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Pancreatic cancer risk after treatment of Hodgkin lymphoma

G. M. Dores[1,2*], R. E. Curtis[1], F. E. van Leeuwen[3], M. Stovall[4], P. Hall[5], C. F. Lynch[6], S. A. Smith[4], R. E. Weathers[4], H. H. Storm[7], D. C. Hodgson[8], R. A. Kleinerman[1], H. Joensuu[9], T. B. Johannesen[10], M. Andersson[11], E. J. Holowaty[12], M. Kaijser[13], E. Pukkala[14], L. Vaalavirta[9], S. D. Fossa[15], F. Langmark[10], L. B. Travis[16], J. F. Fraumeni Jr[1], B. M. Aleman[17], L. M. Morton[1] & E. S. Gilbert[1]

[1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, DHHS, Bethesda; [2]Department of Veterans Affairs Medical Center, Oklahoma City, USA; [3]Department of Epidemiology and Biostatistics, The Netherlands Cancer Institute, Amsterdam, The Netherlands; [4]Department of Radiation Physics, The University of Texas MD Anderson Cancer Center, Houston, USA; [5]Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden; [6]Department of Epidemiology, University of Iowa, Iowa City, USA; [7]Cancer Prevention and Documentation, Danish Cancer Society, Copenhagen, Denmark; [8]Department of Radiation Oncology, University of Toronto, Toronto, Canada; [9]Department of Oncology, Helsinki University Central Hospital, Helsinki, Finland; [10]Cancer Registry of Norway, Oslo, Norway; [11]Department of Oncology, Copenhagen University Hospital, Copenhagen, Denmark; [12]Dalla Lana School of Public Health, University of Toronto, Toronto, Canada; [13]Clinical Epidemiology Unit, Department of Medicine, Karolinska Institute, Stockholm, Sweden; [14]Finnish Cancer Registry, Institute for Statistical and Epidemiological Cancer Research, Helsinki and School of Health Sciences, University of Tampere, Tampere, Finland; [15]Department of Oncology, Oslo University Hospital and University of Oslo, Oslo, Norway; [16]Department of Radiation Oncology, University of Rochester Medical Center, Rochester, USA; [17]Department of Radiation Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

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Background: Although elevated risks of pancreatic cancer have been observed in long-term survivors of Hodgkin lymphoma (HL), no prior study has assessed the risk of second pancreatic cancer in relation to radiation dose and specific chemotherapeutic agents.

Patients and methods: We conducted an international case–control study within a cohort of 19 882 HL survivors diagnosed from 1953 to 2003 including 36 cases and 70 matched controls.

Results: Median ages at HL and pancreatic cancer diagnoses were 47 and 60.5 years, respectively; median time to pancreatic cancer was 19 years. Pancreatic cancer risk increased with increasing radiation dose to the pancreatic tumor location ($P_{trend} = 0.005$) and increasing number of alkylating agent (AA)-containing cycles of chemotherapy ($P_{trend} = 0.008$). The odds ratio (OR) for patients treated with both subdiaphragmatic radiation (≥10 Gy) and ≥6 AA-containing chemotherapy cycles (13 cases, 6 controls) compared with patients with neither treatment was 17.9 (95% confidence interval 3.5–158). The joint effect of these two treatments was significantly greater than additive ($P = 0.041$) and nonsignificantly greater than multiplicative ($P = 0.29$). Especially high risks were observed among patients receiving ≥8400 mg/m^2 of procarbazine with nitrogen mustard or ≥3900 mg/m^2 of cyclophosphamide.

Conclusion: Our study demonstrates for the first time that both radiotherapy and chemotherapy substantially increase pancreatic cancer risks among HL survivors treated in the past. These findings extend the range of nonhematologic cancers associated with chemotherapy and add to the evidence that the combination of radiotherapy and chemotherapy can lead to especially large risks.

Key words: Hodgkin lymphoma, pancreatic cancer, radiotherapy, chemotherapy, second cancer

introduction

Hodgkin lymphoma (HL) survivors benefit from successful HL therapy, with 5-year relative survival increasing between 1975–1977 and 2002–2008 from 72% to 87% among adults and 81% to 97% among children [1]. However, as a consequence of effective therapy, HL survivors are often faced with life-long health risks. Several studies have reported significantly increased risks of pancreatic cancer among long-term HL survivors [2–6], but no prior study of HL survivors has assessed the risk of pancreatic cancer in relation to radiation dose or specific chemotherapeutic agents. In the general US population, pancreatic

*Correspondence to: Dr Graça M. Dores, Veterans Affairs Medical Center, 921 NE 13th Street, Oklahoma City, OK 73104, USA. Tel: +1-405-456-3306; Fax: +1-405-456-1560; E-mail: doresg@mail.nih.gov

Table 1. Characteristics of Hodgkin lymphoma (HL) patients who subsequently developed pancreatic cancer (cases) and matched controls

	Cases ($n = 36$)		Controls ($n = 70$)	
	N	(%)	*N*	(%)
Study center (years included)				
Denmark (1943–1999)	3	(8.3)	4	(5.7)
Finland (1953–2002)	9	(25.0)	18	(25.7)
Iowa, USA (1973–2001)	1	(2.8)	2	(2.9)
The Netherlands (1965–2002)	3	(8.3)	6	(8.6)
Norway (1953–2000)	4	(11.1)	8	(11.4)
Ontario, Canada (1964–2003)	6	(16.7)	12	(17.1)
Sweden (1958–2002)	10	(27.8)	20	(28.6)
Sex				
Male	21	(58.3)	41	(58.6)
Female	15	(41.7)	29	(41.4)
Year of HL diagnosis				
1963–1969	10	(27.8)	19	(27.1)
1970–1974	12	(33.3)	24	(34.3)
1975–1979	8	(22.2)	13	(18.6)
1980–1989	6	(16.7)	14	(20.0)
Age at diagnosis of HL (years)				
12–29	9	(25.0)	18	(25.7)
30–49	10	(27.8)	22	(31.4)
50–59	10	(27.8)	17	(24.3)
60–76	7	(19.4)	13	(18.6)
HL histology				
Nodular sclerosis	7	(19.4)	19	(27.1)
Mixed cellularity	10	(27.8)	20	(28.6)
Lymphocyte predominant	5	(13.9)	8	(11.4)
Lymphocyte depleted	3	(8.3)	6	(8.6)
Unspecified[a]	11	(30.6)	17	(24.3)
HL stage				
I	13	(36.1)	22	(31.4)
II	13	(36.1)	29	(41.4)
III	7	(19.4)	11	(15.7)
IV	3	(8.3)	8	(11.4)
HL relapse during follow-up				
No	17	(47.2)	48	(68.6)
Yes	19	(52.8)	22	(31.4)
HL treatment summary[b]				
RT and AA	22		25	
Initial therapy only	4	(11.1)	13	(18.6)
Initial and subsequent therapy	18	(50.0)	12	(17.1)
RT (no AA)	10		33	
Initial therapy only	9	(25.0)	26	(37.1)
Any subsequent therapy	1	(2.8)	7	(10.0)
AA (no RT)	3		11	
Initial therapy only	3	(8.3)	8	(11.4)
Any subsequent therapy	0	(0.0)	3	(4.3)
RT (initial), unknown AA	1	(2.8)	0	(0.0)
No RT, unknown AA	0	(0.0)	1	(1.4)
Interval from HL to pancreatic cancer (matched time period for controls) (years)				
5–14	16	(44.4)	31	(44.3)
15–24	14	(38.9)	29	(41.4)
25–33	6	(16.7)	10	(14.3)
Age at pancreatic cancer diagnosis (years)				
36–49	6	(16.7)	–	
50–69	18	(50.0)	–	
70–87	12	(33.3)	–	

Continued

Table 1. *Continued*

	Cases ($n = 36$)		Controls ($n = 70$)	
	N	(%)	*N*	(%)
Stage of pancreatic cancer				
I/II	9	(25.0)	–	
III	7	(19.4)	–	
IV	15	(41.7)	–	
Not otherwise specified	5	(13.9)	–	

[a]Includes Hodgkin granuloma (eight cases, eight controls) and unspecified histology (three cases, nine controls).
[b]Treatment summary includes all therapy received (initial and subsequent). Initial treatment was defined from the start of treatment until the occurrence of a >3-month period without treatment. Subsequent therapy may have been given during the same treatment course, sequentially, or separately if a patient had multiple recurrences.
AA, alkylating agent-containing chemotherapy; *N*, number; RT, radiotherapy.

cancer is the fourth most common cause of cancer death, with an overall 5-year relative survival of 5.8% [1]. The high fatality rate associated with pancreatic cancer and the increased incidence of pancreatic cancer among HL survivors highlight the importance of understanding pancreatic cancer risk in relation to HL therapy.

patients and methods

We conducted a matched case–control study within a cohort of 19 882 patients who survived ≥5 years following a diagnosis of first primary histologically confirmed HL as their primary cancer and who were reported to one of six population-based registries or were diagnosed in one of the main hospitals in The Netherlands [7] (Table 1). A total of 43 second primary pancreatic cancers were identified, representing a cumulative incidence of 0.16% [95% confidence interval (CI) 0.09% to 0.23%] at 15 years and 0.54% (95% CI 0.36% to 0.72%) at 30 years in the population-based cohort [8]. Medical records were unavailable or destroyed for seven cases, all of whom were diagnosed before 1975. For the remaining 36 cases, two controls per case were selected by stratified random sampling from the cohort and matched by registry, birth date (within 5 years), calendar year of HL diagnosis (within 5 years), race (Iowa only), and survival without a second malignant tumor at least as long as the interval between the HL diagnosis and occurrence of pancreatic cancer. Medical records were unavailable for seven of the controls originally identified. Additional controls were sought to include two controls per case; for two cases only one matching control could be identified. The final HL population thus consisted of 36 cases and 70 controls. The study was approved by relevant authorities in each study center and was exempted from review by the National Cancer Institute (US) due to use of existing, de-identified data.

data collection

Standardized abstract forms were used to collect demographic, diagnostic, and treatment information from all available records. Histologic confirmation was available for 28 of 36 (78%) cases; for the remaining eight cases, diagnosis of pancreatic cancer was deemed highly likely based on clinical information. Tumor location was specified for 33 of 36 cases, with 28 (85%) of the tumors occurring in the pancreatic head.

radiation treatment and dosimetry

Radiotherapy details for each study subject were abstracted from the medical records, including dates of therapy, beam energy, fields (including size, location, and configuration), and prescribed dose. A custom-designed dose program [9], based on measurements made in water and anthropomorphic phantoms constructed of tissue-equivalent material, was used to calculate the mean radiation dose to the part of the pancreas (head, body, tail) where the tumor was located for cases and to the corresponding anatomical site in matched controls. For the three patients with unknown tumor site, the dose to the pancreas head was used for dose calculations because it was the most common location. Doses were summed over all treatments excluding doses delivered within 5 years of the date of pancreatic cancer diagnosis (or equivalent date for controls) to allow for the latency period associated with radiation carcinogenesis [10].

chemotherapy

For chemotherapy, data were collected on specific drugs and regimens (supplementary Table S1, available at *Annals of Oncology* online), dates and route of administration, number of cycles, and purpose (initial or subsequent treatment). Cumulative doses were recorded for all alkylating agents (AA) and topoisomerase II inhibitors. Statistical analyses included all chemotherapy given before pancreatic cancer diagnosis (comparable date for controls) since, unlike radiation exposure, elevated risks of solid tumors have been observed 1–4 years following receipt of AA [11].

statistical analysis

Conditional logistic regression [12] was used to estimate odds ratios (ORs) for pancreatic cancer risk by comparing the exposure histories of case patients with those of matched controls, using the Epicure software package [13]. Parameter estimates were computed using maximum likelihood methods with likelihood ratio-based hypothesis tests and 95% CIs. Two-sided $P < 0.05$ was considered statistically significant. All analyses included indicator variables for patients with unknown radiation dose and for patients with unknown chemotherapy.

The radiation dose–response relationship was initially evaluated by estimating the OR by categories of dose with adjustment for the number of AA-containing cycles treated as a continuous variable. Additional analyses were based on the model

$$\mathrm{OR} = \exp\left(\sum_j \alpha_j x_j\right)(1 + \beta z)$$

where z is radiation dose in Gy, β is the excess OR per Gy (EOR/Gy), and the x_j are variables measuring chemotherapy. Models that are linear in radiation dose have been used extensively in epidemiologic evaluations of radiation risks [10].

To evaluate interaction of radiation dose and receipt of AA, deviances of multiplicative and additive models were compared with those of more general models that included interaction terms using categorical variables (radiation dose: <10 versus ≥10 Gy; AA cycles: <6 versus ≥6). We used these same categories to evaluate the heterogeneity in risks associated with radiation dose and AA-containing chemotherapy among subjects by gender, age, and calendar year of HL diagnosis, time since HL diagnosis, and age at pancreatic cancer diagnosis by fitting models with separate estimates of the treatment effects and testing for trend and homogeneity in the OR with the variable of interest.

results

The median age at HL diagnosis was 47 years (range 12–76 years); 39% of patients were diagnosed in 1975 or later, and 73% had stage I or II disease. Thirty-three (92%) cases and 58 (83%) controls received radiotherapy for HL. Many of these patients also received AA-containing chemotherapy (22 cases, 25 controls) (Table 1). Pancreatic cancer ($n = 36$) was diagnosed at a median age of 60.5 years (range 36–87 years) and a median of 19 years following HL diagnosis (range 6.5–33 years). Overall survival following pancreatic cancer was poor: 34/36 (94%) of cases were known to have died, with a median survival time of 3.5 months (range 0–5.25 years).

The most commonly administered radiotherapy treatment was the mantle field (52% of patients) with cumulative target doses of 25–45 Gy using conventional fractionation. However, the highest radiation doses to the pancreas were delivered by subdiaphragmatic HL fields (supplementary Figure S2, available at *Annals of Oncology* online). Patients who were treated with at least one of these subdiaphragmatic fields (19 cases, 18 controls) received high doses to the pancreatic tumor site that ranged from 11.9 to 47.3 Gy (mean = 35.4 Gy). In contrast, patients who received supradiaphragmatic radiotherapy only (11 cases, 36 controls) had pancreatic tumor doses that ranged from 0.003 to 3.6 Gy (mean = 0.7 Gy). For each radiation field, doses to the head and body of the pancreas were similar.

Pancreatic cancer risk increased with increasing radiation dose to the pancreatic tumor location ($P_{trend} = 0.005$) to reach an OR of 9.1 (95% CI 1.7–77) at doses of ≥40 Gy, after adjusting for the number of AA-containing cycles of chemotherapy (Table 2). There was no indication of increased risk for patients exposed to relatively low doses 0.5 to <5 Gy (OR = 0.5) of radiation and only a moderate increase for doses in the range of 10 to <40 Gy (OR = 1.8). No patients received doses of 5 to <10 Gy. The OR for patients receiving ≥10 Gy compared with those receiving <10 Gy was 4.3 (95% CI 1.7–15). The EOR per Gy was 0.098 (95% CI 0.015–0.42), and this linear model also provided a reasonable description of the data ($P = 0.19$ when compared with the categorical model shown in Table 2).

After adjusting for radiation dose, pancreatic cancer risk also rose with increasing number of AA-containing cycles of chemotherapy ($P_{trend} = 0.008$), with similar ORs (3.6–3.7) for those receiving 6, 7–10, or >10 cycles. There was little evidence that radiation- or AA-related risks varied by gender, age at HL diagnosis, year of HL diagnosis, or attained age (supplementary Table S3, available at *Annals of Oncology* online).

In analyses of a potential interaction between radiation and AA-containing chemotherapy on pancreatic cancer risk, patients who received both ≥10 Gy to the pancreatic tumor location and ≥6 AA-containing chemotherapy cycles had a 17.9-fold increased risk (95% CI 3.5–158) compared with patients receiving <10 Gy and <6 cycles. This risk was significantly greater than the OR of 3.8 predicted by an additive model [(3.0 – 1) + (1.8 – 1) + 1] ($P = 0.041$) and nonsignificantly greater than the OR of 5.4 predicted by a multiplicative model (3.0×1.8) ($P = 0.29$). Analyses based on continuous variables yielded similar results.

We conducted a series of secondary analyses to identify specific chemotherapeutic agents and regimens that might contribute to the observed association between AA-containing chemotherapy and pancreatic cancer. Table 3 presents analyses that explored the risk of pancreatic cancer associated with individual chemotherapy agents in multivariate models. Risk increased with procarbazine dose [given as part of MOPP (nitrogen mustard, vincristine, procarbazine, prednisone)], with cyclophosphamide dose, and possibly with the number of cycles of topoisomerase II inhibitors (often included in current treatment of HL). When any of the remaining specific AAs or doses from these AAs [nitrogen mustard, procarbazine (not given as part of MOPP), dacarbazine, chlorambucil, carmustine/lomustine] were added to this multivariate model, the OR and dose trends were either nonsignificantly negative, or the P for improvement in fit was >0.5. Pancreatic cancer risks were notably elevated for patients receiving ≥8400 mg/m^2 of procarbazine (equivalent to ≥6 MOPP cycles; nine cases, three controls) or ≥3900 mg/m^2 of cyclophosphamide [equivalent to ≥3 COPP (cyclophosphamide, vincristine, procarbazine, prednisone) cycles; six cases, two controls]. Notably, 9 of the 14 cases and none of the 5 controls who received these doses also received ≥10 Gy to the pancreatic tumor location, further supporting a potential interaction between radiation and chemotherapy, albeit based on small numbers. Additional analyses of risks of pancreatic cancer by several specific chemotherapy regimens are described in supplementary Material S4 and Table S5, available at *Annals of Oncology* online.

discussion

To our knowledge, this international study is the first to evaluate risk of second pancreatic cancer with detailed data on HL therapy, including both individualized reconstruction of the radiation dose to the specific tumor location within the pancreas and cumulative doses of specific chemotherapy agents. We demonstrate that, among HL survivors, risk of subsequent pancreatic cancer increased significantly with both increasing radiation dose to the pancreatic tumor location and increasing number of AA-containing cycles of chemotherapy. Especially high risks (18-fold) were observed among patients who received both subdiaphragmatic radiotherapy and ≥6 cycles of AA-containing chemotherapy.

Our study is also the first among cancer survivors to demonstrate a statistically significant radiation-dose relationship for pancreatic cancer, although such relationships have been observed among patients treated for benign diseases [14, 15]. However,

Table 2. Risk of pancreatic cancer associated with radiation dose to the site of the pancreatic tumor (matched location for controls) and receipt of alkylating agent (AA)-containing chemotherapy for Hodgkin lymphoma (HL)

HL treatment	Cases/Controls (*N*) (36/70)	OR[a] (95% CI)	*P*-value
Radiation dose (Gy)[b]			
0 to <0.5	9/25[c]	1.0	
0.5 to <5[d]	6/24	0.5 (0.1–2.0)	
10[d] to <40	10/12[e]	1.8 (0.5–8.1)	
≥40	9/6	9.1 (1.7–77)	$P_{trend} = 0.0050$
Unknown	2/3	1.0 (0.1–8.7)	
Total	36/70		
EOR per Gy[f]		0.098 (0.015–0.42)	
Chemotherapy (number of AA cycles)[g]			
0	10/33	1.0 (referent)	
1–5	5/9	1.0 (0.2–4.4)	
6	7/12	3.7 (0.9–19)	
7–10	6/8	3.6 (0.8–18)	
>10	7/7	3.7 (0.9–19)	$P_{trend} = 0.008$
Unknown	1/1	4.9 (0.1–172)	
Radiation dose (Gy) and chemotherapy (number of AA cycles)[h]			
<10 and <6	9/28	1.0	
≥10 and <6	6/12	3.0 (0.7–17)	
<10 and ≥6	6/20	1.8 (0.4–9.7)	
≥10 and ≥6	13/6	17.9 (3.5–158)	$P_{multiplicative\ interaction} = 0.29$ $P_{additive\ interaction} = 0.041$

[a]The ORs presented differ from crude ORs because they take account of the matching and of the modest positive correlation between radiation dose and number of AA cycles.
[b]Adjusted for number of AA-containing cycles.
[c]Includes 3 cases and 12 controls who did not receive radiotherapy and one control who received radiotherapy only in the period within 5 years of the date of pancreatic cancer diagnosis in the associated case.
[d]There were no subjects in the 5 to <10 Gy category.
[e]Includes five cases and three controls with doses in the 10 to <30 Gy range and five cases and nine controls in the 30 to <40 Gy range.
[f]Radiation dose was treated as a continuous variable.
[g]Adjusted for radiotherapy (continuous linear variable). In order to reduce the influence of outliers, the continuous variable for the number of AA-containing cycles was truncated at 30 cycles. This truncation affected a case with 66 AA cycles and a control with 41 AA cycles.
[h]Our findings of positive trends with both radiation dose and the number of AA cycles persisted in analyses that excluded one registry at a time except that the trends did not reach statistical significance when Sweden, the registry contributing the largest number of cases, was excluded ($P = 0.053$ for radiation dose; $P = 0.17$ for number of AA cycles). Significant positive trends persisted in analyses that excluded either patients for whom radiotherapy data were incomplete (3 cases, 6 controls) or case sets for whom the pancreatic cancer diagnosis was not histologically confirmed (8 cases, 16 controls).
CI, confidence interval; EOR, excess odds ratio; Gy, Gray; OR, odds ratio.

elevated radiation-related risks following HL were found only among patients who received subdiaphragmatic radiotherapy (≥10 Gy to the pancreas), and our ability to evaluate the shape of the dose–response or risks at lower doses was limited by the small size of our study and the absence of patients with doses of 5–10 Gy. Unlike cancers of many other sites, a statistically significant radiation dose–response for pancreatic cancer has not been demonstrated in atomic bomb survivors in Japan (doses <4 Gy), although a nonsignificant positive association was observed in the most recent evaluation of those data [16].

A new finding in our study was the increased risk of pancreatic cancer in patients receiving ≥6 cycles of AA-containing chemotherapy. Our data add to the growing evidence that AAs are associated with increased risk of nonhematologic malignancies, including lung and stomach cancers following HL [11, 17, 18] as well as gastrointestinal and thyroid cancers following childhood cancer [19–21]. Because chemotherapy for HL may include many different regimens, we had limited ability to evaluate and quantify the effects of individual regimens and drugs, and thus our findings on specific chemotherapy treatments should be interpreted cautiously. We found significant dose–response relationships for both procarbazine (only among patients who received MOPP) and cyclophosphamide, but the elevated risks were limited to patients who were treated with ≥8400 mg/m^2 of procarbazine or ≥3900 mg/m^2 of cyclophosphamide. The biologic mechanisms linking these agents to pancreatic cancer are not clear, but both MOPP and cyclophosphamide are classified as human carcinogens [22]. We also found evidence of

Table 3. Multivariate analysis of pancreatic cancer associated with doses of specific alkylating agents and number of cycles of topoisomerase II inhibitors for Hodgkin lymphoma

Chemotherapy agent(s)	Cases/Controls[a] (*N*)	OR[b]	95% CI	P_{trend}[c]	Mean radiation dose (Gy)	Cases/controls receiving ≥10 Gy
MOPP (Procarbazine dose[d])						
Dose (mg/m^2)						
0	16/44	1.0			11.3	5/11
1–5599	8/9	0.7	0.1–4.5		20.2	6/4
5600–8399	2/13	0.2	0.01–1.5		8.9	1/3
≥8400	9/3	20.3	2.4–716	0.020	20.3	7/0
Cyclophosphamide[e]						
Dose (mg/m^2)						
0	27/64	1.0			11.7	13/15
1–3899	3/3	1.5	0.1–36		35.4	3/3
≥3900	5/2	18.7	1.7–780	0.021	14.5	3/0
Topoisomerase II inhibitors[f]						
Cycles						
0	26/64	1.0			12.6	15/14
1–5	4/0	∞	3.3–∞		21.6	3/0
≥6	5/5	4.4	0.5–58	0.22	15.9	2/3

[a]Table excludes one case and one control with unknown chemotherapy.
[b]Adjusted for radiotherapy (continuous linear dose).
[c]P_{trend} evaluated continuous dose (mg/m^2) variables for each alkylating agent and number of cycles for topoisomerase II inhibitors.
[d]Procarbazine dose given with nitrogen mustard.
[e]In order to reduce the influence of outliers, the continuous variable for cyclophosphamide dose was truncated at 20 000 mg/m^2. This truncation affected two cases with cyclophosphamide doses of 22 754 and 69 579 mg/m^2. Cyclophosphamide was given in combination with other agents (e.g. COPP: cyclophosphamide, vincristine, procarbazine, prednisone) and/or as a single agent.
[f]Includes doxorubicin, mitoxantrone, epirubicin, teniposide, and etoposide. Five of the nine cases and three of the five controls treated with topoisomerase-directed agents received ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), whereas two cases and two controls received ABV (doxorubicin, bleomycin, vinblastine). The overall OR for receipt of topoisomerase II inhibitors was 9.5 (95% CI 1.4–111).
CI, confidence interval; Gy, Gray; OR, odds ratio; MOPP, nitrogen mustard, vincristine, procarbazine, prednisone.

elevated risk of pancreatic cancer in patients treated with topoisomerase II inhibitors (particularly doxorubicin). The association with doxorubicin in our study is of interest, since anthracyclines (including doxorubicin) have been found to increase the risk of subsequent sarcomas and thyroid cancer in childhood cancer survivors [21, 23]. However, we did not observe a significant increase in risk with increasing number of topoisomerase II cycles, and topoisomerase II inhibitors were always given in combination with AAs.

Importantly, the majority of cases in our study received both radiation and AA-containing chemotherapy, which limited our ability to distinguish between the effects of these treatments. The ORs for patients receiving ≥10 Gy radiation without ≥6 AA cycles or ≥6 AA cycles without ≥10 Gy radiation were nonsignificantly elevated. The estimated 18-fold risk for patients receiving both ≥6 AA cycles and ≥10 Gy radiation was threefold higher than the risk that would be predicted under a multiplicative model, although the departure from multiplicativity was not statistically significant. However, the interaction was significantly greater than additive, and thus differs from a study of lung cancer in HL survivors in which the joint effect of radiation and AA treatment was found to be almost exactly additive [11]. The suggestion of a supramultiplicative interaction between chemotherapy and radiotherapy in our study is notable given recent evidence of a synergistic effect between radiation dose ≥25 Gy from subdiaphragmatic radiation and ≥5600 mg/m^2 of procarbazine from a study of stomach cancer following HL [18].

Treatment approaches for HL have changed considerably over the past several decades in an effort to maximize efficacy and minimize toxicity. Although radiotherapy remains an important therapeutic modality, radiation volumes and doses have decreased considerably over time, and subdiaphragmatic radiotherapy is infrequently indicated [24]. While the first-line therapy for many HL patients today includes doxorubicin and dacarbazine [25, 26], procarbazine and cyclophosphamide continue to be used, although often with lower cumulative doses than used in the past. Our findings for topoisomerase II inhibitors are equivocal, but warrant further investigation.

A major strength of our study is the detailed radiation and chemotherapy data abstracted from medical records and individual reconstruction of radiation doses to the location of the pancreatic cancer. Since all patients in our study were diagnosed with HL before 1990, we were unable to assess pancreatic cancer risk in relation to contemporary radiation techniques that utilize lesser volumes and doses. Small numbers limited our ability to

evaluate risks associated with specific chemotherapy regimens or agents and to evaluate interactions.

In summary, our study provides strong evidence that HL patients treated in the past with subdiaphragmatic radiation fields and ≥6 cycles of AA-containing chemotherapy have increased risks of pancreatic cancer. The study extends the range of solid cancers associated with chemotherapy and adds to the evidence that the combination of chemotherapy and radiotherapy can increase risks beyond those predicted by a multiplicative model. For HL patients, radiation dose–response relationships have now been demonstrated for second cancers of the lung, female breast, stomach, and pancreas and, with the exception of breast cancer, increased risks of these cancers have been observed after receipt of AA-containing therapy [11, 18, 27]. Changes in HL therapy over time should reduce second cancer risks compared with those observed with past treatments. In the interim, health care providers caring for long-term HL survivors should be alert to this treatment sequela and encourage a healthy lifestyle to minimize additional cancer risk factors.

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disclosure

The authors have declared no conflicts of interest.

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