

Second Cancers Among Long-Term Survivors of Hodgkin's Disease Diagnosed in Childhood and Adolescence

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Purpose: To quantify the risk of second cancers among long-term survivors of Hodgkin's disease (HD) diagnosed before 21 years of age and to explore sex-, age-, and site-related differences.

Patients and Methods: We analyzed data from 5,925 pediatric HD patients, including 2,646 10-year and 755 20-year survivors, who were reported to 16 population-based cancer registries in North America and Europe between 1935 and 1994.

Results: A total of 157 solid tumors (observed/expected ratio [O/E] = 7.0; 95% confidence interval [CI], 5.9 to 8.2) and 26 acute leukemias (O/E = 27.4; 95% CI, 17.9 to 40.2) were reported. Risk of solid tumors remained significantly increased among 20-year survivors (O/E = 6.6, observed [O] = 40, cumulative risk = 6.5%) and persisted for 25 years (O/E = 4.6, O = 15, cumulative risk = 11.7%). Temporal trends for cancers of thyroid, female breast, bone/connective tissue,

stomach, and esophagus were consistent with the late effects of radiotherapy. Greater than 50-fold increased risks were observed for tumors of the thyroid and respiratory tract (one lung and one pleura) among children treated before age 10. At older ages (10 to 16 years), the largest number of second cancers occurred in the digestive tract (O/E = 19.3) and breast (O/E = 22.9). Risk of solid tumors increased with decreasing age at HD on a relative but not absolute scale.

Conclusion: Children and adolescents treated for HD experience significantly increased risks of second cancers at various sites for 2 to 3 decades. Although our results reflect the late effects of past therapeutic modalities, they underscore the importance of lifelong follow-up of pediatric HD patients given early, more aggressive treatments.

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THE INTRODUCTION IN the mid-1960s of effective combined-modality therapy for Hodgkin's disease (HD)^{1,2} revolutionized the treatment of this lymphoma, resulting in large numbers of long-term survivors. Children and adolescents with HD now demonstrate survival rates of approximately 90% 10 years after therapy.^{3,4} Although treatment for pediatric HD has undergone substantial modification over the last few decades, patients who received earlier, more aggressive therapies remain at risk for possible late sequelae, including second cancers.⁵⁻¹⁸ There are few large studies, however, that address the long-term risks of this serious complication.^{5,6} Most surveys are based on small numbers of HD patients in clinical or hospital-based series,^{5,7-16} with the largest investigation to date including 685 10-year survivors.⁶

In the present investigation, we quantify the long-term risk of second cancers among 5,925 HD patients diagnosed before the age of 21 years, including 2,646 10-year survivors, reported to 16 population-based cancer registries in Europe and North America between 1935 and 1994. The size of this cohort provides a unique opportunity to analyze the risk of solid tumors at several sites, with a particular emphasis on age effects.

PATIENTS AND METHODS

We evaluated all patients who were diagnosed with HD as a first primary cancer before the age of 21 years and who survived 1 or more years. Study sites included nine population-based registries of the

National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program (1973 to 1994), which represents approximately 10% of the United States population, and cancer registries in Connecticut (1935 to 1972), Ontario (1964 to 1992), Sweden (1958 to 1992), Denmark (1943 to 1993), and Finland (1953 to 1994), as well as the affiliated tumor registries of The Netherlands Cancer Institute in Amsterdam and The Dr. Daniel den Hoed Cancer Center in Rotterdam (1955 to 1986). A subgroup (n = 1,670) of patients from Denmark (1943 to 1987), Finland (1953 to 1987), Sweden (1958 to 1987), and the Netherlands (1966 to 1986) was included in earlier surveys,^{6,17} with follow-up extended for the present study. Information on patient demographic characteristics, tumor histology, and vital status is systematically compiled by all cancer registries. Data on initial course of therapy for HD, in terms of broad categories such as radiotherapy

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and/or chemotherapy, are routinely collected by these registries, except Ontario and Sweden. Information on subsequent treatment is not available. Before the early 1970s, therapy for pediatric and adult HD was similar, consisting of high-dose (≥ 40 Gy) extended-field radiotherapy. Thereafter, treatment of HD in children was generally modified to include lower-dose involved-field radiotherapy (ranging from 15 to 25 Gy according to age at treatment), with alkylating agent-based combination chemotherapy used as indicated.^{19,20} Therapy regimens for fully developed adolescents, however, could still incorporate larger doses (35 to 44 Gy) of radiation.²¹

Second malignant neoplasms that developed at least 1 year after diagnosis of HD were ascertained through linkage with cancer registry incidence files. Diagnostic confirmation of cancer cases was undertaken based on routine procedures in place within each registry.²² Cancer sites were grouped according to the World Health Organization's International Classification of Diseases for Oncology.²³ To calculate the risk of second cancers, person-years (PY) of observation were assembled according to age, sex, and calendar-year periods from 1 year after the date of HD diagnosis to the date of last follow-up evaluation, date of death, date of diagnosis of a second cancer, or the end of study (December 31, 1995), whichever occurred first. The calendar year of study end varied by registry: December 31, 1995 (SEER Program, Finland, and the Netherlands); December 31, 1993 (Ontario, Sweden and Denmark); and December 31, 1992 (Connecticut, 1935 to 1972). Cancer incidence rates specific for each region, 5-year age, sex, and 5-year calendar-year intervals were multiplied by the accumulated PY at risk to estimate the number of cancer cases expected. Numbers of observed and expected cancers from each registry were then summed, with the relative risk defined as the ratio of observed to expected cases. Second cancer risks were stratified by sex, age group at HD diagnosis (0 to 9 years, 10 to 16 years, and 17 to 20 years), attained age (< 30 years, 30 to 34 years, 35 to 39 years, and > 40 years), and time since initial diagnosis of lymphoma. Similar analyses were undertaken separately for patients who received radiotherapy as part of their initial management. The number of second cancers ($n = 11$) among patients who received chemotherapy alone was too sparse for meaningful analysis by tumor site.

Statistical tests and 95% confidence limits were based on the assumption that the observed number of second tumors was distributed as a Poisson variable. The methods of Breslow et al²⁴ were used to conduct tests for heterogeneity and linear trend. To compute the absolute risk of second cancers, the expected number of cancers was subtracted from the number of observed cases, and the difference was divided by the PY at risk. The number of excess cases was then expressed per 10,000 PY. Cumulative probabilities of developing solid tumors over time were calculated using life-table methods.²⁵

RESULTS

The final study cohort consisted of 5,925 patients (46% female) diagnosed with HD before the age of 21 years, including 2,588 (44%) from the United States, 2,098 (35%) from Europe, and 1,239 (21%) from Canada. The mean (median) age at HD diagnosis was 16 (17) years. Altogether, 1,591 patients survived 15 or more years, and 755 were observed for up to 20 years after treatment. Average duration of follow-up was 10.5 years, with approximately 81% of the patients diagnosed after 1970.

A total of 195 second cancers were reported compared with 25 expected (observed/expected ratio [O/E] = 7.7; 95% confidence interval [CI], 6.6 to 8.8) (Table 1). Seven- to eight-fold risks of all second cancers taken together occurred in Canada, the United States, and Europe (test of heterogeneity, $P = .47$), with the largest excesses (O/E = 16.0) observed in patients derived from clinical series in the Netherlands. Eighty-one percent of second cancers consisted of solid tumors (O/E = 7.0; 95% CI, 5.9 to 8.2; absolute risk = 24 excess cancers per 10,000 patients per year). Solid tumors occurred an average of 16 years (median, 15 years; range, 1 to 45 years) after HD diagnosis at a mean age of 32 years; subsequent survival was poor (median survival time, 6 months; range, < 1 month to 27 years). Overall, 27-fold risks were noted for acute leukemia (median latency, 6.6 years).

Significantly elevated five- to 15-fold risks occurred for cancers of salivary glands, stomach, colon, rectum, pancreas, lung and respiratory system, thyroid, bone, and connective tissue, with larger excesses for esophageal cancer (Table 1). Breast cancer (O/E = 14.1) accounted for almost 50% of the solid tumors in women; median age at diagnosis of second breast cancer was 33 years (range, 22 to 59 years). Women also experienced a significantly increased six-fold risk of cervical cancer (four squamous cell carcinoma, four adenocarcinoma, and two histologic type not specified; median age at diagnosis was 34 years, range, 28 to 62 years). Among women, the risk of all solid tumors excluding sex-specific sites (O/E = 6.6; 95% CI, 4.8 to 8.9) did not differ significantly from the overall risk observed in men (O/E = 5.2; 95% CI, 3.8 to 6.9). Excess cancers of salivary glands (two mucoepidermoid carcinoma) and esophagus (two adenocarcinoma and two squamous cell carcinoma) were restricted to men.

The risk of solid tumors according to time since HD diagnosis is listed in Table 2 for all patients and for those whose initial course of treatment included radiotherapy. Significant excesses of all solid tumors taken together occurred 1 to 4, 5 to 9, 10 to 14, 15 to 19, and 20 or more years after HD diagnosis, with an upswing in risk at 10 years for cancers of female breast, thyroid, bone, and connective tissue. Elevated risks of cervical cancer and tumors of the digestive tract were apparent only in the second decade of follow-up. Twenty-year survivors of HD remained at significantly increased risk for cancers of female breast (O/E = 8.0), thyroid (O/E = 37.7), uterine cervix (O/E = 10.3), and digestive tract (O/E = 10.8). For acute leukemia, significantly increased 30- to 40-fold risks occurred 1 to 4, 5 to 9, and 10 to 14 years after HD diagnosis with 10-fold risks in the 15 to 19-year interval; no cases of secondary leukemia were reported after 20 years

Table 1. Observed and Expected Numbers of Second Malignant Neoplasms Among 1-Year Survivors of HD Diagnosed Before the Age of 21 Years

| Second Cancer Site(s) | All Patients (n = 5,925) | | | Male Patients (n = 3,188) | | Female Patients (n = 2,737) | |
|---------------------------|--------------------------|------|------------|---------------------------|----------|-----------------------------|----------|
| | O | O/E | 95% CI | O | O/E | O | O/E |
| All second cancers | 195 | 7.7 | 6.6-8.8 | 69 | 6.3* | 126 | 8.8* |
| All solid tumors† | 157 | 7.0 | 5.9-8.2 | 47 | 5.2* | 110‡ | 8.3* |
| All buccal | 4 | 6.1 | 1.6-15.5 | 3 | 7.1* | 1 | 4.3 |
| Salivary glands | 2 | 14.1 | 1.6-51 | 2 | 31.2* | 0 | (E 0.08) |
| Esophagus | 4 | 65.3 | 17.6-167.0 | 4 | 85.8* | 0 | (E 0.01) |
| Stomach | 5 | 13.8 | 4.4-32.1 | 2 | 9.3* | 3 | 20.2* |
| Colon | 4 | 4.7 | 1.3-12.1 | 2 | 4.8 | 2 | 4.7 |
| Rectum | 5 | 12.4 | 4.0-28.9 | 2 | 9.0* | 3 | 16.7* |
| Pancreas | 2 | 10.8 | 1.2-38.9 | 0 | (E 0.11) | 2 | 26.0* |
| Liver, gallbladder | 1 | 5.4 | 0.1-30.0 | 1 | 9.6 | 0 | (E 0.08) |
| Lung, respiratory system§ | 6 | 5.1 | 1.9-11.1 | 4 | 5.6* | 2 | 4.4 |
| Female breast | – | – | – | – | – | 52 | 14.1* |
| All female genital | – | – | – | – | – | 15 | 4.7* |
| Uterine cervix | – | – | – | – | – | 10 | 6.1* |
| Uterus corpus | – | – | – | – | – | 1 | 2.8 |
| Ovary | – | – | – | – | – | 2 | 2.0 |
| Testis | – | – | – | 3 | 1.4 | – | – |
| Bladder | 2 | 4.3 | 0.5-15.4 | 2 | 5.9 | 0 | (E 0.13) |
| Melanoma | 5 | 1.9 | 0.6-4.4 | 3 | 2.7 | 2 | 1.3 |
| Brain and CNS | 3 | 1.5 | 0.3-4.4 | 3 | 2.5 | 0 | (E 0.8) |
| Thyroid | 22 | 13.7 | 8.6-20.7 | 6 | 18.1* | 16 | 12.6* |
| Bone | 5 | 9.7 | 3.1-22.7 | 2 | 5.9 | 3 | 17.0* |
| Connective tissue | 9 | 15.1 | 6.9-28.7 | 4 | 11.6* | 5 | 20.0* |
| Non-Hodgkin's lymphoma | 10 | 6.9 | 3.3-12.8 | 6 | 6.2* | 4 | 8.3* |
| All leukemia | 28 | 20.9 | 13.9-30.3 | 16 | 19.4* | 12 | 23.5* |
| All acute leukemia | 26 | 27.4 | 17.9-40.2 | 16 | 27.8* | 10 | 26.8* |

NOTE. Study includes 5,925 patients diagnosed with HD as a first primary cancer before the age of 21 and who survived 1 or more years.

* $P < .05$.

†Category of all solid tumors excludes lymphohematopoietic disorders. No tumors were observed at the following sites: kidney, prostate, eye, and multiple myeloma. Nine case patients had secondary tumor of unknown or ill-defined primary sites.

‡Six women developed two or more multiple primary cancers. These included three patients with cancers of breast and thyroid; one patient with cancers of thyroid and central nervous system, one patient with cancers of cervix and uterine corpus; and one patient with cancers of breast, connective tissue, and thyroid.

§Includes six patients with cancer of lung (n = 5) or pleura (n = 1).

||Includes 21 acute nonlymphocytic leukemias, one acute lymphoblastic leukemia, and four acute leukemias, type not otherwise specified.

of follow-up. Temporal patterns of solid tumor risk among patients whose initial treatment was known to have included radiotherapy paralleled overall trends. No significant differences in site-specific risks of solid tumors were observed for patients who initially received radiotherapy alone (n = 1,927) compared with those given both radiotherapy and chemotherapy (n = 872) (results not shown).

For all solid tumors taken together, increased risks persisted for 25 years after HD diagnosis (O/E = 4.6; 95% CI, 2.6 to 7.6; observed [O] = 15). Significantly elevated risks were observed for cancers of the digestive tract (O/E = 8.6; O = 5), female breast (O/E = 4.9; O = 4), and uterine cervix (O/E = 18.5; O = 2). Nonsignificant excesses were reported for tumors of the thyroid, lung, and other respiratory sites. The cumulative risk of developing any solid cancer was 6.5% (95% CI, 5.3 to 7.7%) and 11.7% (95% CI, 9.7 to 14.1%) 20 and 25 years after HD diagnosis,

respectively. The respective corresponding population expected risks were 0.9% and 1.5%.

The relative risks (O/E) of all second cancers and those at selected sites are listed by age at HD diagnosis in Table 3. Children treated for HD before age 10 experienced 14-fold risks of all second cancers, with especially large excesses observed for tumors of the respiratory tract (based on one patient with lung cancer and one patient with pleural tumor) and thyroid and acute leukemia. Of 62 solid cancers that developed in patients diagnosed with HD between ages 10 and 16 years, slightly more than 50% occurred in either the female breast (O/E = 22.9) or digestive tract sites (O/E = 19.3). The risk of female breast cancer remained elevated (O/E = 11.6; O = 32) for patients treated at older ages (17 to 20 years), whereas no cases were reported in children given therapy before the age of 10. Relative risks of all solid tumors taken together increased with decreasing age at

Table 2. Risks of All Solid Tumors and Those at Selected Sites According to Time Since Diagnosis of HD and Initial Treatment With Radiotherapy

| Time Since Diagnosis | First Decade | | Second Decade | | Third Decade | | | | | |
|-----------------------------------|----------------------------------------------|--------------|-------------------------------------------------|----------------|-------------------------|-------|----|-------|----|----------|
| | 1 to 4 Years | 5 to 9 Years | 10 to 14 Years | 15 to 19 Years | 20+ Years | | | | | |
| All subjects:* | | | | | | | | | | |
| No. of patients entering interval | 5,925 | 4,088 | 2,646 | 1,591 | 755 | | | | | |
| Person-years† | 19,748 | 16,637 | 10,512 | 5,710 | 3,901 | | | | | |
| Subjects with treatment data:‡ | | | | | | | | | | |
| Any radiotherapy§ | | | | | | | | | | |
| No. of patients entering interval | 2,799 | 2,003 | 1,363 | 811 | 337 | | | | | |
| Person-years | 9,471 | 8,437 | 5,397 | 2,769 | 1,748 | | | | | |
| Second Cancer Site(s) | First Decade | | Second Decade | | Third Decade | | | | | |
| | 1 to 4 Years | 5 to 9 Years | 10 to 14 Years | 15 to 19 Years | 20+ Years | | | | | |
| | O | O/E | O | O/E | O | O/E | | | | |
| All solid tumors¶ | 8 | 2.6# | 23 | 5.2# | 47 | 10.0# | 39 | 9.3# | 40 | 6.6# |
| Any radiotherapy | 3 | 2.1 | 13 | 6.0# | 29 | 12.1# | 21 | 10.3# | 29 | 9.5# |
| Female breast | 0 | (E 0.07) | 3 | 9.7# | 18 | 25.7# | 18 | 18.4# | 13 | 8.0# |
| Any radiotherapy | – | | 2 | 12.2# | 13 | 34.1# | 10 | 19.7# | 10 | 11.7# |
| Thyroid | 1 | 2.9 | 3 | 6.5# | 9 | 22.7# | 3 | 12.0# | 6 | 37.7# |
| Any radiotherapy | 0 | (E 0.17) | 1 | 4.2 | 5 | 25.1# | 1 | 8.9 | 5 | 81.7# |
| Bone/connective tissue | 2 | 5.2 | 2 | 6.3 | 4 | 20.0# | 5 | 43.0# | 1 | 10.6 |
| Any radiotherapy | 2 | 11.5# | 1 | 6.6 | 3 | 30.7# | 4 | 72.0# | 0 | (E 0.04) |
| Uterine cervix | 0 | (E 0.13) | 0 | (E 0.37) | 5 | 10.5# | 2 | 5.3 | 3 | 10.3# |
| Any radiotherapy | – | | – | | 1 | 4.3 | 1 | 5.6 | 3 | 19.9# |
| Other site(s) | First Decade, All Latencies: 1 to 9 Years | | Second Decade, All Latencies: 10 to 19 Years | | Third Decade, 20+ Years | | | | | |
| | O | O/E | O | O/E | O | O/E | | | | |
| Esophagus | 0 | (E 0.005) | 1 | 62.3 | 3 | 74.3# | | | | |
| Any radiotherapy | – | | 0 | (E 0.01) | 2 | 85.5# | | | | |
| Stomach | 0 | (E 0.06) | 3 | 22.4# | 2 | 11.9# | | | | |
| Any radiotherapy | – | | 2 | 28.1# | 2 | 25.0# | | | | |
| Colorectum | 0 | (E 0.29) | 5 | 10.7# | 4 | 8.1# | | | | |
| Any radiotherapy | – | | 3 | 12.7# | 2 | 7.6 | | | | |
| Lung | 1 | 9.8 | 2 | 7.7 | 3 | 5.5# | | | | |
| Any radiotherapy | 0 | (E 0.05) | 0 | (E 0.13) | 1 | 3.4 | | | | |

*Includes 5,925 patients diagnosed with HD as a first primary cancer before the age of 21 years and who 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 (n = 4,022).

§Includes patients whose initial treatment for HD included radiotherapy alone (n = 1,927 1-year survivors) or radiotherapy and chemotherapy (n = 872 1-year survivors).

||Risks for solid tumors that occurred in the first and second decades after diagnosis of HD are shown at 5-year intervals only for those sites at which a total of 10 or more cancers were observed and at 10-year intervals for selected sites with less than 10 cancers.

¶Category of all solid tumors excludes lymphohematopoietic disorders.

#P < .05.

treatment for HD, with an especially striking pattern for thyroid cancer (test of trend, $P < .01$). Because estimates of relative risk can be strongly influenced by age, given the low background rate of cancer in the young, absolute risks are also listed in Table 3. Absolute excesses for solid tumors were similar across age groups, especially when female-specific tumors were excluded (absolute risk = 17, 15, and 11/10,000/yr for ages 0 to 9, 10 to 16, and 17 to 20 years, respectively; test of heterogeneity, $P = .34$).

Table 4 lists the relative and absolute risks of all solid tumors and cancers of the female breast, thyroid, and

digestive tract by attained age. Risk of all solid tumors taken together decreased on both relative and absolute scales after age 40 years; however, the relatively sparse follow-up (PY = 11,530) at older ages should be taken into account. A significant trend ($P < .01$) was observed for female breast cancer, with relative risks decreasing steeply with increasing attained age (O/E = 124.7, 46.5, 27.8, and 2.0 for attained age < 30, 30 to 34, 35 to 39, and ≥ 40 years, respectively). Age at HD diagnosis (≤ 16 years and 17 to 20 years) did not seem to significantly affect second cancer risks by attained age.

Table 3. Selected Second Malignant Neoplasms According to Site and Age at Diagnosis of HD

| Second Cancer Site(s)* | Age at HD Diagnosis | | | | | | | | | | | |
|---------------------------------------------------|---------------------------------|----------|------------|----------------|--------------------------------------|------|-----------|---------------|--------------------------------------|-------|----------|---------------|
| | 0 to 9 Years (n = 525/5,934 PY) | | | | 10 to 16 years (n = 2,149/20,328 PY) | | | | 17 to 20 years (n = 3,251/30,246 PY) | | | |
| | O | O/E | 95% CI | Absolute Risk† | O | O/E | 95% CI | Absolute Risk | O | O/E | 95% CI | Absolute Risk |
| All second cancers | 17 | 14.1 | 8.2-22.6 | 27 | 81 | 10.7 | 8.5-13.4 | 36 | 97 | 5.8 | 4.7-7.1 | 27 |
| All solid tumors‡ | 11 | 11.6 | 5.8-20.8 | 17 | 62 | 9.4 | 7.2-12.1 | 27 | 84 | 5.6 | 4.5-7.0 | 23 |
| All solid tumors, excluding female-specific sites | 11 | 13.3 | 6.6-23.8 | 17 | 36 | 7.5 | 5.2-10.3 | 15 | 43 | 4.3§ | 3.1-5.8 | 11 |
| All digestive | 1 | 13.3 | 0.2-73.8 | 2 | 12¶ | 19.3 | 10.0-33.8 | 6 | 9 | 6.0 | 2.7-11.3 | 2 |
| Lung, respiratory system | 2# | 65.8 | 7.4-237.4 | 3 | 1 | 3.0 | 0.04-16.6 | 0.3 | 3 | 3.7 | 0.7-10.8 | 1 |
| Female breast | 0 | (E 0.05) | | – | 20 | 22.9 | 14.0-35.4 | 20 | 32 | 11.6 | 8.0-16.4 | 19 |
| Uterine cervix | 0 | (E 0.03) | | – | 3 | 7.0 | 1.4-20.5 | 3 | 7 | 5.9 | 2.4-12.1 | 4 |
| Melanoma | 0 | (E 0.09) | | – | 2 | 2.5 | 0.3-9.2 | 1 | 3 | 1.7 | 0.3-4.9 | 0.4 |
| Thyroid | 4 | 76.5 | 20.6-196.0 | 7 | 9 | 17.9 | 8.2-33.9 | 4 | 9 | 8.6§ | 3.9-16.3 | 3 |
| Bone | 0 | (E 0.07) | | – | 4 | 18.6 | 5.0-47.7 | 4 | 1 | 4.3 | 0.1-24.1 | 0.3 |
| Connective tissue | 2 | 44.4 | 5.0-160.2 | 3 | 1 | 4.9 | 0.1-27.1 | 0.4 | 6 | 17.4 | 6.3-37.8 | 2 |
| Non-Hodgkin's lymphoma | 0 | (E 0.09) | | – | 5 | 11.0 | 3.6-25.7 | 2 | 5 | 5.6 | 1.8-13.0 | 1 |
| All acute leukemia | 6 | 46.3 | 16.9-100.8 | 10 | 14 | 41.2 | 22.5-69.1 | 7 | 6 | 12.5§ | 4.6-27.3 | 2 |

Abbreviation: PY, person-years.

NOTE. Includes 5,925 patients diagnosed with HD as a first primary cancer before the age of 21 and who survived 1 or more years.

*Risks are shown only for those sites at which a total of five or more cancers were observed.

†Absolute (excess) risk per 10,000 persons per year.

‡Category of all solid tumors excludes lymphohematopoietic disorders.

§Test for trend (O/E), $P < .01$.

||Female-specific sites include 52 breast, 10 uterine cervix, one uterine corpus, two ovary, and two genital sites not otherwise specified.

¶Includes the following digestive tract cancers: three esophagus, three stomach, two rectum, two pancreas, one colon, and one site not otherwise specified.

#Includes two patients with cancer of lung (n = 1) and pleura (n = 1).

DISCUSSION

Our results are based on the largest cohort of children and adolescents with HD studied to date (more than 5,900 patients), enabling us to provide new information on second cancer risk among 25-year survivors. In addition, the sizable data set permitted description of age and latency patterns for second cancer risk at a broad spectrum of anatomic sites. We found that 20-year survivors of HD experienced significantly increased risks of cancers of the female breast, thyroid, digestive tract, lung, uterine cervix, and bone and connective tissue. These elevated risks persisted for more than 25 years after HD for most tumors. Our findings with regard to secondary leukemia are consistent with the existing literature,^{5-8,11,14} thus, we now focus on the long-term risks of solid tumors, emphasizing treatment effects and age trends, for which little data are available.

Since the 1970s, treatment of childhood and adolescence HD has typically included radiotherapy, either given alone or in combination with chemotherapy.²¹ Previous clinical series^{5,7,12} of pediatric HD indicate that 92% to 97% of patients may receive radiotherapy, as single- or combined-modality therapy, to treat initial disease or relapse. Thus, our finding that excess risk for all solid tumors among patients known to be initially treated with radiotherapy was

similar to overall risks is not unexpected. These results likely reflect the fact that most of the subjects in our cohort received radiotherapy at one point in their treatment history, although we lacked information on subsequent therapy. The overall temporal trend of second cancer risk for thyroid, breast, bone/connective tissue, stomach, and esophagus, with the largest excesses observed 10 or more years after HD diagnosis, is compatible with the late effects of radiotherapy, as observed in studies of adult HD²⁶⁻³⁰ and other radiation-exposed cohorts.³¹ New information in our survey includes the persistence of elevated risks for thyroid and breast cancer for more than 25 years after treatment for pediatric HD. For children who received radiotherapy for various benign conditions,³² excess risks of thyroid cancer have been shown to exist for more than 40 years of follow-up.

For pediatric HD, there has been little detailed documentation of solid tumor risk at sites other than thyroid and breast.⁵⁻⁷ Particularly interesting observations in our study include the increased risk for cancers of esophagus, salivary glands, and lung, all of which have been linked with radiation exposure.³³⁻³⁸ Two of the four cases of esophageal cancer consisted of adenocarcinoma, a rare histologic type associated with Barrett's esophagus³⁹ and gastroesophageal

Table 4. Relative and Absolute Risks of All Solid Tumors and Those at Selected Sites by Age at Diagnosis of HD and Attained Age

| Attained Age | Age at HD Diagnosis | | | | | |
|----------------------|----------------------------------|----------|-----|--------------------------------------|----------|-----|
| | ≤ 16 Years (n = 2,674/26,262 PY) | | | 17 to 20 Years (n = 3,251/30,246 PY) | | |
| | O | O/E | AR* | O | O/E | AR* |
| All solid tumors | | | | | | |
| < 30 years | 33 | 15.6† | 23 | 26 | 12.6† | 29 |
| 30-34 years | 15 | 9.3† | 24 | 26 | 10.6† | 35 |
| 35-39 years | 19 | 13.6† | 48 | 17 | 5.0† | 19 |
| 40+ years | 6 | 2.5‡ | 11 | 15 | 2.1†‡ | 10 |
| Female breast | | | | | | |
| < 30 years | 6 | 124.7† | 11 | 8 | 83.9† | 19 |
| 30-34 years | 7 | 46.5† | 26 | 8 | 29.6† | 23 |
| 35-39 years | 6 | 27.8† | 35 | 9 | 15.5† | 25 |
| 40+ years | 1 | 2.0‡ | 4 | 7 | 3.9†‡ | 13 |
| Thyroid | | | | | | |
| < 30 years | 7 | 34.7† | 5 | 2 | 7.9 | 2 |
| 30-34 years | 4 | 23.2† | 7 | 5 | 19.8† | 7 |
| 35-39 years | 2 | 20.2† | 5 | 0 | (E 0.28) | – |
| 40+ years | 0 | (E 0.08) | – | 2 | 7.5 | 2 |
| All digestive tumors | | | | | | |
| < 30 years | 3 | 24.5† | 2 | 1 | 7.7 | 1 |
| 30-34 years | 3 | 27.3† | 5 | 2 | 11.6† | 3 |
| 35-39 years | 5 | 42.1† | 13 | 3 | 10.3† | 4 |
| 40+ years | 2 | 5.8 | 5 | 3 | 3.3 | 3 |

Abbreviations: PY, person-years; AR, absolute (excess) risk.

*Absolute (excess) risk per 10,000 persons per year.

† $P < .05$.

‡Test for trend (O/E), $P < .01$.

reflux.⁴⁰ Barrett's esophagus has also been described as a sequela of chemotherapy in children⁴¹ and adults⁴² with cancer; whether other risk factors for esophageal cancer^{39,43,44} are operant among the young with HD is not clear. We also observed significantly increased risks of mucoepidermoid carcinoma of the salivary gland, which has been linked to radiation exposure in the atomic bomb survivors³⁵ and children treated for benign conditions of the head and neck.^{33,34} Wolden et al⁷ previously reported large excesses of salivary gland cancer among patients with pediatric HD; however, information on histologic type was not presented.

Small analytic studies have previously linked elevated risks of lung cancer after adult HD to radiotherapy³⁶ and, possibly, to chemotherapy.³⁷ Their role in the development of pulmonary tumors in the young, however, has not been fully explored. Because only a small percentage of pediatric HD patients receive chemotherapy alone, it is difficult to gauge the impact of cytotoxic drugs on solid tumor risk. Although studies of pediatric HD^{5,7} frequently compare second cancer risk among subjects who initially received radiotherapy alone with risk among patients given combined-modality therapy, differences have not been detected. Moreover, most reports have not provided detailed data on second cancer risk at specific sites, including lung. In our

study, increased risks of pulmonary tumors persisted throughout 3 decades after HD diagnosis, akin to observations in adult series.^{26,29} The early excesses are not consistent with the late carcinogenic effects of radiotherapy, suggesting that additional factors (eg, cigarette smoking) may contribute to secondary lung cancer among HD patients.

Although elevated risks of cervical cancer have been described in some^{26,45} but not all^{27,28,46} adult HD series, we provide the first report, to our knowledge, of a six-fold increased risk of cervical cancer among patients with pediatric HD. It is unlikely that radiation for HD contributes significantly to the subsequent occurrence of cervical cancer, given the relative radioresistance of this organ.³⁸ Emergence of excess cervical cancers 10 years after HD diagnosis may reflect the acquisition of human papillomavirus infection, an established risk factor,⁴⁷ as adolescents become sexually active. Whether defects in cellular immunity inherent to HD may facilitate the development and progression of human papillomavirus-related neoplasia in women with lymphoma is not clear.⁴⁸

In contrast to findings reported in adult series of HD survivors,^{22,29,49,50} we did not observe an increased risk of melanoma. Although the lack of elevated risks may be a result of underreporting of melanoma cases to cancer

registries, only one clinical series of pediatric HD has noted excess cancers of this type.⁷ Risk factors for melanoma include immunosuppression, ultraviolet radiation, and the occurrence of dysplastic cutaneous nevi.⁴⁹ It is perhaps noteworthy that children with hematologic malignancies may develop significantly increased numbers of melanocytic nevi, a possible precursor of melanoma, after chemotherapy.^{51,52} Melanoma has not been linked to prior exposure to ionizing radiation.³⁸

Investigations of the effect of age at HD diagnosis on the development of second cancers among pediatric patients have resulted in conflicting data. In some series,^{5,11} risks of second cancers have been found to increase with increasing age at lymphoma diagnosis, whereas others have either observed the opposite trend⁶ or reported no apparent age effect.^{7,8,12,14} We found that risks of all solid tumors excluding female-specific sites decreased with increasing age at HD diagnosis when measured on a relative scale. However, these high relative risks of second cancers in younger HD patients likely reflect the low underlying rates. Absolute excesses of solid tumors, a measure that is independent of baseline cancer incidence, remained constant across age categories in our study. Whether increased relative risks will persist once survivors of childhood HD enter the age range in which cancer expectation increases is an important question.

Studies of the atomic bomb survivors suggest that the young, particularly children less than 10 years of age, may be especially susceptible to the late carcinogenic effects of ionizing radiation.³¹ Young age at exposure to radiation is an especially important risk factor for cancers of the thyroid^{32,53} and breast^{31,54,55}. Elevated risks of breast cancer in our study were concentrated in patients treated at age 10 and older, as reported in other HD series.^{5,6,11-13,56} Although breast tissue at the time of puberty is known to be highly radiosensitive,^{57,58} the role of well-established risk factors (eg, reproductive history) and possibly others (eg, genetic predisposition and the direct and indirect roles of chemotherapy^{13,56}) on the development of radiotherapy-associated breast cancer remains to be clarified.

Surveys of radiation-exposed subjects have reported increasing risks of digestive tract tumors, particularly stomach cancer, with decreasing age at exposure.^{59,60} Children and adolescents with HD also experience larger excesses of cancers of the stomach, esophagus, and rectum than do adults.^{26-29,50,59} We found significantly increased risks of all digestive tumors taken together across all age subgroups of HD diagnosis, including those treated before age 10. Similarly, the elevated risk of respiratory cancer extended to all age categories. To date, only Wolden et al⁷ have reported an

increased risk of lung cancer after pediatric HD, but they were unable to detect an age effect.

Few studies^{10,13,59} have investigated the risk of secondary malignancies after HD by attained age, and no investigation includes risk estimates for patients diagnosed with HD before age 20. For clinical series that include patients diagnosed with HD at any age, including the elderly, relative risks of second cancers seem to diminish with increasing attained age.^{10,13,59} Although our data suggests a possible reduction in relative and absolute risks after age 40 for all solid tumors, including thyroid and female breast, the small number of PY in this age group limits our conclusions; it is clear that additional follow-up is needed as more pediatric HD patients survive into mid-adulthood. Among women exposed to the atomic bomb before age 20, excess relative risks of breast cancer were found to decrease after age 35.³¹

Strengths of our study include the large number of long-term survivors of pediatric and adolescent HD in a population-based setting, enabling detailed analyses by age, tumor site, and latency period. Our findings, however, must be interpreted in the light of weaknesses inherent to cancer registry-based data. Underreporting of second cancers is likely to occur among patients who migrate from the catchment area of the registries; thus, risk estimates among long-term survivors are likely to be conservative. However, losses to follow-up because of migration are not of a major concern in Scandinavian countries, which have nationwide registration. Another limitation of registry data includes the lack of detailed, comprehensive information on cancer treatment. Although we are unable to provide risk estimates of second cancer in relation to specific therapeutic modalities, our findings remain valuable for monitoring the site-specific risk of second cancers among long-term survivors of pediatric HD.

The development of second cancers remains an ongoing concern for many HD patients treated with past therapeutic modalities. This is especially true for pediatric and adolescent HD, which have a resultant lifetime for the manifestation of late effects. As new treatment protocols attempt to optimize cure rates for young HD patients while reducing early and late complications, it is important to re-evaluate site-specific risks of second cancers with respect to age at HD therapy. Additional studies are needed to fully characterize patient groups at especially high risk, in terms of level of exposure to radiation and cytotoxic agents, as well as genetic, immunologic, and other influences. Patients treated for HD at a young age should also be informed of the effects of smoking, diet, and other lifestyle habits on the risk of cancers at specific sites, such as lung, digestive tract, and cervix.

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