

Second Malignant Neoplasms Among Long-Term Survivors of Hodgkin's Disease: A Population-Based Evaluation Over 25 Years

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Purpose: To quantify the relative and absolute excess risks (AER) of site-specific second cancers, in particular solid tumors, among long-term survivors of Hodgkin's disease (HD) and to assess risks according to age at HD diagnosis, attained age, and time since initial treatment.

Patients and Methods: Data from 32,591 HD patients (1,111 25-year survivors) reported to 16 population-based cancer registries in North America and Europe (1935 to 1994) were analyzed.

Results: Two thousand one hundred fifty-three second cancers (observed-to-expected ratio [O/E] = 2.3; 95% confidence interval [CI] = 2.2 to 2.4), including 1,726 solid tumors (O/E = 2.0; 95% CI, 1.9 to 2.0) were reported. Cancers of the lung (observed [Obs] = 377; O/E = 2.9), digestive tract (Obs = 376; O/E = 1.7), and female breast (Obs = 234; O/E = 2.0) accounted for the largest number of subsequent malignancies. Twenty-five years after HD diagnosis, the actuarial risk of

developing a solid tumor was 21.9%. The relative risk of solid neoplasms decreased with increasing age at HD diagnosis, however, patients aged 51 to 60 years at HD diagnosis sustained the highest cancer burden (AER = 79.2/10,000 patients/year). After a progressive rise in relative risk and AER of all solid tumors over time, there was an apparent downturn in risk at 25 years. Temporal trends and treatment group distribution for cancers of the esophagus, stomach, rectum, female breast, bladder, thyroid, and bone/connective tissue were suggestive of a radiogenic effect.

Conclusion: Significantly increased risks of second cancers were observed in all HD age groups. Although significantly elevated risks of stomach, female breast, and uterine cervix cancers persisted for 25 years, an apparent decrease in relative risk and AER of solid tumors at other sites is suggested.

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THE REMARKABLE GAINS in survival attributable to successful treatments for Hodgkin's disease (HD) over the past three decades have been accompanied by a significantly increased risk of second neoplasms.¹ Second cancers now comprise the leading cause of death among 15-year survivors of this lymphoma.² Few population-based studies, however, quantify site-specific excesses among large

numbers of long-term survivors,^{3,4} address second cancer risk by age at HD diagnosis,³ provide estimates of absolute excess risk (AER),³ or consider attained age.³ The AER provides the optimal measure of disease burden in a population because relative risks are affected by underlying cancer incidence rates, which increase with increasing age. Accordingly, we evaluated the absolute and relative site-specific risks of second cancers among 32,591 HD patients, including 2,861 20-year survivors, taking into account time since treatment, age at treatment, and attained age. In particular, we sought to determine whether the increased risks of second cancers reported within 15 to 20 years after treatment for HD⁴⁻¹⁰ persist into the third decade of follow-up.

PATIENTS AND METHODS

Patients with a first primary diagnosis of HD (1935 to 1994) who survived 1 or more years were identified from population-based cancer registries in Ontario, Sweden, Denmark, Finland, Connecticut, and nine areas of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program. In the Netherlands, patients were identified from affiliated tumor registries of the Netherlands Cancer Institute in Amsterdam and The Dr Daniel den Hoed Cancer Center. Features of each cancer registry have been described elsewhere.¹¹ To ensure complete reporting from population-based registries, a subgroup of patients (21%) described in previous reports^{3,12} are included, with follow-up for 927 Dutch patients extended to 1995.¹²

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Participating cancer registries routinely collect data on patient demographics, tumor characteristics, and vital status. Except in Ontario and Sweden, general information regarding initial treatment received for HD is available in terms of broad categories, such as radiotherapy and/or chemotherapy. Data on subsequent therapy are not collected. Before 1960, small doses of radiation, if any, were used to treat early-stage HD,^{13,14} although 25 to 30 Gy were administered to involved nodal and proximal areas at some medical centers.¹⁵ In the 1960s, doses of 40 to 44 Gy to involved fields were often given,¹⁶ whereas from the mid-1970s through 1994, smaller doses (30 to 40 Gy) were commonly used when given without cytotoxic drugs;^{13,16} when combined with chemotherapy, an average of 30 Gy was administered.¹³ Children and adolescents may have received smaller doses, as previously described.³ Radiation doses received by various organs during mantle and inverted Y radiotherapy (35 Gy) for adult HD are provided in the Appendix. Treatment with single chemotherapeutic agents (mechlorethamine and triethylenemelamine) was introduced into clinical practice after 1947, usually for the treatment of advanced HD.¹⁵ After the late 1960s, combination therapy with mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) was increasingly administered,¹⁷ and doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) was added to treatment options in the mid-1970s.¹⁸

Cancer registry incidence files were searched for second malignant, invasive neoplasms that developed at least 1 year after diagnosis of HD, with confirmation based on routine procedures at each site.¹¹ The risk of second cancers was estimated by compiling person-years (PY) of observation according to age, sex, and calendar-year periods from 1 year after the date of HD diagnosis to the date of death, date of last follow-up evaluation, date of diagnosis of second cancer, or the end of the study, whichever occurred first. Study end date varied between registries: December 31, 1995 (the SEER Program, Finland, and the Netherlands), December 31, 1993 (Denmark, Sweden, and Ontario), and December 31, 1992 (Connecticut 1935 to 1972). Cancer incidence rates specific for each region, 5-year age groups, sex, and 5-year calendar-year intervals were multiplied by the accumulated PY at risk to estimate the number of cancer cases expected. The observed and expected numbers of second cancers from each registry were then summed, with the relative risk expressed as the ratio of observed-to-expected (O/E) cases. The AER was determined by subtracting the expected number from the observed number of second cancers and then dividing the difference by the number of PY at risk. The number of excess second cancers was expressed per 10,000 HD patients per year. Risks of second cancers were stratified by sex, age group at HD diagnosis, attained age, time since HD diagnosis, and initial treatment (radiotherapy, chemotherapy, or chemotherapy and radiotherapy). Statistical tests and 95% confidence intervals (CI) were based on the assumption that the observed number of second cancers was distributed as a Poisson variable. Tests for heterogeneity and linear trend were conducted using the methods of Breslow et al.¹⁹ Cumulative probabilities of developing solid tumors over time were calculated using life-table methods.²⁰

RESULTS

The average age at diagnosis of HD for the 32,591 study patients (57.4% male) was 37 years (Table 1). Six thousand one hundred ninety-five, 2,861, and 1,111 patients were followed for 15, 20, and 25 years, respectively. Second malignancies developed in 2,153 patients (O/E = 2.3; 95% CI, 2.2 to 2.4; AER = 47.2) (Table 2). Second cancer risk was significantly elevated in each registry (O/E = 1.9 to

2.3), with the largest excesses (O/E = 4.8) observed in patients from the Netherlands.

Significantly elevated two-fold risks were observed for all solid tumors taken together (observed [Obs] = 1,726; O/E = 2.0; 95% CI, 1.9 to 2.0), with respiratory sites contributing the largest number of cancers (Obs = 416; O/E = 2.8). Significant two- to six-fold excesses were evident for cancers of lip, tongue, salivary gland, gum and mouth, pharynx, esophagus, stomach, lung, female breast, uterine cervix, thyroid, bone, and connective tissue, and risks of a smaller magnitude were observed for malignant melanoma and cancers of the colon, liver and gallbladder, pancreas, kidney, bladder, and brain and CNS. No cancer occurred significantly below expectation.

The relative risk and AER of all solid tumors taken together were similar in men and women. When sex-specific cancers were excluded, relative risks remained comparable (O/E = 2.1 and 2.2, respectively), however, AER were larger in men (AER = 32.2) than women (AER = 20.1), due to a substantially greater number of lung cancers (Obs = 284, AER = 12.7). Breast cancer accounted for the largest AER of neoplasms among women (AER = 10.5). Significantly elevated risks for malignant melanoma and cancers of tongue, liver/gallbladder, and brain/CNS seemed confined to men, whereas significant seven-fold excesses of bone tumors seemed restricted to women.

The risks of all solid tumors and cancers at selected sites are listed in Table 3 according to primary treatment and time since diagnosis of HD. Significantly elevated relative risks of solid tumors were observed 1 to 9 years (O/E = 1.6; AER = 20), 10 to 14 years (O/E = 2.4; AER = 50), 15 to 19 years (O/E = 2.5; AER = 63), 20 to 24 years (O/E = 3.0; AER = 110), and \geq 25 years (O/E = 1.8; AER = 60) after diagnosis of HD. Although risks peaked in the 20- to 24-year interval, significant excesses persisted for cancers of female breast (O/E = 3.3) and uterine cervix (O/E = 7.7) among 25-year survivors. After 25 years of follow-up, a downturn in relative risk of all second cancers was observed in each registry that contributed patients to this period, including those with nationwide registration. Significantly increased risks for all solid tumors taken together were observed after therapy with either radiation alone (Obs = 632; O/E = 2.3; 95% CI, 2.1 to 2.4) or chemotherapy alone (Obs = 211; O/E = 1.7; 95% CI, 1.5 to 1.9); significantly higher risks occurred after combined-modality therapy (Obs = 149; O/E = 3.1; 95% CI, 2.6 to 3.6). For patients whose treatment included radiotherapy, solid tumor risk increased with time to reach 4.4 in the 20- to 24-year interval after HD, but an overall downturn (O/E = 2.4; 95% CI, 1.7 to 3.2; Obs = 42) was observed thereafter. Among 25-year survivors, significantly increased risks were observed for cancers of stomach, breast, and uterine cervix. After chemotherapy alone,

Table 1. Characteristics of 32,591 1-Year Survivors of HD Reported to Population-Based Cancer Registries*

Characteristics	No. of Patients	%	Person-Years of Follow-Up	No. of Second Primary Cancers
All patients	32,591	100	254,243	2,153
Male	18,714	57.4	141,767	1,240
Female	13,877	42.6	112,476	913
Age at diagnosis of HD				
< 21 years†	5,925	18.2	56,509	195
21-30 years	9,174	28.1	83,022	378
31-40 years	5,821	17.9	47,365	314
41-50 years	3,688	11.3	27,363	371
51-60 years	3,244	10.0	20,431	437
≥ 61 years	4,739	14.5	19,552	458
Calendar year of diagnosis of HD				
1935-1964	3,878	11.9	32,773	231
1965-1979	12,496	38.3	137,684	1,311
1980-1994	16,217	49.8	83,786	611
Registry				
United States SEER Program‡ (1973-1994)§	11,230	34.5	74,875	577
Ontario (1964-1992)	5,716	17.5	47,745	341
Sweden (1958-1992)	4,808	14.8	39,672	406
Denmark (1943-1993)	4,063	12.5	31,377	294
Finland (1953-1994)	3,336	10.2	26,777	202
The Netherlands (1955-1986)	1,780	5.5	19,266	223
Connecticut (1935-1972)	1,658	5.1	14,530	110
Survival¶				
1-9 years	32,591	100	174,757	1,204
10-14 years	11,326	34.8	42,865	450
15-19 years	6,195	19.0	22,113	254
20-24 years	2,861	8.8	9,307	167
≥ 25	1,111	3.4	5,201	78

*All patients were diagnosed with HD as a first primary cancer and survived 1 or more years. One hundred four HD patients subsequently developed two or more cancers. The most common third or higher order solid tumors that were specified occurred in the female breast (Obs = 36), lung (Obs = 26), bladder (Obs = 14), and colon (Obs = 13); these neoplasms are not included in the tables. Sixteen patients developed separate primary cancers of the same site, most commonly involving the female breast (Obs = 11). Numbers in tables may not sum to respective totals because of rounding.

†This group was previously described.³

‡The registries participating in the SEER Program included the states of Connecticut, Hawaii, Iowa, New Mexico, and Utah and the metropolitan areas of Detroit, Atlanta, Seattle-Puget Sound, and San Francisco-Oakland.

§Calendar year of diagnosis of Hodgkin's disease.

||Three hundred sixty-one patients were followed for 30 or more years.

¶Represents number of patients alive at the beginning of the interval.

relative risks for solid tumors were significantly elevated only within the first 15 years of follow-up, with nonsignificant 50% to 70% excesses in later intervals, based on sparse numbers.

Significant excesses of lung cancer occurred throughout the first 25 years after HD diagnosis then decreased to expectation. The histologic distribution (38% squamous cell, 24% adenocarcinoma, 16% small-cell, 20% unspecified, and 2% other) of lung cancers for which morphology was recorded (Obs = 318) was similar to the pattern of first primary lung cancers reported to the SEER Program.²² Women treated with radiotherapy for HD experienced a 2.5-fold increased risk of breast cancer (Obs = 122; 95% CI, 2.0 to 2.9), compared with no excess risk after chemotherapy alone (O/E = 1.1; 95% CI, 0.6 to 1.8; Obs = 15), albeit based on small numbers. Breast cancer risk was significantly elevated in the intervals of 10 to 14, 15 to 19, 20 to 24, and ≥ 25 years (*P* trend < .001) after HD, with

somewhat larger risks in women treated with radiotherapy. Risk for cancers of all digestive tract sites taken together was significantly elevated after therapy with radiation alone (O/E = 1.8; 95% CI, 1.5 to 2.2; Obs = 128) or combined-modality therapy (O/E = 2.8; 95% CI, 1.9 to 4.0; Obs = 30) but not chemotherapy alone (O/E = 1.2; 95% CI, 0.9 to 1.7; Obs = 37). In contrast to colon cancer, significantly increased risks of rectal cancer occurred only among long-term HD survivors given radiotherapy. A significant two-fold risk of bladder cancer was observed 10 to 14 and 15 to 19 years after HD, with four- to six-fold excesses after radiotherapy in the 15- to 19- and 20- to 24-year intervals. Fifteen-fold risks for bone/connective tissue cancers occurred 10 to 14 and 15 to 19 years after radiotherapy. Discernible temporal trends were not apparent for excess cancers of brain, kidney, or pancreas or malignant melanoma (data not shown).

Table 2. Relative and Absolute Site-Specific Risks of Second Malignant Neoplasms Among 32,591 1-Year Survivors of HD

Cancer Site	All Patients				Males			Females		
	Obs	O/E	95% CI	AER	Obs	O/E	AER	Obs	O/E	AER
Second cancers, all	2,153	2.3†	2.2-2.4	47.2	1,240	2.2†	48.4	913	2.3†	45.6
Solid tumors, all†	1,726	2.0†	1.9-2.0	33.1	969	1.9†	32.4	757	2.0†	33.9
Buccal, all‡	96	3.4†	2.8-4.2	2.7	67	3.1†	3.2	29	4.5†	2.0
Lip	21	3.9†	2.4-5.9	0.6	16	3.3†	0.8	5	9.5†	0.4
Tongue	14	2.8†	1.5-4.7	0.4	12	3.3†	0.6	2	1.6	0.1
Salivary gland	16	6.1†	3.5-9.9	0.5	8	5.0†	0.5	8	7.7†	0.6
Gum, other mouth	18	2.5†	1.5-4.0	0.4	11	2.1†	0.4	7	3.6†	0.4
Pharynx	27	3.3†	2.2-4.9	0.7	20	3.1†	1.0	7	4.1†	0.5
Digestive, all§	376	1.7†	1.5-1.8	5.9	231	1.7†	6.4	145	1.7†	5.2
Esophagus	29	2.8†	1.8-4.0	0.7	17	2.1†	0.6	12	4.7†	0.8
Stomach	80	1.9†	1.5-2.4	1.5	57	2.0†	2.0	23	1.8†	0.9
Small intestine	5	1.5	0.5-3.5	0.1	3	1.4	0.1	2	1.6	0.1
Colon	129	1.6†	1.4-1.9	2.0	71	1.6†	1.9	58	1.7†	2.1
Rectum	52	1.2	0.9-1.6	0.4	32	1.2	0.3	20	1.3	0.4
Liver, gallbladder	29	1.6†	1.1-2.3	0.4	19	1.9†	0.6	10	1.3	0.2
Pancreas	40	1.5†	1.1-2.0	0.5	24	1.5	0.5	16	1.5	0.5
Respiratory, all¶	416	2.8†	2.5-3.1	10.5	314	2.7†	13.8	102	3.4†	6.4
Larynx	18	1.6	0.9-2.5	0.3	16	1.6	0.4	2	1.6	0.1
Lung#	377	2.9†	2.6-3.2	9.7	284	2.7†	12.7	93	3.4†	5.8
Female breast**	234	2.0†	1.8-2.3	10.5	-	-	-	234	2.0†	10.5
Female genital, all††	106	1.6†	1.3-1.9	3.4	-	-	-	106	1.6†	3.4
Uterine cervix‡‡	37	2.0†	1.4-2.7	1.6	-	-	-	37	2.0†	1.6
Uterine corpus	34	1.4	1.0-1.9	0.8	-	-	-	34	1.4	0.8
Ovary	27	1.3	0.8-1.9	0.5	-	-	-	27	1.3	0.5
Prostate§§	98	1.0	0.8-1.2	-0.1	98	1.0	-0.1	-	-	-
Testis	13	1.4	0.8-2.4	0.3	13	1.4	0.3	-	-	-
Kidney	42	1.5†	1.1-2.1	0.6	30	1.6†	0.8	12	1.4	0.3
Bladder	66	1.4†	1.1-1.8	0.8	49	1.3	0.8	17	1.9†	0.7
Malignant melanoma	52	1.7†	1.3-2.3	0.9	38	2.2†	1.5	14	1.1	0.1
Eye	3	1.4	0.3-4.1	0.03	3	2.3	0.1	-	-	-
Brain & central nervous system¶¶	36	1.5†	1.1-2.1	0.5	25	1.8†	0.8	11	1.2	0.1
Thyroid	47	4.1†	3.0-5.5	1.4	11	3.1†	0.5	36	4.6†	2.5
Bone###	9	3.8†	1.7-7.2	0.3	3	2.0	0.1	6	7.1†	0.5
Connective tissue***	32	5.1†	3.5-7.2	1.0	20	5.1†	1.1	12	5.0†	0.9
Other solid tumors†††	100	2.5†	2.1-3.1	2.4	67	2.8†	3.1	33	2.1†	1.5
Non-Hodgkin's lymphoma	162	5.5†	4.7-6.4	5.2	103	5.5†	5.9	59	5.6†	4.3
Multiple myeloma	14	1.2	0.7-2.1	0.1	7	1.0	-0.01	7	1.6	0.2
Leukemia, all	249	9.9†	8.7-11.2	8.8	159	9.7†	10.1	90	10.2†	7.2
Acute lymphoblastic leukemia	11	7.1†	3.6-12.8	0.4	8	7.9†	0.5	3	5.7†	0.2
Acute nonlymphocytic leukemia	169	21.5†	18.3-25.0	6.3	111	23.1†	7.5	58	18.9†	4.9
Chronic lymphocytic leukemia	9	0.9	0.4-1.8	-0.02	7	1.1	0.02	2	0.7	-0.1
Chronic myeloid leukemia	13	1.3	0.7-2.2	0.1	7	1.0	0.02	6	1.7	0.2
Other lymphohematopoietic disorders††††	2	2.2	0.3-7.9	0.04	2	3.6	0.1	-	-	-

*Excludes HD and nonmelanoma skin cancer.

†P < .05.

‡Excludes lymphohematopoietic disorders.

§Includes International Classification of Disease for Oncology (ICD-O) codes 140-149.²¹

||Includes ICD-O codes 150-159.

¶Histology was recorded for 68 stomach cancers and included 64 adenocarcinomas (including linitis plastica [Obs = 3], signet ring cell [Obs = 9], mucinous [Obs = 4], and tubular [Obs = 1] cancers), one lobular carcinoma, and three unspecified carcinomas. Site of stomach cancer (specified for 58 patients) was recorded as pylorus, fundus, or body (45%); cardia or fundus (7%); cardia (14%); fundus (3%); pylorus (7%); antrum (5%); body (5%); lesser curvature (2%); greater curvature (3%); or overlapping areas (9%).

#Includes ICD-O codes 160-165.

**Includes 318 lung cancers with specified histology (38% squamous cell, 24% adenocarcinoma, 16% small-cell, 20% unspecified, and 2% other), 56 lung cancers for which histology was not available and mesothelioma (Obs = 3).

††For female-specific sites, the number of patients and person-years was 13,877 and 112,476, respectively.

‡‡Includes ICD-O codes 179-184.

§§For 31 cervical cancers with specified histology, 74% were squamous cell, 19% were adenocarcinoma, and 6% were epithelial neoplasms.

|||For male-specific sites, the number of patients and person-years was 18,714 and 141,767, respectively.

¶¶Histology was recorded for 51 urinary bladder cancers (90% transitional cell, 4% squamous, 2% adenocarcinoma, 2% epithelial, and 2% unspecified carcinoma) and 36 kidney cancers (64% adenocarcinoma, 31% transitional-cell, and 5% unspecified).

###Brain and central nervous system cancers with specified histology (Obs = 30) included glial (63%), meningeal (23%), peripheral nerve sheath (10%), and vascular (3%) tumors.

***Seventy eight percent (Obs = 7) of bone cancers involved the axial skeleton, and 22% (Obs = 2) involved the appendicular skeleton.

†††Histology of 29 sarcomas included 17% vascular tumors, of which two of five were Kaposi's sarcoma; 52% fibromas; 10% myomas; 7% lipomas; 3% synovial tumors; and 10% unspecified. All myomas and vascular sarcomas occurred in males. Of 27 sarcomas with specified site, 67% involved the axial skeleton and 33% involved the appendicular skeleton.

††††Includes ill-defined (Obs = 75), miscellaneous (Obs = 22), and solid tumors of unknown primary site (Obs = 3) not itemized in table.

§§§Includes myelodysplastic syndrome (Obs = 1) and lymphohematopoietic disorder, not otherwise specified (Obs = 1).

Table 3. Selected Second Malignant Neoplasms According to Initial Treatment and Time Since Diagnosis of HD*

	Time Since Diagnosis									
	1-9 Years		10-14 Years		15-19 Years		20-24 Years		≥ 25 Years	
All subjects:										
No. of patients entering interval	32,591		11,326		6,195		2,861		1,111	
Person-years†	174,757		42,865		22,113		9,307		5,201	
Subjects with treatment data‡										
Any radiotherapy§										
No. of patients entering interval	13,793		5,402		2,931		1,211		461	
Person-years	79,055		20,436		10,072		3,884		2,347	
Second cancer site(s)										
Second cancers, all	Obs	O/E	Obs	O/E	Obs	O/E	Obs	O/E	Obs	O/E
Any radiotherapy	488	2.3	206	3.2	132	3.5	83	4.5	44	2.3 #
Chemotherapy alone**	221	2.1	48	2.6	14	1.7	3	1.4	4	1.6
Solid tumors, all††††	897	1.6	369	2.4	234	2.5	153	3.0	73	1.8 #
Any radiotherapy	378	1.9	162	2.7	124	3.5	75	4.4	42	2.4 #
Chemotherapy alone	156	1.6	35	2.0	13	1.7	3	1.5	4	1.7
Esophagus	6	0.9	7	4.1	9	8.4	5	8.3	2	3.8#
Any radiotherapy	3	1.3	4	6.2	4	10.2	4	19.5	0	(E 0.22)¶¶
Stomach	35	1.3	24	3.7	10	2.6	7	3.2	4	2.1§§
Any radiotherapy	14	1.4	11	4.4	5	3.4	4	5.4	4	5.3 #
Colon	64	1.3	33	2.5	16	2.0	11	2.5	5	1.3
Any radiotherapy	21	1.3	10	2.1	6	2.2	4	2.9	3	1.8
Rectum	26	1.0	11	1.6	8	1.8	6	2.4	1	0.5
Any radiotherapy	10	1.1	3	1.1	7	4.4	4	4.9	1	1.1§§
Lung	226	2.7	74	3.4	39	2.9	33	4.6	5	0.8
Any radiotherapy	106	3.3	36	4.1	21	4.0	14	5.5	2	0.7
Female breast	79	1.2	59	2.7	55	3.8	23	3.0	18	3.3 #
Any radiotherapy	32	1.2	32	3.2	33	5.0	13	3.9	12	4.1 #
Uterine cervix	20	1.7	8	2.3	2	1.0	3	3.5	4	7.7 §§
Any radiotherapy	8	1.5	2	1.2	1	1.1	2	4.7	4	12.4 ¶¶
Bladder	33	1.2	15	1.9	11	2.3	6	2.2	1	0.4
Any radiotherapy	11	1.1	5	1.8	6	3.6	5	5.9	1	1.0§§
Thyroid	19	2.6	14	6.6	7	6.1	6	12.3	1	3.4¶¶
Any radiotherapy	5	1.6	7	7.3	2	4.1	4	23.8	1	7.8#
Bone/connective tissue	18	3.2	13	8.8	7	8.4	2	4.9	1	3.6
Any radiotherapy	9	4.2	9	15.4	5	15.9	0	(E 0.13)	0	(E 0.10)
Non-Hodgkin's lymphoma	89	4.9	44	8.2	15	4.7	9	5.7	5	4.4
Any radiotherapy	36	5.7	28	13.9	6	5.4	6	13.4	2	4.9
Acute nonlymphocytic leukemia	140	27.7	23	17.2	2	2.6	4	10.1	0	(E 0.32)#
Any radiotherapy	50	24.7	10	18.0	1	3.3	2	14.6	0	(E 0.13)¶¶

*Includes 32,591 patients who were diagnosed with HD as a first primary cancer and survived 1 or more years.

†Indicates number of person-years within interval.

‡Data on initial course of therapy was reported to the SEER Program and cancer registries in Connecticut, Denmark, Finland, and the Netherlands (Obs = 22,067). No information on subsequent treatment is available.

§Includes patients whose initial treatment for HD included radiotherapy alone (Obs = 10,328 1-year survivors; 92,039 person-years) or radiotherapy and chemotherapy (Obs = 3,465 1-year survivors; 23,754 person-years).

||P < .05.

¶¶Test for trend (O/E), P < .01.

#Test for trend (O/E), P ≤ .001.

**Includes patients whose initial treatment for HD included chemotherapy alone (n = 5,288 1-year survivors; 28,715 person-years). Because of the small number of second cancers in the 15 to 19 year (Obs = 14), 20 to 24 year (Obs = 3) and ≥ 25 year (Obs = 4) intervals, site-specific risks are not shown. Overall risk of ANLL among all patients treated with chemotherapy alone was 36.1 (Obs = 39; 95% CI = 25.6 to 49.3).

††Excludes lymphohematopoietic disorders.

‡‡Histology of salivary gland cancers (Obs = 16) included mucoepidermoid (50%), squamous cell (19%), adenocarcinoma (19%), epithelial (6%), and complex mixed and stromal (6%) neoplasms. Mucoepidermoid and squamous cell cancers were detected a median of 5 years (range, 3 to 9 years) after HD compared with a median latency of 18 years for adenocarcinomas (range, 6 to 23 years). Of 24 esophageal cancers with specified histology, 17 were squamous cell tumors (median latency, 18 years; range, 3 to 28 years) and seven were adenocarcinomas (median latency, 12 years; range 5 to 24 years). Cancers of the small intestine with specified histology included two adenocarcinomas and two sarcomas; these were detected a median of 3 years (range, 1 to 22 years) after HD. Fifty percent of testicular cancers with specified histology (Obs = 12) were seminomas and 50% were nonseminomatous germ cell tumors, occurring a median of 4 years (range, 1 to 13 years) after HD. Two of three eye cancers were malignant melanoma, which developed 7 and 11 years after HD; the third case, a squamous cell cancer, occurred 2 years after HD. Thyroid cancers occurred a median of 12 years (range, 1 to 26 years) after HD. Ninety-three percent of thyroid cancers with specified histology (Obs = 41) were adenocarcinomas (papillary [Obs = 22]; follicular [Obs = 7]; and unspecified [Obs = 9]) and 7% were epithelial malignancies. There were no reported cases of medullary or anaplastic thyroid cancers.

§§Test for trend (O/E), P < .05.

|||For female-specific sites, the number of patients entering the 1-9, 10-14, 15-19, 20-24, and ≥ 25 year intervals was 13,877, 5,052, 2,806, 1,303, and 508, and the corresponding number of person-years was 76,560, 19,181, 10,094, 4,254, and 2,387, respectively. For female-specific sites, the number of patients treated with any radiotherapy entering the 1 to 9, 10 to 14, 15 to 19, 20 to 24, and ≥ 25 year intervals was 6,199, 2,494, 1,387, 582, and 232, and the corresponding number of person-years was 25,992, 37,811, 19,999, 10,399, 8,464, and 9,811, respectively.

The relative risk and AER of all second cancers and those at selected sites are presented in Table 4 by age at diagnosis of HD. The relative risk of all second cancers taken together decreased with increasing age at HD diagnosis ($P < .001$), whereas the AER tended to increase ($P < .001$); the apparent decline in both parameters observed in the ≥ 61 age category might reflect the shorter follow-up (mean = 4.1 years) in this age group. Similar trends by age were observed for all solid tumors considered together, acute nonlymphocytic leukemia, and cancers of the digestive tract and lung.

The site-specific burden of cancer varied according to age at HD diagnosis. For patients treated before age 21 and 21 to 30 years, the AER of breast cancer superseded that of all other second cancers. For individuals diagnosed with HD at 31 to 40, 41 to 50, or 51 to 60 years, the largest AER was due to lung cancer, and for those treated after age 60, non-Hodgkin's lymphoma (AER = 12.8) and lung cancer (AER = 12.3) accounted for the largest excesses.

The relative risk and AER of all solid tumors and those at selected sites are listed in Table 5 according to age at HD diagnosis and age at second cancer occurrence. Within each age category, the AER and relative risk of all solid tumors taken together decreased with increasing attained age. In women less than 21 years at HD diagnosis, the AER of breast cancer decreased moderately with advancing age, although the relative risk diminished sharply. Despite a decrease in the relative risk of breast cancer with increasing age in patients treated between ages 21 and 40, the AER exhibited only a subtle decline. For women treated for HD after age 40, relative risk and AER of breast cancer decreased to expectation by age 60. The largest AER of cancers of lung and digestive tract were observed in patients older than 40 years of age at HD diagnosis.

The actuarial risk of developing any solid tumor 25 years after HD was 21.9% overall; among males, the risk was 19.3% (95% CI, 17.5% to 21.1%) and among females 24.8% (95% CI, 22.4% to 27.2%) (Fig 1). At 25 years, the actuarial risk of lung cancer was significantly higher in males (6.2%; 95% CI, 5.0% to 7.4%) than females (3.2%; 95% CI, 2.2% to 4.2%), whereas the risk of digestive tract cancers was similar in both sexes. The actuarial risk of female breast cancer 25 years after HD was 9.3% (95% CI, 7.5% to 11.1%).

In Fig 2, the cumulative incidence of all solid tumors is depicted according to calendar period of HD diagnosis: 1935 to 1964, 1965 to 1979, and 1980 to 1994. For patients diagnosed with HD between 1965 and 1979, the actuarial risk of developing a solid tumor 25 years after treatment was 23.8% (95% CI, 21.8% to 25.8%) compared with 16.9% (95% CI, 14.4% to 19.4%) among those diagnosed in the earliest calendar year period. After 14 years of follow-up, the cumulative incidence of all solid tumors in patients treated

between 1965 to 1979 did not differ significantly from those treated between 1980 to 1994. Additional follow-up is required to assess the magnitude of the long-term risk of second cancers among patients treated between 1980 to 1994.

DISCUSSION

Our results are based on the largest population-based study of HD patients to date, including over 2,800 20-year survivors, which enabled us to assess cancer risk over three decades. The sizable number of patients and second cancers also enabled us to quantify relative risk and AER in terms of both age at HD diagnosis and attained age. Data describing second cancer risk 20 or more years after treatment for HD are sparse,^{3,4,6,10,12,23,24} with each published study based on five to 40 solid tumors in this time interval. Few studies have estimated second cancer risk in 25-year survivors of HD.¹² Some investigators have described a persistent increase in relative risk of solid tumors over 20 years,^{6,10,23,24} whereas others have noted a decrease in relative risk, but continued increase in AER.^{3,12} We report an overall downturn in relative risk and AER of all solid tumors at 25 years. Despite this declining overall trend, it is apparent that 25-year survivors of HD remain at increased risk for cancers of breast, esophagus, stomach, and uterine cervix.

The site-specific risk of solid tumors according to age at HD diagnosis has been addressed in several surveys.^{3,5,6,9,12,24,25} Studies of atomic bomb survivors have shown that the young may be especially susceptible to the carcinogenic effects of radiation.²⁶ However, a major finding in our study is the consistently increased relative risk and AER of solid tumors in each age category of HD diagnosis. Thus, despite the high relative risks of second cancers reported among children and adolescents with HD,^{3,10,23} we found that patients diagnosed with HD at older ages sustain the greatest second cancer burden.

The two studies of HD patients^{3,12} that have attempted to separate the effects of age at treatment and attained age on second cancer risk, based on 157 and 106 solid tumors, respectively, are included in the current report. Based on 1,726 solid tumors, we show that the AER and relative risk of solid tumors seem to decline with advancing attained age. The decline in relative risk with increasing attained age might be expected, given the increase in baseline risk with advancing age in the general population, but the attenuation in AER indicates that the tumor burden is diminishing.

Temporal trends and treatment group distribution for site-specific cancer excesses followed two general patterns. For several solid tumor sites (ie, esophagus, stomach, colon, rectum, female breast, and bladder), risks did not increase until 10 years after HD diagnosis and remained elevated for at least a decade, suggestive of the late effects of radiother-

Table 4. Relative and Absolute Risks of Second Cancers at Selected Sites by Age at Diagnosis of HD

	Age at HD Diagnosis					
	< 21 Years	21-30 Years	31-40 Years	41-50 Years	51-60 Years	≥ 61 Years
No. of patients, total	5,925	9,174	5,821	3,688	3,244	4,739
No. of person-years, total	56,509	83,022	47,365	27,363	20,431	19,552
Second cancers, all						
Obs	195	378	314	371	437	458
O/E	7.7*	4.3*	2.7*	2.5*	2.0*	1.3*†
AER	30.0	34.9	42.0	80.5	107.5	51.7†
Solid tumors, all‡						
Obs	157	291	227	301	365	385
O/E	7.0*	3.6*	2.1*	2.1*	1.8*	1.2*†
AER	23.8	25.3	25.4	58.7	79.2	27.0†
Buccal, all§						
Obs	4	18	15	12	22	25
O/E	6.1*	6.6*	3.8*	2.2*	3.2*	3.0*
AER	0.6	1.8	2.3	2.4	7.4	8.4†
Digestive tract, all#						
Obs	22	44	42	76	85	107
O/E	10.0*	3.9*	2.1*	2.3*	1.6*	1.0†
AER	3.5	3.9	4.6	15.4	15.1	1.1
Stomach						
Obs	5	14	12	18	14	17
O/E	13.8*	7.1*	3.4*	3.0*	1.5	0.9†
AER	0.8	1.4	1.8	4.4	2.2	-1.5
Colon						
Obs	4	14	9	22	29	51
O/E	4.7*	3.5*	1.3	2.0*	1.6*	1.4*¶
AER	0.6	1.2	0.4	3.9	5.1	6.9†
Rectum						
Obs	5	4	8	10	12	13
O/E	12.4*	1.8	1.9	1.5	1.1	0.7†
AER	0.8	0.2	0.8	1.1	0.7	-2.6
Lung						
Obs	5	34	52	84	129	73
O/E	5.5*	5.4*	4.0*	3.5*	3.4*	1.5*†
AER	0.7	3.3	8.2	21.8	44.6	12.3†
Female breast**						
Obs	52	67	29	33	21	32
O/E	14.2*	3.7*	1.2	1.7*	1.0	1.1†
AER	18.6	12.9	2.6	13.0	0.3	1.7†
Uterine cervix††						
Obs	10	11	4	4	5	3
O/E	6.1*	2.1*	0.9	1.4	2.2	1.2
AER	3.2	1.5	-0.1	1.2	3.2	0.5
Thyroid						
Obs	22	15	3	1	0	6
O/E	13.7*	4.4*	1.4	0.8	(E 1.25)	3.7*†
AER	3.6	1.4	0.2	-0.1	-0.6	2.2¶
Bone/connective tissue						
Obs	14	10	5	6	3	3
O/E	12.6*	5.7*	3.7*	5.1*	2.3	1.5†
AER	2.3	1.0	0.8	1.8	0.8	0.5
Non-Hodgkin's lymphoma						
Obs	10	31	38	24	25	34
O/E	6.9*	7.5*	8.7*	5.3*	4.3*	3.8*†
AER	1.5	3.2	7.1	7.1	9.4	12.8†
Acute nonlymphocytic leukemia						
Obs	21	36	35	30	31	16
O/E	39.2*	31.7*	35.7*	28.6*	21.2*	5.9*†
AER	3.6	4.2	7.2	10.6	14.5	6.8†

* $P < .05$.†Test for trend (O/E, AER), $P < .001$.

‡Excludes lymphohematopoietic disorders.

§International Classification of Disease for Oncology (ICD-O) morphology codes 140-149.²¹||Test for trend (O/E, AER), $P < .05$.¶Test for trend (O/E, AER), $P < .01$.

#ICD-O morphology codes 150-159.

**For female-specific sites, the number of patients in the age categories of < 21, 21-30, 31-40, 41-50, 51-60, and ≥ 61 years at HD diagnosis was 2,737, 4,106, 2,344, 1,274, 1,171, and 2,245, and the corresponding number of person-years was 25,992, 37,811, 19,999, 10,399, 8,464, and 9,811, respectively.

††Adenocarcinoma of the cervix was restricted to women ≤ 30 years of age at HD diagnosis and accounted for 38% of the histologically confirmed cancers in this age group.

Table 5. Relative and Absolute Risks of Selected Solid Tumors by Attained Age and Age at Diagnosis of HD

	Age at Diagnosis of HD								
	≤ 20 Years			21-40 Years			> 40 Years		
	No. of Patients	Person-Years		No. of Patients	Person-Years		No. of Patients	Person-Years	
Attained age									
< 40 years	5,475	44,978		8,370	39,053		–	–	
40-59 years	444	11,274		6,294	81,620		4,117	16,045	
≥ 60 years	6	256		331	9,715		7,554	51,302	
	Obs	O/E	AER	Obs	O/E	AER	Obs	O/E	AER
Solid tumors, all*									
< 40 years	136	10.5†	27.3	174	8.0†	39.0	–	–	–
40-59 years	20	2.3†	10.1	314	2.6†	23.5	270	4.6†	131.5
≥ 60 years	1	1.3‡	7.8§	30	0.7†‡	–13.4‡	781	1.3†‡	32.0‡
Female breast									
< 40 years	44	32.3†	20.7	26	6.8†	12.2	–	–	–
40-59 years	8	3.9†	11.4	68	2.2†	10.7	27	2.8†	32.2
≥ 60 years	–	–‡	–	2	0.3†‡	–11.4§	59	1.0‡	–0.9‡
Lung									
< 40 years	3	11.7†	0.6	12	18.6†	2.9	–	–	–
40-59 years	2	3.6	1.3	70	5.8†	7.1	90	8.8†	49.7
≥ 60 years	–	–	–	4	0.6‡	–2.8	196	1.9†‡	18.5‡
Digestive tract, all¶									
< 40 years	17	18.0†	3.6	20	9.9†	4.6	–	–	–
40-59 years	5	4.4†	3.4	58	3.0†	4.7	60	4.6†	29.3
≥ 60 years	–	–§	–	8	0.8‡	–2.1	208	1.2†‡	5.5‡

*Excludes lymphohematopoietic disorders.

†P < .05.

‡Test for trend (O/E, AER), P < .001.

§Test for trend (O/E, AER), P < .01.

||For female breast cancer, the number of patients in the ≤ 20 years of age at diagnosis of HD and categories of attained age < 40, 40-59, and ≥ 60 years was 2,521, 211, and five and the number of person-years was 20,586, 5,190, and 216, respectively. The number of patients in the 21-40 years of age at diagnosis of HD and categories of attained age < 40, 40-59, and ≥ 60 years was 3,678, 2,614, and 158 and the number of person-years was 18,167, 34,937, and 4,706, respectively. The number of patients in the > 40 years of age at diagnosis of HD and categories of attained age 40-59 and ≥ 60 years was 1,345 and 3,345 and the number of person-years was 5,427 and 23,248, respectively.

¶International Classification of Disease for Oncology (ICD-O) morphology codes 150-159.²¹

apy and consistent with the known radiogenicity of some, but not all, of these sites.²⁷⁻³⁰ For other solid tumors (ie, lung, melanoma, thyroid, and bone/connective tissue), excess risks were apparent in most latency periods after HD diagnosis, favoring a role for other influences, including chemotherapy, or heightened surveillance, possibly in addition to radiation. Several surveys have linked cancers of lung, thyroid, and bone to prior radiation exposure.^{29,31-36}

A new finding in our study is that a significantly increased risk of breast cancer persists for more than 25 years after HD diagnosis. Elevated risks of female breast cancer have been well documented in several populations exposed to therapeutic radiation at a young age (reviewed³⁷). For young women treated with mantle-field radiation for HD, premature ovarian failure related to pelvic irradiation and/or MOPP chemotherapy might be expected to attenuate radiation-related breast cancer excesses; whether this effect might be tempered by hormone replacement therapy²⁵ is unclear.

The risk of lung cancer according to age at adult HD has been described in few population-based studies. Our obser-

vation that the largest AER of lung cancer occurs among patients diagnosed with HD at age 41 to 50 and 51 to 60 might reflect longer exposure times to tobacco. The shortened interval for the development of lung cancer after therapy for HD is consistent with other reports.^{38,39} A recent study by Travis et al⁴⁰ described significantly increased risks of lung cancer beginning 1 to 4 years after initial treatment with alkylating agents and 5 to 9 years after radiotherapy. Tobacco use seemed to multiply treatment-related lung cancer risk.⁴⁰

In contrast to prior surveys of adult HD patients,^{4,6,24} we found a significantly elevated risk of esophageal cancer. Our observation complements the significant 31- to 169-fold increased risks of esophageal cancer previously noted in pediatric and young adult HD populations.^{3,12,41} During mantle radiotherapy for HD, the esophagus can receive doses of 35 Gy (Appendix) and significant excesses of esophageal cancer have been reported after radiation therapy for breast cancer.⁴² Chemotherapy has been linked with the development of

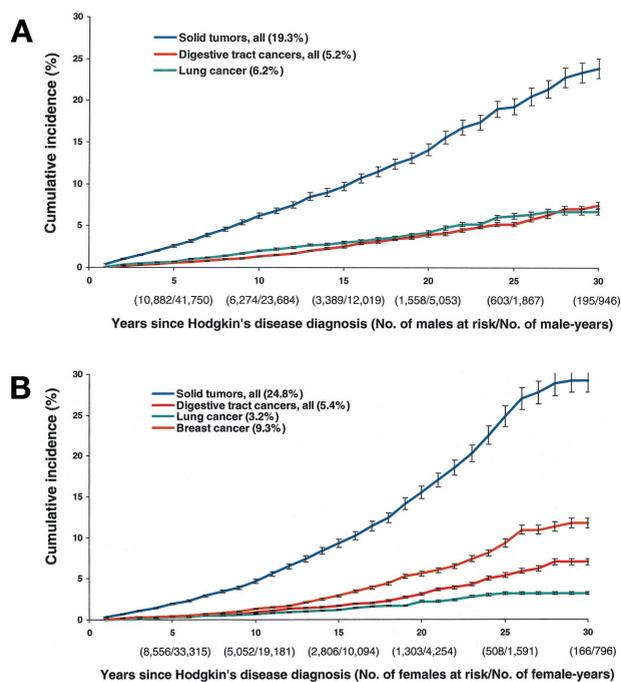


Fig 1. (A) Cumulative risk of all solid tumors, all digestive tract cancers, and lung cancer among 18,714 1-year male HD survivors. (B) Cumulative risk of all solid tumors, all digestive tract cancers, lung cancer and breast cancer among 13,877 1-year female HD survivors. Percentages in parentheses indicate the actuarial risk at 25 years. Vertical lines represent 95% CI for point estimates.

Barrett's esophagus in humans⁴³⁻⁴⁵ and with esophageal cancer in laboratory animals.^{46,47}

During radiotherapy for HD, the stomach can receive doses of 4.2 to 13.0 Gy (Appendix). Sustained elevations in stomach cancer risk have been described in other irradiated cohorts receiving 0.23 Gy to 26.2 Gy to the stomach,^{27-30,48} but analytic studies of HD patients have not been conducted to date. Combined-modality therapy for HD has been associated with significantly larger risks of stomach cancer compared with treatment with either radiation or chemotherapy alone.^{5,24} Orally-administered nitroso compounds induce stomach cancers in laboratory animals,^{47,49-51} but to our knowledge, specific chemotherapy agents have not been implicated in human stomach cancer.

Several surveys report an excess of colon cancers^{3-7,12,24,41,52} after HD, but in only one series was risk evaluated according to age at HD and time since diagnosis.⁵ We observed significantly elevated colon cancer risks in most age groups, with a progressive increase in AER with advancing age. Our data are not consistent with a radiogenic effect for colon cancer, and generally fewer than 50% of these second tumors in other surveys of HD patients have occurred within

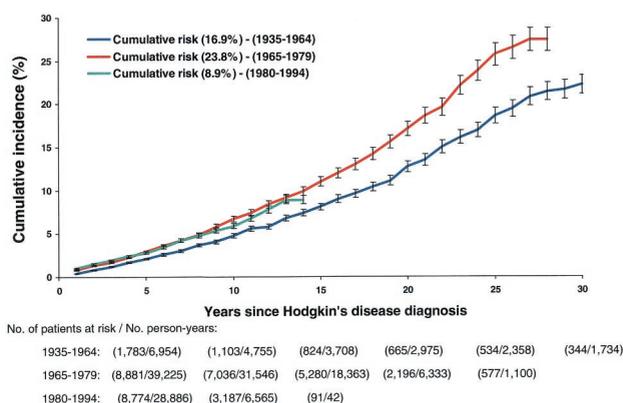


Fig 2. Cumulative risk of all solid tumors among 32,591 1-year survivors of HD according to calendar year of diagnosis. Percentages in parentheses indicate the actuarial risk at 25 years (1935-1964, 1965-1979) or 14 years (1980-1994). Vertical lines represent 95% CI for point estimates.

radiation fields.^{7,9,24,52} Radiation doses to the colon of 0.1 to 24.9 Gy during treatment for benign and malignant diseases^{27-29,48,53} have not been followed by increased risks of cancers at this site, although data from the atomic bomb survivors (mean colon dose, 0.23 Gy)²⁶ are suggestive of a radiogenic etiology. High doses of radiation (30 to 60 Gy) have been linked with rectal cancer 20 years after treatment for cervical cancer,²⁷ but increased risks have not been detected in patients exposed to lower doses.^{29,30,48}

Our study is among the first to report a significant excess of bladder cancer after HD.⁴⁻⁷ The bladder may receive doses of 30 Gy during inverted Y radiotherapy for HD (Appendix), and increasing doses of radiation have been strongly linked to increasing risk of bladder cancer in other series.³⁰ Cyclophosphamide, a known bladder carcinogen,⁵⁴ may also have been included in some chemotherapy regimens for HD.

Bone cancer risk has been related to radiation dose and cumulative amount of alkylating agents in children treated for cancer,^{33,34,55} but few data exist for adult HD patients.⁵ We found excess bone/soft tissue sarcomas in all age groups. In our series, a radiogenic effect for bone/connective tissue cancers in adult HD patients is supported by the temporal pattern and distribution between treatment groups.

Treatment regimens for HD have undergone appreciable modification over the past 35 years, and evaluation of second cancer risk among long-term survivors often reflects the effects of earlier, more aggressive protocols. Quantification of long-term risks, however, is essential to continue to maximize HD cure rates while minimizing toxic effects. Population-based studies are associated with less selection bias than hospital or clinic-based series; however, our results also must be interpreted in the context of weaknesses inherent to registry data. Migration of patients outside of the

registry catchment areas would result in underreporting of second cancers, and thus our findings may represent conservative estimates of risk. This is less of an issue in Nordic countries, where cancer data is collected nationwide. Interpretation of our results must also consider that only initial treatment information was available and that, given the multiple comparisons undertaken in this study, some statistically significant associations could be due to chance alone.

The apparent downturn in second cancer risk in patients older than 60 years of age at HD diagnosis should be viewed circumspectly given the relatively short follow-up period for this group. Similarly, the number of patients in the latency period beyond 25 years is comparatively smaller than those included in other time intervals; thus, our finding that long-term relative risk and AER of second cancers may decrease must be interpreted with caution. We estimated an actuarial probability of 21.9% for the development of a solid

tumor at 25 years; however, early censoring because of deaths from other causes (ie, HD) may tend to exaggerate the 25-year estimate, especially when a number of second malignancies occur in later follow-up periods when fewer patients are at risk.⁵⁶ Using alternative methods that adjust for competing causes of death,⁵⁷ we calculate the cumulative incidence of solid tumors to be 11.7%. Additional studies with further follow-up will help to more precisely define second cancer risk, particularly when taking treatment era into account. Future investigations should incorporate comprehensive treatment data for HD to assess the contribution of therapy, environmental influences, gene-environment interactions, and other factors in second cancer risk.

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APPENDIX

The appendix listing estimated dose to selected organs and sites after radiation treatment is available online at www.jco.org.

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