the established role of tobacco smoking in lung cancer *(22)*, but confounding by tobacco is unlikely to account for the statistically significant dose–response relations seen for treatment with alkylating agents and radiotherapy or the observed temporal trends. Truncation of smoking data collection 1 year before diagnosis of lung cancer (and a comparable date in control patients) mitigated possible bias in the reporting of tobacco use, and similar risk estimates were generated with the use of only smoking data recorded within 1 year of Hodgkin's disease diagnosis. Nonetheless, the magnitude of the estimated risks for lung cancer should be interpreted cautiously, given the possible residual and enhancing effects of tobacco.

The mechanisms by which alkylating agents are associated with subsequent excesses of lung cancer are not entirely clear. Alkylating agents exert their antitumor effect by direct reaction with DNA bases *(23);* methylating drugs, such as procarbazine,

Table 5. Risk of lung cancer in patients with Hodgkin's disease according to type of treatment and smoking category

Treatment for Hodgkin's disease		RR (95% CI) by smoking category [No. of case patients; control patients]*	
Radiation ⩾5 Gy	Alkylating agents	Nonsmoker, light, other†	Moderate–heavy‡
No	No	1.0§ [11 case patients; 76 control patients]	6.0 (1.9 to 20.4) $P = .002$ [10 case patients; 22 control patients]
Yes	No	7.2 (2.9 to 21.2) $P<.001$ [33 case patients; 73 control patients]	20.2 (6.8 to 68) $P<.001$ [20 case patients; 17 control patients]
No	Yes	4.3 (1.8 to 11.7) $P<.001$ [40 case patients; 105 control patients]	16.8 (6.2 to 53) $P<.001$ [33 case patients; 30 control patients]
Yes	Yes	7.2 (2.8 to 21.6) $P<.001$ [28 case patients; 60 control patients]	49.1 (15.1 to 187) $P<.001$ [24 case patients; 10 control patients]

*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. RR = relative risk; CI = confidence interval.

†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.

‡Moderate (one to two packs per day) and heavy (two or more packs per day) current cigarette smokers.

§Reference group.

can result in the same type of DNA adduct (O^6-methylguanine), a mutagenic and carcinogenic DNA adduct *(24)*, that is generated by 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), a tobacco metabolite that is a potent lung-specific carcinogen in laboratory animals *(25)*. Levels of O^6-methylguanine in lymphoma patients receiving chemotherapy are linearly correlated ($P<.01$) with cumulative dose of procarbazine *(26)*. O^6-Methylguanine is routinely repaired by the cellular protein O^6-methylguanine methyl transferase (MGMT) in an irreversible, self-destructive reaction *(23)*. Lung cancer risk has been associated with impaired removal of O^6-methylguanine adducts *(27)* and with polymorphisms of MGMT codon 143 *(28)*. Inhibition of MGMT transcription by promoter methylation may be a common event in lung carcinogenesis *(29)*. Because pyridyloxobutyl DNA adducts formed by tobacco-generated NNK can also inhibit MGMT *(30)*, smoking and alkylating agents may function as cocarcinogens. Further studies are needed to elucidate the carcinogenic mechanisms *(25–29,31,32)* that underlie the higher risks of lung cancer that were associated with alkylating agents in several smoking categories in our study. Our findings of excess lung cancer risk were not limited to MOPP *(6)* but extended to other alkylating agents, a finding that is consistent with experiments in laboratory animals in which a number of different cytotoxic drugs induce solid tumors *(18)*. Although Swerdlow et al. *(6)* suggested that mechlorethamine might be more carcinogenic than procarbazine, they were unable to evaluate this hypothesis with dose data. We found highly statistically significant relations between cumulative dose of both mechlorethamine and procarbazine and lung cancer risk among MOPP-treated patients. Both mechlorethamine and procarbazine as well as chlorambucil, when administered systemically, are carcinogenic to rodent lungs *(18)*, and mechlorethamine is similar in chemical structure to sulfur mustard, an established human lung carcinogen *(33)*.

Kaldor et al. *(4)* previously reported an elevated risk (RR = 2.1; 95% CI = 1.0 to 4.2) of lung cancer in patients with Hodgkin's disease treated with chemotherapy alone compared with those given radiotherapy only or both modalities. Although an increase in lung cancer risk with cumulative number of chemotherapy cycles was not evident, these investigators concluded that the risk of lung cancer after chemotherapy for Hodgkin's disease might be at least comparable to and possibly larger than the risk after radiotherapy. van Leeuwen et al. *(5)* found no overall association between chemotherapy for Hodgkin's disease or number of cycles and lung cancer risk, but they included a total of only 30 lung cancer case patients.

Although ionizing radiation is a known pulmonary carcinogen *(34)*, the relation of therapeutic exposures to lung cancer risk has been addressed in only a few populations and over limited dose ranges *(4–6,35)*. In previous analytic studies of lung cancer after radiotherapy for either breast cancer or Hodgkin's disease, dose to the specific location where the lung cancer arose was not determined *(4–6,35)* and smoking data were often unavailable *(4,6,35)*. Because radiation dose across the lung can vary more than 10-fold during mantle radiotherapy when blocking techniques are considered, utilization of an average dose to the entire lobe *(5)* or an average dose to the left or right lung *(4)* can distort quantification of radiation-associated risk. In addition, the number of patients was small in previous studies, such as the Dutch study where only six case patients and nine control patients received an average radiation dose to the entire lung lobe of 9 Gy or more *(5)*. In our study, 233 patients (91 case patients and 142 control patients) received 15 Gy or more to the specific site of tumor origin, and evidence was convincing of an upward trend in lung cancer risk with increasing radiation dose up to 40 Gy or more. This highly statistically significant dose–response relation underscores the importance of continuing to minimize the therapeutic doses of radiotherapy to treat Hodgkin's disease *(36)* without sacrificing efficacy. It is interesting to note that the risk of radiation-induced lung cancer persisted at very high doses, where the effects of tissue destruction and regeneration may have played important roles in the carcinogenic processes. Risks at lower doses, while elevated, were low and not statistically significant and indicate the important role that dose reduction can play in reducing risk.

To our knowledge, our study is the first to show that excess lung cancers after alkylating agents occur considerably earlier than the latent period characteristic of radiotherapy-associated

solid tumors, in which statistically significantly elevated risks are generally not observed until 10 years or more after exposure *(17)*. These different latencies may reflect different mechanisms for cancer induction. The peak latency of 5–9 years for lung cancer following radiotherapy for Hodgkin's disease that we observed is consistent with previous reports *(2,9,37)*. The reduced latency of radiation-related lung cancer may reflect a susceptibility state associated with the defects in cellular immunity *(38)* or genomic instability *(39,40)* that occur in patients with Hodgkin's disease. It is noteworthy that excesses of lung cancer have been reported also in patients with other lymphopoietic malignancies *(41,42)* and in organ transplant recipients *(43)*. Whether the immunologic defects associated with Hodgkin's disease also contribute to alkylating agent-related lung cancer should be considered. It also seems possible that the immunosuppressive effects of tobacco smoking *(31)* may accentuate the immune alterations associated with Hodgkin's disease *(38)*.

We previously reported a sevenfold risk of SCLC after primary therapy with radiation among Hodgkin's disease patients in the Surveillance, Epidemiology, and End Results (SEER) Program,[1] despite the limitation that SEER Program treatment data are incomplete *(9)*. Statistically significant associations between radiation and SCLC have been observed among high-dose atomic bomb survivors and uranium miners *(44,45)*. In the current study, radiotherapy for Hodgkin's disease was associated with statistically significantly increased risks of all major histopathologic categories of lung cancer. Excesses of lung cancer after treatment with alkylating agents were similarly not restricted to any morphologic group. In contrast, it has been suggested that the increased risk of lung cancer after any treatment for Hodgkin's disease that includes chemotherapy is confined to adenocarcinomas ($n = 14$ case patients) and does not extend to non-adenocarcinomas, i.e., all other histologic types grouped together ($n = 35$ case patients) *(6)*. Swerdlow et al. *(6)* were unable to examine the relation between radiation therapy for Hodgkin's disease and lung cancer morphology, and most other studies *(4,5)* did not address associations between treatment for Hodgkin's disease and histologic type of lung cancer.

The age distribution of patients with Hodgkin's disease in our investigation was skewed to older individuals, who tended to develop lung cancer with a shorter latent period after treatment. Although not statistically significant, the risks of lung cancer after therapy with either alkylating agents or radiation increased with age. Previously, only the study of British patients with Hodgkin's disease examined the effect of age on lung cancer risk, showing larger excesses after MOPP chemotherapy in patients treated at age 50 years or more compared with younger subjects *(6)*. Since large numbers of molecular events appear to be required for lung carcinogenesis *(46)*, the probability of a critical number likely increases with increasing age, a possible surrogate for longer smoking duration. The high prevalence of smoking among control patients in our series was unexpected and exceeds general population estimates of 25%–40% *(47)*.

In our investigation, the use of alkylating agents in the treatment of Hodgkin's disease was associated with statistically significantly increased risks of lung cancer, even when adjusted for the effects of radiotherapy and tobacco use. A causal association is supported by the magnitude of risk, the dose–response relation, plausible biologic mechanisms including studies in laboratory animals *(18)*, and consistency with earlier studies by Tucker et al. *(19)*. Our data also suggest that alkylating agents, particularly mechlorethamine, are less potent on a relative scale in inducing lung cancers than in inducing leukemia. Whereas risks of leukemia after cumulative mechlorethamine doses of 67 mg/m^2 or greater to treat Hodgkin's disease may reach 60- to 80-fold *(48)*, the risks of lung cancer were on the order of sixfold to eightfold in our study. Despite the smaller RRs, however, the absolute risks (or burden) could be far greater for lung cancer than for leukemia, in view of the considerably higher baseline rate of lung cancer in the general population.

Given the wide variety of solid tumors induced by alkylating agents in laboratory animals *(18)* and the increasing use of chemotherapy in Hodgkin's disease *(49)*, it will be important to clarify the type-specific risks of cancers among patients treated with these agents, including possible interactions with the risks following radiotherapy *(17)*. Our data suggest that excess lung cancer risk after combined therapy with radiation and alkylating agents was as expected if the individual risks were summed. These findings are similar to the relation of radiation and cyclophosphamide to the bladder cancer risk of patients with non-Hodgkin's lymphoma *(11)*. However, the influence of timing and intensity of exposures to radiation and alkylating agents on solid tumor risks has not been well explored. On the other hand, smoking appeared to interact multiplicatively with radiation therapy and with chemotherapy in our study.

A major limitation of our study, as well as of previous studies of lung cancer after Hodgkin's disease *(4–6)*, is the uncertainty in the estimates of risks associated with treatment, in view of the large risk conferred by tobacco use. While radiotherapy and chemotherapy information was readily available in the medical records, information on smoking habits was not systematically recorded in formats that would be optimal for epidemiologic purposes. Furthermore, because of the small number of lung cancers in nonsmokers, the interaction of alkylating agents and/or radiation with tobacco use could be evaluated only by comparing moderate-to-heavy smokers with all other patients combined. Although a multiplicative interaction was consistent with our data and an additive interaction could be rejected, this finding should be interpreted cautiously, because of our inability to analyze the association with more finely stratified categories. To our knowledge, however, no other studies have attempted to address the interaction of alkylating agents for Hodgkin's disease and smoking on lung cancer risk. Because data on duration of smoking had not been uniformly and prospectively recorded for all patients, we could also not reliably develop accurate measures of cumulative tobacco use such as pack-years.

An inherent limitation of studies of second tumors following Hodgkin's disease is the lack of a nonexposed comparison group, given that treatment requires radiotherapy, chemotherapy, or both *(50)*. However, many of our analyses emphasized exposure–response relations either by using continuous variables or by presenting risks for several ordered categories of exposure. With the latter approach, the inclusion of patients with low exposures in the referent group is unlikely to inflate treatment-associated risks, although it may underestimate them.

Because our investigation was conducted among patients in the general population covered by well-defined reporting areas, it is unlikely to suffer from selection biases that may exist in hospital- or clinic-based series. It is unclear, however, whether our findings will apply to patients with cancers other than Hodg-

kin's disease, in light of the immune defects characteristic of this lymphoma *(38)* and the high prevalence of smokers among case patients and control patients in our study. It should be noted that our evaluation also may not reflect current practice with regard to the type or cumulative doses of drugs, the radiotherapy modalities, or the combined therapies being administered. For example, ABVD (i.e., the combination of doxorubicin, bleomycin, vinblastine, and dacarbazine) is commonly used today but was rarely given during the years of our study. Thus, generalization of our findings to current practice should be done with caution and should be weighed against the remarkable gains in survival provided by effective treatments for Hodgkin's disease. Before the introduction of combination chemotherapy, patients with advanced Hodgkin's disease had a 5-year survival rate of less than 10% *(51)*, which increased to 66%–75% with MOPP chemotherapy *(52)*. The MOPP regimen remains one of the standards against which treatments for adult Hodgkin's disease are evaluated *(53)*, and component drugs are retained within sequential MOPP/ABVD and MOPP/ABV (i.e., combination of doxorubicin, bleomycin, and vinblastine) hybrid regimens *(53,54)*. The use of eight cycles of MOPP/ABV results in total doses of about 48 mg/m^2 mechlorethamine and 5600 mg/m^2 procarbazine, respectively *(53)*. At these cumulative amounts, our data would predict a lung cancer RR of 3–6 when compared with patients who received no alkylating agents and/or a radiation dose to the lung of 5 Gy or less.

On the basis of the overall analyses of 199 lung cancers in our study, it can be roughly estimated that 19 cases (9.6%) were due to treatment alone, 126 (63.3%) were due to treatment and smoking in combination, 48 (24.1%) were due to smoking alone, and six (3%) represented tumors in which neither smoking nor therapy played a role. Thus, the combined effect of treatment and smoking accounted for the bulk of lung cancers in our series, underscoring the importance of smoking cessation in the management of patients with Hodgkin's disease. It is clear that the tremendous improvement in the treatment of Hodgkin's disease outweighs the therapy-related risks of lung cancer and other late effects, especially when compared with the burden imposed by tobacco.

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NOTES

[1]*Editor's note:* SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.

We thank Diane Fuchs (Westat, Inc., Rockville, MD) for administrative assistance in conducting the field studies; Virginia Hunter (Toronto, ON, Canada), Judie Fine (New Haven, CT), Carmen Radolovich (Toronto), Darlene Dale (Toronto), Judy Anderson (Iowa City, Iowa), Lori Odle (Iowa City), Connie Mahoney (Iowa City), Susanne Hein (Copenhagen, Denmark), Inge Bilde Hansen (Copenhagen), Sandra van den Belt (Amsterdam, The Netherlands), and Gloria Gridley (Bethesda, MD) for support in data collection; Catherine Kasper and Rita Weathers (Houston, TX) for assistance with radiation dosimetry estimates; Denise Duong (Bethesda) for secretarial help; and Jeremy Miller, Laura Capece, and George Geise (Information Management Services, Rockville, MD) for computing support. We also thank Drs. Graca Dores and Margaret A. Tucker (Bethesda) for critical review of the manuscript. We are also indebted to the many hospitals and physicians worldwide who allowed access to treatment records, including the following hospitals in Connecticut: Hartford Hospital, Yale-New Haven Hospital, St. Francis Hospital and Medical Center, Bridgeport Hospital, Waterbury Hospital, Hospital of St. Raphael, Danbury Hospital, New Britain General Hospital, Norwalk Hospital, St. Vincent's Medical Center, Standford Hospital, Middlesex Hospital, St. Mary's Hospital, Lawrence and Memorial Hospital, Manchester Memorial Hospital, Greenwich Hospital Association, Veterans Memorial Hospital, Griffin Hospital, Bristol Hospital, University of Connecticut Health Center and John Dempsey Hospital, William W. Backus Hospital, Park City Hospital, Charlotte Hungerford Hospital, Windham Community Memorial Hospital, Milford Hospital, Day Kimball Hospital, Rockville General Hospital, Bradley Memorial Hospital, The Sharon Hospital, New Milford Hospital, Johnson Memorial Hospital, and Winsted Memorial Hospital.

Manuscript received July 2, 2001; revised November 28, 2001; accepted December 12, 2001.