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Abnormalities of the Thyroid in Survivors of Hodgkin's Disease: Data from the Childhood Cancer Survivor Study*

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ABSTRACT

Treatment for Hodgkin's disease (HD) is associated with a variety of thyroid abnormalities, including hypothyroidism, hyperthyroidism, and thyroid neoplasms. Due to the small sample size and short follow-up time of most published studies, it has been difficult to appreciate the full extent of the problem and to characterize the interaction between various patient and treatment variables. To overcome these limitations we have assessed thyroid status in 1,791 (959 males) HD survivors from among 13,674 participants in the Childhood Cancer Survivor Study, a cohort of 5-yr survivors of childhood and adolescent cancer diagnosed between 1970 and 1986. Thyroid abnormalities were ascertained as part of a 22-page questionnaire sent to participants. Survivors were a median of 14 yr (range, 2–20 yr) at diagnosis of HD and a median of 30 yr (range, 12–47 yr) at follow-up. Seventy-nine percent of subjects were treated with radiation (median dose of radiation to the thyroid, 3500 cGy; range, 0.37–5500 cGy). Control data were available from 2,808 (1,346 males) sibling controls. Thirty-four percent of the entire cohort has been diagnosed with at least one thyroid abnormality. Hypothyroidism was the most common disturbance, with a relative risk of 17.1 ($P < 0.0001$) compared to sibling controls. Increasing dose of radiation, older age at diagnosis of HD, and female sex were all independently associated with an increased risk of hypothyroidism. Actuarial risk of hypothyroidism for subjects treated with 4500 cGy or more is 50% at 20 yr from diagnosis. Hyperthyroidism was reported by 5% of survivors, which was 8-fold greater ($P < 0.0001$) than the incidence reported by the controls. Thyroid dose of 3500 cGy or more was the only risk factor identified for hyperthyroidism. The risk of thyroid nodules was 27 times ($P < 0.0001$) that in sibling controls. Female sex and radiation dose to the thyroid of 2500 cGy or more were independent risk factors for thyroid nodules. The actuarial risk of a female survivor developing a thyroid nodule is 20% at 20 yr from diagnosis. Thyroid cancer was diagnosed in 20 survivors, which is 18 times the expected rate for the general population. After taking into account the possibility that some of the relative risk estimates may be exaggerated due to ascertainment bias, abnormalities of the thyroid are still extremely common in young adult survivors of childhood HD, particularly among females treated with high doses of radiation to the neck. (*J Clin Endocrinol Metab* **85:** 3227–3232, 2000)

INDIVIDUALS treated for Hodgkin's disease (HD) during childhood and adolescence have an excellent prognosis, and the majority will go on to become long-term survivors. Despite the prospect of prolonged, disease-free survival, HD survivors remain at risk of developing a number of late complications (1–4). Abnormalities of the thyroid gland, including hypothyroidism, hyperthyroidism, and thyroid neoplasms, all have been reported to occur at a higher rate among HD survivors compared to the general population (5–7). It has been difficult, however, to determine the full extent of the problem due to the relatively short follow-up time of most prior studies. Additionally, potential interactions between various patient and treatment variables in the genesis of these thyroid problems have been difficult to characterize due to the small sample size of the majority of published studies.

In an attempt to overcome the limitations inherent in most single institution studies, we report on the spectrum of thyroid abnormalities recorded by a large number of long-term HD survivors who participated in a multiinstitutional study that examined a variety of health outcomes. This cohort is unique, in that detailed treatment information has been abstracted from each individual's medical record, and estimated radiation doses to the thyroid have been calculated for subjects exposed to external radiotherapy. Presented herein are the results from the first 1791 participants in this ongoing study.

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Materials and Methods

Childhood Cancer Survivor Study (CCSS)

The CCSS is a retrospective cohort study, involving the collaborative efforts of 25 of the largest pediatric oncology centers in North America. Eligibility criteria included diagnosis of an eligible cancer and initial

treatment at 1 of the 25 collaborating centers; diagnosis date between January 1, 1970, and December 31, 1986; age less than 21 yr at diagnosis; survival for at least 5 yr from diagnosis (individuals who survived for 5 yr but subsequently died were still eligible for this study); and diagnosis of leukemia, central nervous system malignancies (all histologies), HD, non-Hodgkin's lymphoma, kidney tumor, neuroblastoma, soft tissue sarcoma, or bone tumor. The study was approved by the institutional review board at each participating center, and each participant or parent, if the participant was less than 18 yr of age, signed informed consent before participation.

Baseline data were collected for all members of the study cohort (both survivors and sibling controls) using self-administered questionnaires. The baseline questionnaire included questions on demographics, medication use, and medical conditions. In the section on medical conditions, participants were specifically asked if they had ever been given a diagnosis of an underactive or overactive thyroid, thyroid nodule, or any subsequent cancer and, if yes, the age or date of the diagnosis. For individuals who indicated that they had been diagnosed as having thyroid cancer, verification of the diagnosis was made by requesting copies of the pathology report from the treating institution. All submitted material was reviewed by a single pathologist (Dr. Sue Hammond, Children's Hospital, Columbus, OH).

Cancer treatment information

Detailed medical information was abstracted from the medical record of each survivor-participant. Data collected included all treatments for the primary diagnosis, including the initial treatment, treatment for any relapse, and preparatory regimens for bone marrow transplant. Information about cancer treatment included qualitative information on 42 selected chemotherapeutic agents, quantitative information on 28 selected chemotherapeutic agents, surgeries performed from the time of diagnosis, and quantitative radiation data on field size, site, and dose. Initially, each patient's tumor dose for each field was assigned to one of the following dose categories: 1–999, 1000–2499, 2500–3499, 3500–4499, 4500–5499, and more than 5500 cGy.

For this study, thyroid doses were calculated only for the field that contributed the highest dose to the thyroid. The calculation was based on tumor dose and whether the thyroid was in, near (≤3 cm), or out of the primary radiation portal. The radiation dose to the thyroid was assumed to be equal to the HD dose if the thyroid was within the primary radiation beam. If the thyroid was near or out of the primary radiation beam, the off-axis thyroid dose was calculated by the distance from the primary radiation beam. For patients treated with blocked fields, the estimate of the dose to the thyroid was based on the distance from the blocked edge. This method underestimates the dose to the thyroid for some patients, but provides a minimum estimated dose received.

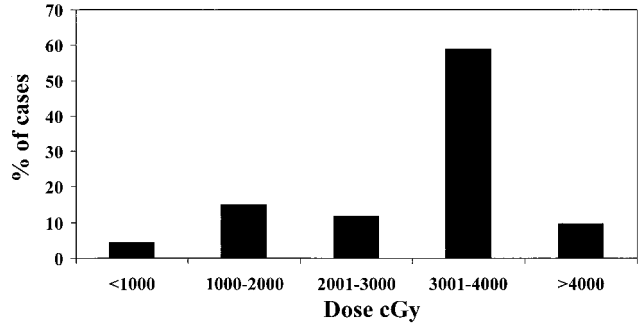

FIG. 1. Distribution of radiation doses to the thyroid (n = 1210). ■, Percentage of patients who were treated with a specific dose range.

HD cases

A total of 20,312 eligible pediatric cancer cases were registered by the 25 participating centers. To date, of those cases eligible, 13,674 (67%) have agreed to participate and have completed the 22-page self-administered questionnaire. There were 2,710 (13%) subjects with a diagnosis of HD among the 20,312 cases registered; 299 (11%) have been lost to follow-up, 267 (11%) are pending further data, and 353 (15%) refused participation. The remaining 1,791 agreed to participate and constitute the study population for this analysis.

There were 959 males and 832 females. The median age at diagnosis was 14 yr (range, 2–20 yr); 94 cases (5%) were 5 yr or less, 283 cases (16%) were 6–10 yr, 718 cases (40%) were 11–15 yr, and 696 cases (39%) were 16 yr or more at diagnosis of HD. The median age at follow-up was 30 yr (range, 12–47 yr). Radiation therapy was given to a total of 1414 patients with or without chemotherapy. Sufficient data were available to estimate the dose of radiation to the thyroid gland in 1210 cases. The median dose of radiation to the thyroid was 3500 cGy (range, 0.37–5500 cGy; Fig. 1). A total of 92 survivors had been treated with chemotherapy alone. At the time of this analysis, details of treatment were not available for 285 subjects, and thus they were not included in analyses of treatment-related factors.

A cohort of sibling controls was assembled by mailing questionnaires to the nearest-age living sibling of half the CCSS cohort. At the time of this analysis, data were available from a total of 2808 (1346 males) siblings of the entire CCSS cohort, including 348 (150 males) siblings of the participants with HD. Their median age was 25 yr (range, 1–56 yr).

Data analysis

Our analysis was divided into three parts. The first part investigated three abnormal thyroid conditions (underactive, overactive, and thyroid nodules) as separate outcomes. The incidence rates of each thyroid condition were computed separately for the HD survivors and the sibling controls by the number of new occurrences divided by the total number of person-years at risk. Each individual was considered to be at risk for the thyroid condition until the earliest of the following events occurred: death, development of the thyroid condition, or completion of questionnaire. The ratio of the incidence rates for the survivor cohort over the sibling cohort yielded a relative risk (RR) estimate for the survivors. As some of the survivors and siblings were from the same families, our analysis accounted for the within-family correlation using the generalized estimating equation approach for Poisson rates (8). Significance tests and 95% confidence intervals were based on the robust inference of the generalized estimating equation approach.

To investigate the factors that modify the risk for the thyroid conditions, we tabulated the incidence rates for the three thyroid conditions by various demographic and treatment categories using only the survivor cohort, measuring person-years from date of cancer diagnosis to time of death, development of the condition, or questionnaire completion. After the exploratory tabulation, we used Poisson regression models (9) to summarize the RR associated with the significant demographic and treatment characteristics, simultaneously. Kaplan-Meier curves were produced to show the time of occurrence of the conditions after diagnosis.

The third part of our analysis investigated the RR of developing thyroid cancer for the survivors compared to the U.S. general population. The age-sex specific incidence rates of thyroid cancer were obtained from the Surveillance, Epidemiology, and End Results Program of the NCI (10). Standardized incidence ratios were computed for each gender,

TABLE 1. Incidence of thyroid abnormalities in HD survivors compared to controls

Abnormality	HD survivors		Controls		RR (95% CI)	*P* value
	Cases	Rate/1000 py	Cases	Rate/1000 py		
Underactive	456	9.6	39	0.6	17.1 (12.5–24.2)	<0.0001
Overactive	82	1.6	13	0.2	8.0 (4.6–15.1)	<0.0001
Nodules	146	2.9	7	0.1	27.0 (13.6–63.9)	<0.0001

py, Person-years.

and significance tests and 95% confidence intervals were computed using the standard statistical for the standardized incidence ratio analysis (9).

Results

Among the 1791 participants, 611 (34%) indicated that they had been diagnosed with at least 1 thyroid abnormality; 91 subjects had been diagnosed with 2 different thyroid abnormalities, and 3 survivors had been diagnosed with 3 separate thyroid problems. Twenty-eight percent of the cohort has been diagnosed as having an underactive thyroid gland, 5% has been diagnosed as having an overactive thyroid gland, and 9% indicated a positive history of thyroid nodule(s).

Underactive thyroid

For subjects with a history of HD, the incidence of an underactive thyroid gland was significantly increased compared to that in sibling controls (RR, 17.1; $P < 0.0001$; Table 1). Hypothyroidism developed a mean of 7 yr (0–27 yr) after diagnosis of HD. The results of the multivariate analysis revealed that for HD survivors, each of the following variables had an independent effect on the rate of hypothyroidism: dose of neck irradiation, time since diagnosis of HD, age at diagnosis, and sex (Table 2). Although the incidence of hypothyroidism tended to be lower in subjects treated with radiation plus chemotherapy compared to those treated with radiation alone, controlling for dose of radiation to the thyroid eliminated these differences. The actuarial risk of developing an underactive thyroid 20 yr after a diagnosis of HD was 30% for subjects whose thyroid received 3500–4499 cGy and 50% for subjects whose thyroid received 4500 cGy or more (Fig. 2). For the patients who were treated with chemotherapy but no radiotherapy, seven (7.6%) had been diagnosed with an underactive thyroid.

TABLE 2. Risk factors for underactive thyroid

Covariate	Relative risk (95% CI)	*P* value
Radiation dose to thyroid		
<3500 cGy	3.8 (1.7–10.8)	0.004
3500–4499 cGy	5.5 (2.5–15.3)	0.0002
≥4500 cGy	10.7 (4.7–30.6)	<0.0001
Time since dx <5 yr	2.1 (1.7–2.6)	<0.0001
Female sex	1.7 (1.4–2.1)	<0.0001
Age at dx >15 yr	1.5 (1.2–1.9)	0.0001

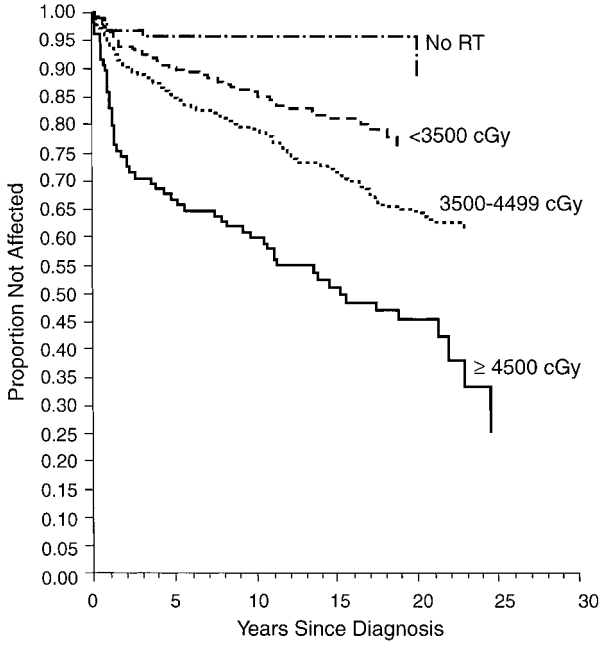

FIG. 2. Probability of developing an underactive thyroid after diagnosis of HD. Patients are grouped according to dose of thyroid irradiation. RT, Radiation.

Although the incidence of an overactive thyroid gland in subjects with HD was significantly greater than the incidence recorded in sibling controls (RR, 8; $P < 0.0001$; Table 1). The mean time between diagnosis of HD and development of hyperthyroidism was 8 yr (range, 0–22 yr). Dose of neck irradiation and time since diagnosis of HD were each independent predictors of an overactive thyroid gland (Table 3 and Fig. 3). Only 1 (1.1%) of the 92 survivors treated with chemotherapy alone had been diagnosed with an overactive thyroid.

Among the 456 subjects who had been told that they had an underactive thyroid gland, 380 (83%) indicated that they were currently taking some form of thyroid hormone replacement.

Overactive thyroid

TABLE 3. Risk factors for overactive thyroid

Covariate	Relative risk (95% CI)	*P* value
Time since dx <3 yr	2.2 (1.3–3.9)	0.005
Radiation dose to thyroid ≥3500 cGy	2.2 (1.2–4.7)	0.02

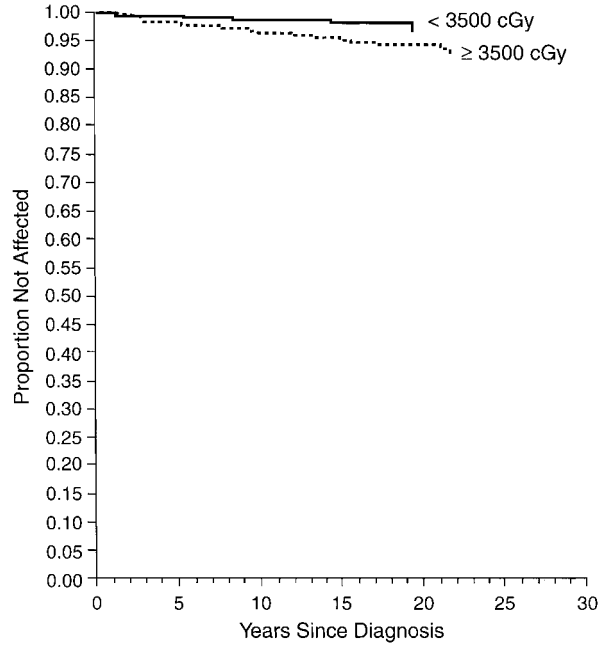

FIG. 3. Probability of developing an overactive thyroid after diagnosis of HD. Comparison between patients who received either less than 3500 cGy or 3500 cGy or more thyroid irradiation.

Among the 82 subjects who had been diagnosed with an overactive thyroid gland, 2 (2.4%) indicated that they were currently receiving antithyroid medication, whereas 17 (20%) indicated that they had undergone surgery to remove the thyroid gland.

Thyroid nodule

For HD survivors, the incidence of thyroid nodules was significantly increased when compared to that in sibling controls (RR, 27; $P < 0.0001$; Table 1). Thyroid nodules were diagnosed a mean of 14 yr (range, 0–27 yr) after diagnosis of HD. The multivariate analysis revealed that time since diagnosis of HD, sex, and dose of radiation to the thyroid were each independently associated with the development of thyroid nodules (Table 4). The actuarial risk of a female HD survivor developing a thyroid nodule 20 yr after being diagnosed with HD was 20% (Fig. 4). Among the survivors treated with chemotherapy but no radiotherapy, only one (1.1%) was diagnosed with thyroid nodule.

Of the 146 cases with thyroid nodules, 75 (51%) indicated that they had undergone thyroid surgery, and 102 (70%) were currently receiving thyroid hormone replacement.

Thyroid cancer

Among the 146 cases of thyroid nodules, 11 (7.5%) were found to have thyroid cancer. Additionally, there were 9 cases of thyroid cancer among the survivors who denied having had thyroid nodules. Thus, there were a total of 20 cases of thyroid cancer among the HD survivors (Table 5). The RR of thyroid cancer in the HD survivors was 18.3 compared to that in the general population, based on Surveillance, Epidemiology, and End Results Program data. The characteristics of patients diagnosed with thyroid cancer are indicated in Table 6.

TABLE 4. Risk factors for thyroid nodules

Covariate	Relative risk (95% CI)	*P* value
Time since dx ≥10 yr	4.8 (3.0–7.8)	0.0001
Female sex	4.0 (2.5–6.7)	0.0001
Radiation dose to thyroid ≥2500 cGy	2.9 (1.4–6.9)	0.007

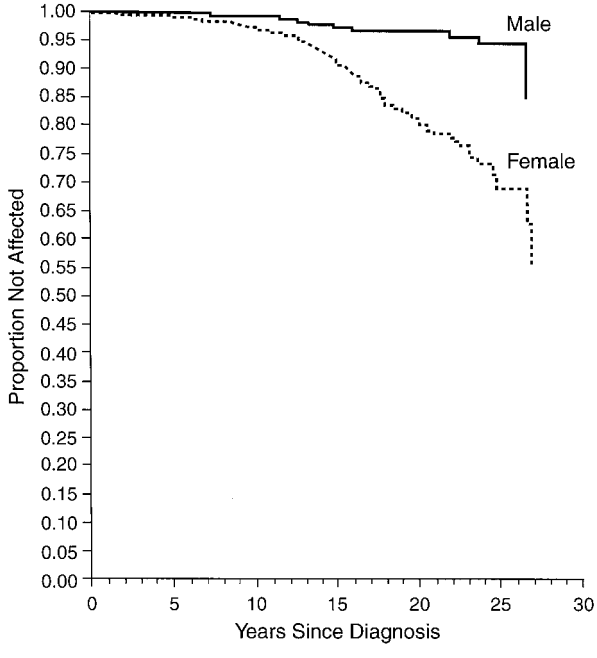

FIG. 4. Probability of developing a thyroid nodule after diagnosis of HD.

TABLE 5. Risk of thyroid cancer in HD survivors

Sex	Thyroid cancers		O/E ratio[a]	95% CI		*P* value
	Observed	Expected		Lower	Upper	
Male	6	0.2	30.0	11.9	60.8	0.0001
Female	14	0.9	15.7	8.9	25.5	0.0001
All persons	20	1.1	18.3	11.4	27.6	0.0001

[a] Compared to SEER data.

TABLE 6. Characteristics of cases with thyroid cancer

Variable	(n = 20)
Sex: M:F	6:14
Age at HD diagnosis, yr (median, range)	12.5, 6–20
Age at thyroid cancer diagnosis (median, range)	26, 13–40
Interval from HD to thyroid cancer (median, range)	15.5, 5–26
Thyroid irradiation: yes:no	15:1[a]
Dose of thyroid irradiation, cGy (median, range)	3500, 2500–3500
Histopathology	
Papillary carcinoma	15
Follicular carcinoma	5

[a] Treatment information not known for four cases.

Medical follow-up

As part of the baseline questionnaire, all participants were asked whether a physician or other member of a healthcare team had seen them during the preceding 2-yr period. The HD survivors were significantly more likely to have been seen than the sibling controls (91% *vs.* 83%; $P = 0.001$).

Discussion

In the current study we examined the incidence of and risk factors for abnormalities of the thyroid gland in 1791 survivors of HD diagnosed during childhood and adolescence. The data are based on responses to a self-administered questionnaire as well as extensive treatment information that was abstracted from individual medical records. In keeping with the data of prior, smaller series, thyroid abnormalities proved to be extremely common in this cohort of young adult survivors.

The most frequent disturbance of the thyroid was hypothyroidism, with a RR of 17.1 compared to that in siblings. It is important to note, however, that this RR is almost certainly an overestimate, as it fails to take into account the possibility that survivors were more likely to have been screened for thyroid dysfunction than were the healthy controls. It is possible that many more cases of subclinical hypothyroidism were diagnosed among the HD survivors compared to the sibling controls. Nonetheless, the cumulative incidence of hypothyroidism was 28% for HD survivors,

whereas the prevalence of subclinical hypothyroidism among healthy young adults is, at most, 5–6% (11, 12). Thus, even if every case of hypothyroidism identified among the HD survivors was due to subclinical disease, the incidence in survivors would be, at minimum, 4–5 times higher than expected.

The major risk factors identified in this study for an underactive thyroid were increasing dose of radiation, female sex, and older age at diagnosis. Whereas higher doses of irradiation have been found consistently to increase the risk of hypothyroidism (5–7, 13), the importance of age at diagnosis of HD and sex has been less clear. Hancock *et al.* (5) also found an increased incidence of hypothyroidism among their pediatric HD survivors in subjects who were treated at an older age. This was confounded, however, by the fact that in the Hancock study older subjects were more likely to have been treated with higher doses of radiation. Female sex has been identified as a risk factor in some adult series (5), but, to our knowledge, has not been demonstrated previously to be a risk factor for radiation-induced hypothyroidism after treatment during childhood/adolescence (6, 13–19).

Lymphangiogram is an additional factor that has been associated with hypothyroidism in some (13, 14, 20), but not all, studies (15). In the current study data regarding use of lymphangiogram were not routinely abstracted from the subjects' medical records, and thus, we were not able to include that information in our multivariate analysis.

The time course of the development of an underactive thyroid described in the current study is quite similar to the data reported by others. The greatest risk of hypothyroidism occurred during the first 5 yr after treatment, but new cases continued to emerge more than 20 yr after the diagnosis of HD (5).

The development of hyperthyroidism after treatment for HD has been reported by several groups, primarily in adult subjects treated with neck irradiation (5, 21, 22). Most commonly the clinical picture is identical to that of Graves' disease and is characterized by a diffusely enlarged thyroid gland, elevated levels of thyroid hormone, suppressed levels of TSH, increased thyroidal uptake of radioactive iodine, and the development of autoantibodies to the thyroid. Acute thyroiditis occurring during or shortly after neck irradiation can also cause hyperthyroidism, but this type of hyperthyroidism is usually transient and in most cases subclinical (23). Because of the small number of cases reported in the literature, it has been difficult to determine the true incidence of hyperthyroidism and to establish what the important risk factors might be.

In the present study the overall incidence of hyperthyroidism in HD survivors was 8-fold greater than that reported in sibling controls. It is noteworthy that the incidence of self-reported hyperthyroidism in our sibling controls (20 cases/100,000) is remarkably similar to the incidences of Graves' disease (17.7 and 19.8 cases/100,000) reported in 2 large population-based series in which the diagnosis of hyperthyroidism was established using standard clinical and hormonal criteria (24, 25). Moreover, the absolute risk of developing hyperthyroidism in our pediatric HD survivors (150–160 cases/100,000) is nearly identical to that reported by Hancock *et al.* (5) (170–188 cases/100,000). In the latter series, the majority of individuals were more than 20 yr of age at the time they were diagnosed and treated for HD.

The only patient or treatment variable associated with a greater risk of hyperthyroidism in our cohort was higher dose of radiation, similar to what was observed by the Stanford group (5). We did not observe a significant difference in the incidence of hyperthyroidism between males and females, in keeping with the observations of others (5, 22).

Thyroid neoplasms, both benign and malignant, are known to occur with increased frequency after neck irradiation. The incidence of thyroid nodules among HD survivors has varied from 2–65% (5, 7, 13, 16, 26, 27) depending upon the length of follow-up and the methods employed by the investigators (*i.e.* palpation *vs.* ultrasound) to examine the thyroid. The RR of thyroid cancer in pediatric HD survivors (9.7–67) has also varied greatly (5, 28–31). In our cohort, 9% of HD survivors reported a thyroid nodule, which was 27 times the incidence reported by sibling controls. Thyroid cancer was diagnosed in 20 subjects, which resulted in an overall RR of 18.3 compared to the general population. All thyroid cancers were well differentiated, and the majority were papillary carcinoma, as reported consistently by others. The latency period for the development of thyroid cancer varied from 5–26 yr.

Thyroid neoplasms were more likely to occur in females and in those treated with higher doses of radiation to the thyroid. For thyroid cancer, however, the absolute excess risk was greater for males than females. We did not find an association between younger age at treatment and the subsequent development of a thyroid neoplasm, as has been reported by others (28, 32, 33). This may be due to the relatively small number of individuals in our cohort who were treated during early childhood. In addition, most of the other series included primarily individuals who received low doses (<1000 cGy) of radiation to the thyroid, in contrast to the current study in which the dose to the thyroid was 1000 cGy or more in 95% of cases. Thus, at higher doses of radiation, age at exposure may not be as important a risk factor.

Considering that the HD survivors had an exposure that is known to result in thyroid neoplasms (*i.e.* radiation to the neck), it is likely that they have been subjected to more consistent and frequent medical surveillance (*e.g.* thyroid palpation and ultrasound) than the sibling controls. Such screening practices, particularly thyroid ultrasound, have been demonstrated to greatly increase the detection of thyroid nodules and thyroid cancer (26, 27). When these practices are applied to survivors but not to controls, the RR estimates can be greatly inflated (34). Thus, the RR estimates for thyroid nodules and thyroid cancer derived from this study are likely to be overestimated; unfortunately, we do not have sufficient data to quantify the extent of the surveillance bias.

The relationship between thyroid abnormalities and radiation dose has important implications for the treatment of HD. Our findings underscore the need to perform dose calculations to the neck, where a compensating device may be necessary to prevent the thyroid dose from exceeding the prescribed dose to the tumor. Current combined modality regimens for pediatric HD employ lower doses to limited

fields (4). This should result in a lower rate of thyroid abnormalities in future generations of HD survivors.

There are some limitations to this study, in addition to the issue of ascertainment bias, that need to be taken into account when interpreting our findings. For the three main end points of the study (*i.e.* incidences of hypothyroidism, hyperthyroidism, and thyroid nodules), we have relied solely on patient report; we did not attempt to verify these diagnoses by independent chart review or physician report. Thus, we cannot be certain of the precise rate of these thyroid abnormalities, nor do we know the exact diagnosis (*e.g.* antibody-positive *vs.* antibody-negative hypothyroidism, Graves' disease *vs.* toxic nodular goiter) in either our HD survivors or the sibling controls. However, the high concordance between self-report of hypothyroidism and use of thyroid medication in HD survivors, the high rate of thyroid surgery among the subjects with a diagnosis of thyroid nodules, and the similar rates of hyperthyroidism reported by our controls and population-based studies support the validity of these self-reported diagnoses. In further support of our data are the findings of a recent study of childhood cancer survivors that employed medical record validation of patient-reported complications. In that study the correlation between self-report and the medical record for endocrine disorders was nearly 100% (Louie, A. D., *et al.*, personal communication).

In conclusion, young adult HD survivors who were treated with high doses of radiation to the thyroid gland are at substantially increased risk for the development of a spectrum of abnormalities of the thyroid. Female survivors are at particularly high risk for developing hypothyroidism and thyroid nodules. Healthcare providers who encounter adult HD survivors will need to incorporate these findings into their clinical practice. Periodic testing of thyroid function along with careful palpation of the thyroid gland must be performed routinely and throughout the entire lifespan of HD survivors.

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