Risk of esophageal cancer following radiotherapy for Hodgkin lymphoma

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Supplementary Materials:

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METHODS

Study Population

Patients were derived from a cohort of 19,882 individuals who survived ≥5 years following diagnosis with first primary, histologically confirmed Hodgkin lymphoma (HL) during 1943-1992 and followed through 2005. The cohort included 17,447 patients from population-based cancer registries in Denmark (1943-1999), Finland (1953-2002), Norway (1953-2000), Sweden (1958-2002), Iowa (US, 1973-2001), and Ontario (Canada, 1964-2003), and 2,435 patients from a hospital-based cohort in The Netherlands (1965-2002).[1]

A total of 37 cases of second primary esophageal cancer occurring ≥5 years after HL were identified; one case was excluded because no medical record could be found. Two controls per case were selected by stratified random sampling from the cohort, individually matching by registry, race, birth date (±5 years), HL diagnosis date (±5 years), and survival without subsequent cancer at least as long as the matched case's interval from HL to esophageal cancer. Patients from Norway also were matched on hospital of HL diagnosis (Radium Hospital versus others) because data were initially collected from patients treated at the Radium Hospital, and the study was subsequently expanded to include all patients from Norway. Medical records were obtained for 97% of initially eligible controls; additional controls were sought to identify two controls per case. For one case only one appropriate control could be found, resulting in a final study population of 36 cases and 71 controls. The study was approved by relevant authorities in each study center and exempted from review by the National Cancer Institute because analyses used existing, de-identified data.

Data Collection

Detailed information on patient demographics, HL diagnosis, HL treatments, and potential esophageal cancer risk factors (cigarette smoking, alcohol consumption, height, weight, and family history of cancer in a first-degree relative) was abstracted from medical records onto standardized forms. Data were collected from all available records, including hospital, clinic, radiotherapy, physician, and cancer registry records.

Radiotherapy data included dates of administration, reason for treatment (primary or recurrence), beam energy, dose delivered, and field location and configuration. Patients generally were treated with cumulative target doses of 25-40 Gy using conventional fractionation. Radiation doses were reconstructed for each patient using a custom-designed dose program, based on measurements in water and anthropomorphic phantoms constructed of tissue-equivalent material.[2] Doses were estimated at 24 points located centrally in the esophagus, anterior to the midpoint of each vertebrae and intervertebral disc from C6 to T10, plus the gastroesophageal junction (T10/T11, 2 cm left of midline), as described previously.[3,4] Analyses included all radiotherapy treatments received ≥5 years preceding esophageal cancer diagnosis (comparable date for controls) because of the long latent period typically observed for radiation-related cancer. The 2 patients (1 case, 1 control) who received radiotherapy within 5 years of esophageal cancer diagnosis (comparable date for the control) were treated with subdiaphragmatic fields, and dose to the esophagus from these treatments was low (<1 Gy).

For cases, pathology and surgery records were reviewed to confirm esophageal cancer diagnosis. Additionally, endoscopy reports and imaging studies were reviewed to obtain data on the esophageal tumor location (proximal/distal ends, length), which were translated to bony landmarks for radiation dose reconstruction.

Chemotherapy data included dates and route of administration, reason for treatment (primary or recurrence), and specific regimens or drugs. Because chemotherapy may induce subsequent malignancies after a short latency period, all treatments given prior to esophageal cancer diagnosis (comparable date for controls) were considered. Analyses evaluated the number of cycles of any alkylating agent (AA)-containing chemotherapy, receipt of specific chemotherapy regimens (see Table 2 footnote), and cumulative dose (mg/m^2) for specific AAs with >2 exposed cases.

Abstracted data on cigarette smoking and alcohol consumption included amount and status (current use at the time of specific medical record report or year quit). Former smokers were identified by medical record reports indicating that the patient quit ≥5 years preceding esophageal cancer diagnosis (comparable date for controls). To minimize potential bias arising from more complete information for cases than controls, data on smoking, alcohol, and family history of cancer in a first-degree relative were restricted to records ≥1 year preceding esophageal cancer diagnosis (comparable date for controls). Body-mass index (BMI, kg/m^2) was computed at HL diagnosis.

Statistical Analysis

The relative risk of esophageal cancer in relation to HL treatments was estimated from conditional logistic regression with odds ratios (ORs) and corresponding 95% confidence intervals (CIs) using maximum likelihood methods. Analyses of radiotherapy risks used dose to the esophageal tumor midpoint (mean of the middle three points; comparable location for controls); for the 2 (6%) cases with unknown tumor location, analyses used dose to the esophagus midpoint (mean of T6/7, T7, and T7/8). The dose to the tumor midpoint was highly correlated with the mean dose to the entire esophagus (C6-gastroesophageal junction; cases, r=0.77; controls, r=0.86). Radiation-related risk estimates were similar for the two dose estimates, thus the more precise dose to the tumor location is presented only.

Analyses considered both categorical and continuous radiation dose. For the categorical analysis, the referent group of <30 Gy was chosen in order to include 4 informative case sets (i.e., the case and at least one control have different values) in the conditional logistic regression model to improve stability of the risk estimates; for the remaining 5 cases with <30 Gy, all matched controls also received <30 Gy to that location in the esophagus and, thus, were uninformative in the conditional logistic regression model. Because patients in the referent group were exposed, the OR underestimates the risk at doses ≥30 Gy relative to an unexposed group. For the continuous analysis, the excess odds ratio per Gy (EOR/Gy) was estimated by the model $OR=\exp(\sum_j \alpha_j x_j)[1+\beta z]$, where z is radiation dose in Gy, β is the EOR/Gy, and the x_j are covariates (e.g., chemotherapy). Heterogeneity in the radiation-related esophageal cancer risks was evaluated under the multiplicative model, comparing the model fit using separate ORs for each subgroup to that using a single estimate with a likelihood ratio test. Missing data on chemotherapy (1 case) and radiotherapy (1 control) were handled by including indicator variables in the conditional logistic regression models; results were similar when these individuals were excluded from the analysis (data not shown).

To advance understanding of radiation-related esophageal cancer risk more generally, we directly compared our study results with an earlier study of esophageal cancer following radiotherapy for breast cancer,[3] the only other study of second esophageal cancer among cancer survivors with estimated radiation dose to the tumor location. Analyses included original, individual-level data from both studies, comparing radiation-related esophageal cancer risk among HL and breast cancer survivors using a likelihood ratio heterogeneity test, as described above.

Cumulative incidence of second primary esophageal cancer was estimated using the Gooley method in analyses with death and other second cancers as competing risks.[5] All analyses were conducted using SAS software (version 9.2) or Epicure.[6]

RESULTS

Esophageal squamous cell carcinoma was inversely associated with overweight/obesity in our study cohort (Supplementary Table 2), similar to observations for esophageal cancer in the general population.[7] We did not see the expected risks of esophageal cancer associated with history of cigarette smoking or alcohol consumption, but many of the patients in our study population may not have yet accumulated the years of exposure typically associated with risk.[7]

Of the 32 cases with esophageal cancer who were deceased, 14 had relapsed HL at some point during follow-up. The median time from HL relapse to death among these 14 cases was 9.8 years (range, 4.4-33.7 years). Cause of death data were obtained from all study centers except the Netherlands. Of the 25 deceased cases from study centers other than the Netherlands, the cause of death was listed as esophageal/upper GI cancer for 18 (72%), HL for 1 (4%), heart disease for 1 (4%), pneumonia for 1 (4%), and missing/unknown for 4 (16%). For comparison, of the 16 deceased controls from study centers other than the Netherlands, the cause of death was listed as hematologic malignancy for 5 (31%), heart disease for 7 (44%), lung cancer for 2 (13%), accident for 1 (6%), and missing/unknown for 1 (6%). Together, these data suggest that HL relapse was not an important contributor to death among the cases.

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Supplementary Table 1. Radiation-related risk of esophageal cancer after Hodgkin lymphoma (HL) by patient subgroup

	Radiation dose to esophageal tumor location 0-29.9 Gy (Reference)		Radiation dose to esophageal tumor location ≥30 Gy				
	Cases (N=36)	Controls (N=71)	Cases (N=36)	Controls (N=71)			
Characteristic	**N(%)**	**N(%)**	**N(%)**	**N(%)**	**OR**	**(95%CI) ***	**$P_{homogeneity}$ †**
Total	9(100%)	35(100%)	27(100%)	35(100%)	4.3	(1.4, 13.2)	
Esophageal cancer histology							
Adenocarcinoma	3(33%)	11(31%)	6(22%)	7(20%)	4.6	(0.5, 42.4)	0.847
Squamous cell carcinoma	6(67%)	22(63%)	18(67%)	24(69%)	3.6	(0.9, 13.4)	
Sex							
Male	8(89%)	26(74%)	14(52%)	17(49%)	3.6	(0.9, 13.8)	0.665
Female	1(11%)	9(26%)	13(48%)	18(51%)	6.2	(0.7, 53.0)	
Age at HL diagnosis (years)							
<35	3(33%)	12(34%)	15(56%)	23(66%)	2.4	(0.6, 9.5)	0.236
≥35	6(67%)	23(66%)	12(44%)	12(34%)	10.3	(1.2, 85.2)	
Age at esophageal cancer diagnosis (years)							
<55	5(56%)	16(46%)	16(59%)	26(74%)	2.1	(0.6, 7.2)	0.029
≥55	4(44%)	19(54%)	11(41%)	9(26%)	∞		
Time since HL diagnosis (years)							
<15	5(56%)	18(51%)	11(41%)	14(40%)	4.0	(0.8, 20.0)	0.913
≥15	4(44%)	17(49%)	16(59%)	21(60%)	4.5	(0.9, 22.1)	
AA chemotherapy							
No AA-containing chemotherapy	3(33%)	13(37%)	14(52%)	21(60%)	15.2	(1.7, 137.2)	0.874
Any AA-containing chemotherapy	5(56%)	22(63%)	13(48%)	14(40%)	13.8	(1.7, 109.9)	

Abbreviations: alkylating agent (AA), confidence interval (CI), Gray (Gy), Hodgkin lymphoma (HL), odds ratio (OR).

* OR (95%CI) compared patients who received ≥30 Gy to the esophagus tumor location to those who received <30 Gy or no radiotherapy. 95%CIs are Wald CIs.

† $P_{homogeneity}$ compared the risk estimates between patient subgroups using a likelihood ratio test.

Supplementary Table 2. Risk of esophageal cancer after Hodgkin lymphoma (HL) associated with cigarette smoking, alcohol consumption, body-mass index, and family history of cancer

Characteristic	Cases (N=36) N(%)	Controls (N=71) N(%)	OR	(95%CI) *
Cigarette smoking				
Never	9(25%)	17(24%)	1.0	(referent)
Ever	15(42%)	27(38%)	1.1	(0.3, 4.4)
Unknown	12(33%)	27(38%)	0.8	(0.3, 2.6)
Smoking status				
Current	9(25%)	22(31%)	0.8	(0.2, 3.7)
Former	6(17%)	5(7%)	3.0	(0.4, 23.0)
Cigarettes per day				
1-19	5(14%)	8(11%)	1.4	(0.2, 7.8)
≥20	7(19%)	16(23%)	0.7	(0.1, 3.8)
Amount unknown	3(8%)	3(4%)	2.4	(0.3, 20.4)
Alcohol consumption				
Never	5(14%)	7(10%)	1.0	(referent)
Ever	16(44%)	33(46%)	0.7	(0.2, 2.6)
Unknown	15(42%)	31(44%)	0.8	(0.2, 3.1)
Consumption status				
Current	14(39%)	28(39%)	0.6	(0.1, 2.5)
Former	2(6%)	5(7%)	1.0	(0.1, 7.3)
Drinks per day				
<1	11(31%)	12(17%)	1.0	(0.2, 4.2)
≥1	4(11%)	10(14%)	0.4	(0.1, 2.9)
Amount unknown	1(3%)	11(15%)	0.1	(0.0, 1.3)
Body-mass index (kg/m^2) †				
<18.5	2(8%)	0(0%)	~	
18.5-24.9	15(63%)	20(43%)	1.0	(referent)
≥25.0	3(13%)	21(45%)	0.3	(0.1, 1.0)
Unknown	4(17%)	6(13%)	2.8	(0.4, 19.0)
Family history of cancer				
None	18(50%)	36(51%)	1.0	(referent)
First-degree relative	5(14%)	7(10%)	0.9	(0.2, 3.5)
Unknown	13(36%)	28(39%)	0.6	(0.2, 1.8)

Abbreviations: confidence interval (CI), Hodgkin lymphoma (HL), odds ratio (OR).

* OR (95%CI) was adjusted for continuous radiation dose. 95%CIs are Wald CIs.

† Analyses of body-mass index were restricted to esophageal squamous cell carcinoma.