Cancer Mortality Following Treatment for Adult Hyperthyroidism

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Context.—High-dose iodine 131 is the treatment of choice in the United States for most adults with hyperthyroid disease. Although there is little evidence to link therapeutic ^{131}I to the development of cancer, its extensive medical use indicates the need for additional evaluation.

Objective.—To evaluate cancer mortality among hyperthyroid patients, particularly after ^{131}I treatment.

Design.—A retrospective cohort study.

Setting.—Twenty-five clinics in the United States and 1 clinic in England.

Patients.—A total of 35 593 hyperthyroid patients treated between 1946 and 1964 in the original Cooperative Thyrotoxicosis Therapy Follow-up Study; 91% had Graves disease, 79% were female, and 65% were treated with ^{131}I.

Main Outcome Measure.—Standardized cancer mortality ratios (SMRs) after 3 treatment modalities for hyperthyroidism.

Results.—Of the study cohort, 50.5% had died by the end of follow-up in December 1990. The total number of cancer deaths was close to that expected based on mortality rates in the general population (2950 vs 2857.6), but there was a small excess of mortality from cancers of the lung, breast, kidney, and thyroid, and a deficit of deaths from cancers of the uterus and the prostate gland. Patients with toxic nodular goiter had an SMR of 1.16 (95% confidence interval [CI], 1.03-1.30). More than 1 year after treatment, an increased risk of cancer mortality was seen among patients treated exclusively with antithyroid drugs (SMR, 1.31; 95% CI, 1.06-1.60). Radioactive iodine was not linked to total cancer deaths (SMR, 1.02; 95% CI, 0.98-1.07) or to any specific cancer with the exception of thyroid cancer (SMR, 3.94; 95% CI, 2.52-5.86).

Conclusions.—Neither hyperthyroidism nor ^{131}I treatment resulted in a significantly increased risk of total cancer mortality. While there was an elevated risk of thyroid cancer mortality following ^{131}I treatment, in absolute terms the excess number of deaths was small, and the underlying thyroid disease appeared to play a role. Overall, ^{131}I appears to be a safe therapy for hyperthyroidism.

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A complete list of the members of the Cooperative Thyrotoxicosis Therapy Follow-up Study Group appears at the end of this article.

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HYPERTHYROID DISEASE is relatively common, particularly among women. The incidence of Graves disease, the cause of over 80% of hyperthyroidism in the United States, is between 0.02% and 1%.[1-3] Hyperthyroidism can be treated with radioiodine (iodine 131), surgery (subtotal thyroidectomy), or antithyroid drugs, but ^{131}I is the treatment of choice for most adults in the United States.[4] The extensive use of ^{131}I therapy has raised concern regarding its potential carcinogenic and leukemogenic effects, although there is little evidence to support this concern.[5-9] Public interest in the late health effects of ^{131}I exposure was rekindled by the 1986 Chernobyl accident and acknowledgment of past ^{131}I releases from nuclear reactors and bomb testing.

The Cooperative Thyrotoxicosis Therapy Follow-up Study began in 1961. It included 35 609 patients with hyperthyroidism treated between 1946 and 1964 at one of 26 study clinics. When the study ended in 1968, after a mean follow-up of 8.2 years, thyroid cancer incidence and mortality[10] and leukemia incidence[5] were not significantly elevated in the ^{131}I-treated patients compared with other patients. In a more recent follow-up of patients from the Mayo Clinic, Rochester, Minn, and Massachusetts General Hospital, Boston, total cancer mortality was not associated with ^{131}I therapy.[11,12] However, the incidence of cancers in organs that concentrate iodine was elevated (relative risk [RR], 1.8; 95% confidence interval [CI], 1.1-3.2) among the ^{131}I-treated patients at the Mayo Clinic,[13] and

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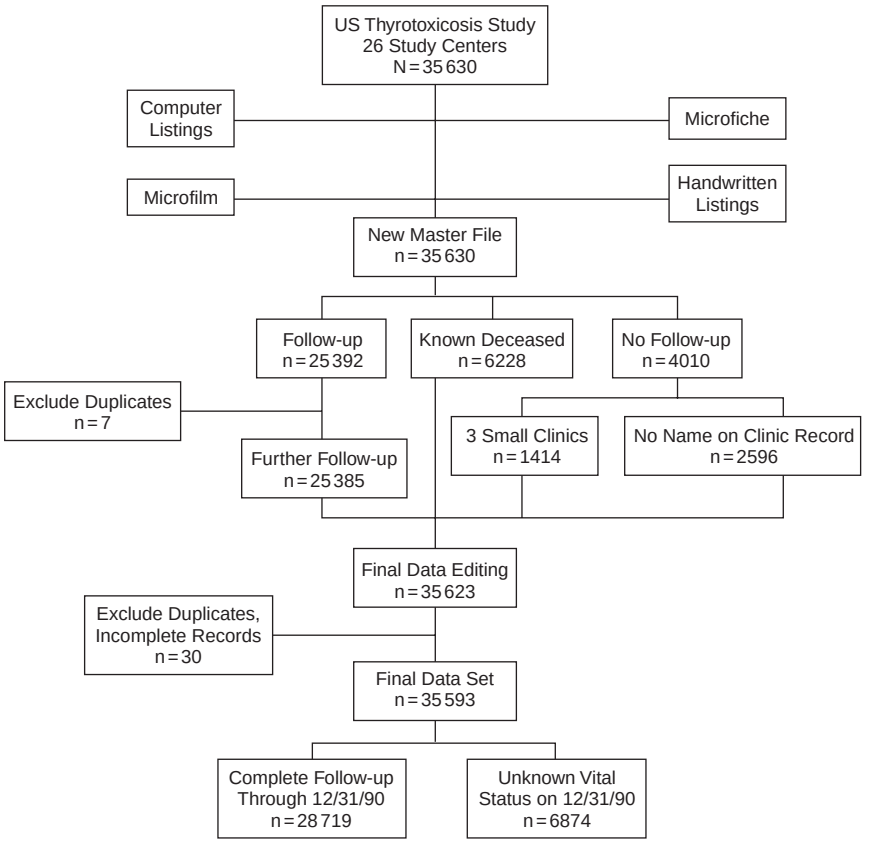
breast cancer incidence was slightly increased (RR, 1.3; 95% CI, 0.8-1.9) in the Massachusetts General Hospital patients.[14] Although no association between ^{131}I exposure and mortality from leukemia (standardized mortality ratio [SMR], 0.98; 95% CI, 0.64-1.42) or breast cancer (SMR, 0.86; 95% CI, 0.69-1.02) was seen among Swedish hyperthyroid patients, a significant excess of respiratory (SMR, 1.26; 95% CI, 1.04-1.49) and digestive (SMR, 1.14; 95% CI, 1.03-1.25) cancer mortality was observed. During the first 10 years of follow-up, there was an excess of thyroid cancer mortality (SMR, 3.22; 95% CI, 1.54-5.98), which completely disappeared after 10 years (SMR, 0.66; 95% CI, 0.08-2.37).[15] To assess the long-term carcinogenic effects of treatment for hyperthyroidism, we conducted a mortality follow-up, through 1990, of the original Cooperative Thyrotoxicosis Therapy Follow-up Study population.

Table 1.—Study Population by Treatment Center

Treatment Center	No. (%) of Patients*
Mayo Clinic, Rochester, NY	5068 (14.2)
Lahey Clinic, Boston, Mass	4282 (12.0)
Mount Sinai Hospital, New York, NY	3169 (8.9)
Cedars Sinai Medical Center, Los Angeles, Calif	2514 (7.1)
Columbia Presbyterian Hospital, New York, NY	2373 (6.7)
Massachusetts General Hospital, Boston	2345 (6.6)
Los Angeles County, Los Angeles, Calif†	1786 (5.0)
New York Hospital–Cornell Medical Center, New York	1473 (4.1)
University of Michigan, Ann Arbor	1275 (3.6)
University Hospitals of Cleveland, Cleveland, Ohio	1111 (3.1)
University of California, San Francisco	1064 (3.0)
Beth Israel Hospital, Boston, Mass	1042 (2.9)
University of Maryland, Baltimore	978 (2.7)
Montefiore Medical Center, New York, NY	952 (2.7)
White Memorial Hospital, Los Angeles, Calif	841 (2.4)
University of Cincinnati, Cincinnati, Ohio	785 (2.2)
St Louis University, St Louis, Mo‡	762 (2.1)
Ochsner Clinic, New Orleans, La‡	585 (1.6)
Memorial Sloan-Kettering Hospital, New York, NY	573 (1.6)
Strong Memorial Hospital, Rochester, NY‡	466 (1.3)
Cleveland Metropolitan General Hospital, Cleveland, Ohio	450 (1.3)
Sheffield, England	1699 (4.8)

*Includes the 35 593 in final study population.
†Includes Veterans Affairs Wadsworth, Veterans Affairs Long Beach, University of California, Los Angeles, University of Southern California, and some private clinics.
‡For technical reasons, follow-up for these centers was not conducted during the current study.



Description of study data flow.

METHODS

The original Cooperative Thyrotoxicosis Therapy Follow-up Study included all hyperthyroid patients treated with ^{131}I, thyroid surgery, antithyroid drugs, or any combination of these treatments, between January 1, 1946, and December 31, 1964, at 25 US and 1 British medical center (Table 1). Comprehensive clinical data were abstracted from medical records and hyperthyroidism was classified as Graves disease in 91% of the patients, toxic nodular goiter in 8%, and unknown in 1%. Forty percent of the patients were known to have received some treatment for hyperthyroidism prior to study entry; 75% of these patients had received antithyroid drugs only, 22% had undergone thyroidectomy alone or in combination with antithyroid drugs, and 2% had received ^{131}I therapy with or without other treatments. Follow-up information was obtained from the treating physician or clinic or from the patient when no medical source was available. At the end of the first follow-up, 6228 patients (17.5%) had died and 1432 (4.0%) were lost to follow-up. The original study methods have been described by Saenger et al,[5] Dobyns et al,[10] Becker et al,[16] and Tompkins.[17]

Using computer lists, microfiche, microfilm cassettes, and handwritten material, a master file of 35 630 patients from the original study was assembled in 1984 (Figure). The National Cancer Institute worked with 4 regional study centers, Harvard University, Boston, Memorial Sloan-Kettering Cancer Center, New York, NY, University of Southern California, Los Angeles, and Research Triangle Institute, Research Triangle Park, NC, to conduct a second mortality follow-up of the study cohort. Follow-up was not attempted for 4010 patients, including 1414 patients from 3 small treatment centers not in the geographical areas of the other centers and 2596 patients whose names had been removed from the medical records by the treatment clinics after completion of the first study. The exclusion of these patients from further follow-up was due to technical reasons and was in no way related to patient characteristics. With these exclusions, 31 620 patients were eligible for further follow-up. Since 6228 patients were known to have died during the first follow-up, 25 392 patients remained to be traced. After supplemental identification data were abstracted, study subjects were traced using records from the National Death Index, Health Care Financing Administration, Social Security Administration, state vital statistics offices, state motor vehicle administrations, local tracing resources, and commercial tracing companies. Copies of death certificates were obtained for deceased patients and were coded according to the *International Classification of Diseases, Eighth Edition* (*ICD-8*).[18] Causes of death from the first study were recoded from the *International Classification of Diseases, Seventh Edition* (*ICD-7*)[19] to *ICD-8* by trained nosologists. After final editing of the data tape, 35 593 patients were included in the study cohort.

In the main analyses, we compared the observed number of deaths with the expected number based on US national mortality rates. Person-years at risk were computed for each patient from the date of study entry (the first time a patient visited a participating study clinic during the study enrollment period) until the date of death, the date last known to be alive for those lost to follow-up, or the end of follow-up (December 31, 1990) for those known to be alive. Standardized mortality ratios (the ratio of observed to expected number of deaths) and 95% CIs were computed assuming a Poisson distribution for the observed number. Cause-specific expected numbers of deaths were calculated by applying the

age-, sex-, race-, and calendar-year–specific mortality rates to the appropriate person-years at risk.[20] Because we were using US mortality rates as the comparison population, the 1699 patients from England had to be excluded from these analyses. In addition, we excluded 146 patients for whom information on sex, date of birth, or date of study entry was missing, leaving 33 748 patients.

The SMR analyses were performed separately for patients with Graves disease and toxic nodular goiter and for 7 treatment categories: ^{131}I treatment only; ^{131}I treatment and surgery; ^{131}I treatment and drugs; ^{131}I treatment, surgery, and drugs; surgery only; surgery and drugs; and drugs only. Because results were virtually the same for the 4 groups of patients treated with ^{131}I and for the 2 surgery groups, we present results for combined treatment groups. Dates of onset of treatment were unknown for patients receiving drug therapy; however, since 98% of the ^{131}I-treated patients and 78% of patients who underwent surgery received their first treatment within 2 years of study entry, study entry date was used as a surrogate date for evaluation of latency. Only 231 patients had surgery before ^{131}I treatment. Since deaths occurring within 1 year of study entry are not likely to be caused by treatment for hyperthyroidism, these deaths were excluded in all analyses related to treatment. As in all mortality analyses using US national mortality rates as a comparison, patients with preexisting cancers were not excluded because they are included in the national rates.

Doses from ^{131}I to 17 organs were estimated for study subjects by multiplying the amount of administered activity by the dose factors (age [1, 5, 10, 15, and >15 years old], and 24-hour thyroid uptake [0%, 25%, 35%, 45%, and 55%]) provided for each organ in current International Commission on Radiological Protection tables.[21] Fewer than 500 patients were aged 15 years or younger and most patients (70%) had at least one 24-hour thyroidal ^{131}I uptake greater than 55%. Because many clinics treated all patients with a standard amount of administered activity, thyroid uptake measurements were not performed before treatment. We estimated these uptakes using the experience of the 3162 uptakes performed within 1 month prior to treatment, modeled on sex, age at treatment, number of treatments, calendar year of treatment, clinic, type of hyperthyroidism, and administered activity of ^{131}I. We did not estimate dose to the thyroid because gland size, dose distribution, and effective half-life must be known. However, at least 50 to 70 Gy delivered to the thyroid is usual when treating hyperthyroidism.[22] Only 3 other organs received an average ^{131}I dose above 100 mGy: stomach (178 mGy), bladder (128 mGy), and small intestine (108 mGy). The average estimated dose to the red bone marrow was 42 mGy and to the breast was 32 mGy. Using a different method of estimation, Saenger et al[5] reported the mean bone marrow dose to be between 80 and 160 mGy. Their estimate is 2 to 4 times higher than ours, probably because based on information from the literature at that time,[23,24] they assumed that the blood dose was 1.7 times the administered activity and that the bone marrow dose was between 46% and 86% of the blood dose. More recently, Zanzonico et al[25] reconstructed doses for 468 patients from the original study group and their results were similar to ours: for patients with Graves disease, average doses to the bladder, red bone marrow, and breast were 190 mGy, 50 mGy, and 30 mGy, respectively. To ensure that the imputed uptakes did not significantly affect the analyses, we also estimated doses assuming all unknown uptakes to be 25% and 55% (the lower and upper limits used in the International Commission on Radiological Protection tables). Dose estimates based on 55% uptakes were similar to those based on the imputed uptakes. When 25% uptakes were assumed, dose estimates were somewhat lower, but few hyperthyroid patients would have uptakes below 50%.

Because of particular interest in thyroid, hematopoietic, and lymphoproliferative malignancies, we used Poisson regression methods for analysis of grouped cohort time-to-exposure data to evaluate the relationship between deaths from hematopoietic and lymphoproliferative malignancies and ^{131}I administered activity, as well as estimated absorbed bone marrow dose. For thyroid mortality, we could only assess administered activity of ^{131}I because we were unable to estimate organ doses. Since these analyses did not use an external comparison, we included the patients from England, but excluded patients with cancers diagnosed before study entry. The data were cross-classified by sex, age at treatment (0-29, 30-39, 40-49, 50-59, and ≥60 years), time since treatment (0-4, 5-9, 10-19, and ≥20 years), type of hyperthyroidism (Graves disease, toxic nodular goiter), administered ^{131}I activity (0, 0.01-4, 5-6, 7-9, 10-14, 15-19, and ≥20 mCi), and for the analysis of hematopoietic and lymphoproliferative malignancies, red bone marrow dose estimates (0, 0.1-14, 15-19, 20-24, 25-29, 30-39, 40-49, 50-79, and ≥80 mGy). We fit a linear excess RR dose-response model (the background disease rate among the nonexposed × [1 + the excess RR]), taking the described covariates into consideration. Background rates were stratified by sex, age at treatment, time since treatment, and type of hyperthyroidism. Maximum likelihood parameter estimates were obtained, and likelihood ratio tests were used to assess the significance of the dose response.[26] Trend tests were calculated using ^{131}I exposure as a continuous variable. EPICURE software (HiroSoft International Corp, Seattle, Wash) was used for these analyses.[27]

RESULTS

At the end of follow-up, the 35 593 study subjects (79% female) had 738 831 person-years of follow-up. The mean age at study entry was 46 years and 3% were younger than 20 years. There were 10 760 patients (30.2%) still alive, 17 959 (50.5%) were deceased, and 6874 (19.3%) were lost to follow-up. Eighty-eight percent of the study population had 5 to 10 years of follow-up and 76% had 10 years or more. The mean length of follow-up from first clinic visit was 21 years (range, 1-44 years). Overall follow-up was better for men (83% vs 79% for women), older patients (86% for those ≥50 years at study entry vs 77% for those <50 years), and patients treated with surgery (88% vs 78% for ^{131}I and 75% for drug treatment). The difference by treatment group is due to the low proportion of surgery patients (13%) in the group of 4010 patients for whom follow-up was not conducted for technical reasons. There were no differences in follow-up by treatment among the 31 620 patients for whom follow-up was conducted in the current study (92%, 92%, and 90% for surgery, ^{131}I treatment, and drug treatment, respectively).

Approximately 65% of the study subjects had been treated with ^{131}I; 25% had received ^{131}I treatment alone and 39% had received ^{131}I in addition to surgery and/or drugs (Table 2). The average ^{131}I administered activity was 6.1 mCi (SD, 5.2) per treatment. Patients treated with ^{131}I received 1.8 treatments on average, resulting in a cumulative mean total administered activity of 10.4 mCi (5th-95th percentile = 3, 27 mCi). Both the mean number of treatments and cumulative administered activity were higher in patients with toxic nodular goiter (2.1 treatments and 17.0 mCi) compared with patients with Graves disease (1.7 treatments and 10.0 mCi). The mean ^{131}I thyroidal uptake was 62.4% among the 20 639 patients for whom an uptake value was recorded at first examination. Slightly more than 40% of the patients underwent surgery, almost always in conjunction with antithyroid drugs. Only 4% of the patients received drug therapy alone. Women were younger and had surgery somewhat more frequently than men, and patients receiving surgery or drug therapy alone were

slightly younger than those treated with ^{131}I. Patients with Graves disease were more likely to receive ^{131}I treatment (65% of the Graves patients) than surgery (30.7%) or antithyroid drugs (3.8%). In contrast, 43.2% of the patients with toxic nodular goiter received ^{131}I therapy compared with 54.5% treated surgically and 2.3% treated with drugs.

At the time of study entry, 1082 patients had a history of 1338 prior cancers. Twenty-three percent of these patients died of a malignancy during the study period. Patients treated with drug therapy alone had the highest crude rate (39.3 in 1000 patients) of previous cancers, those treated with ^{131}I had an intermediate rate (14.2 in 1000 patients), and those treated surgically had the lowest rate (5.5 in 1000 patients), except for patients with a history of prior thyroid cancer who most often were treated surgically for their hyperthyroidism.

All Treatments

All Patients.—Overall, 16 683 deaths (49.4%) occurred among the 33 748 patients from the United States with known date of birth, date of study entry, and sex. Cause of death was known for all but 111 of the deceased subjects. Cancer was the primary cause of death for 2950 patients, whereas 2857.6 deaths from cancer (SMR, 1.03) were expected (Table 3). The risk of death from cancer varied by years of follow-up, but was significantly elevated only during the first 4 years (SMR, 1.31; 95% CI, 1.19-1.43), particularly during the first year (SMR, 1.52; 95% CI, 1.25-1.84). During the entire study period, deaths from cancers of the lung (SMR, 1.11), breast (SMR, 1.17), kidney (SMR, 1.31), and thyroid (SMR, 2.77) were significantly elevated compared with the US population. For all 4 cancer types, the SMRs were highest within 5 years of study entry, and only thyroid cancer mortality remained significantly higher than expected 10 or more years after study entry (SMR, 2.01; 95% CI, 1.10-3.37).

Mortality from cancers of the liver, larynx, uterus, and prostate occurred significantly below expectation. No excess deaths from lymphoma, leukemia, or hematopoietic and lymphoproliferative malignancies as a group were apparent over the entire study period, but leukemia mortality was increased 5 to 9 years after study entry (SMR, 1.62; 95% CI, 1.01-2.45).

Because 79% of the study population was female, their mortality experience dominates the overall evaluations. Among women, 2252 cancer deaths were observed compared with 2101.8 expected (SMR, 1.07; 95% CI, 1.03-1.12), and an excess of lung (SMR, 1.28; 95% CI, 1.14-1.44), breast (SMR, 1.17; 95% CI, 1.07-1.28), kidney (SMR, 1.37; 95% CI, 1.00-1.83), and thyroid (SMR, 2.66; 95% CI, 1.70-

Table 2.—Selected Characteristics of Study Population by Treatment

Treatment	Female, No. (%)	Male, No. (%)	Total, No. (%)	Age, Mean, y*	Follow-up, Mean, y
Iodine 131	18 020 (63.8)	5000 (68.1)	23 020 (64.7)	49.0	18.9
Iodine 131 only	7029 (24.9)	1999 (27.2)	9028 (25.4)	49.9	18.0
Iodine 131 and drugs	7999 (28.3)	2440 (33.2)	10 439 (29.3)	49.5	18.5
Iodine 131 and surgery	757 (2.7)	135 (1.8)	892 (2.5)	48.3	19.7
Iodine 131 and surgery and drugs	2235 (7.9)	426 (5.8)	2661 (7.5)	44.5	23.1
Surgery (no iodine 131)	9119 (32.3)	2080 (28.3)	11 199 (31.5)	41.6	26.2
Surgery only	654 (2.3)	164 (2.2)	818 (2.3)	50.8	22.7
Surgery and drugs	8465 (30.0)	1916 (26.1)	10 381 (29.2)	40.8	26.5
Drugs only	1094 (3.9)	260 (3.6)	1374 (3.8)	44.9	17.8
Total†	**28 248 (100.0)**	**7345 (100.0)**	**35 593 (100.0)**	46.5	21.2

*Data are mean age at the time of study entry.
†Total includes 15 female and 5 male patients with unknown or other treatment.

Table 3.—Observed and Expected Cancer Mortality Among US Hyperthyroid Patients*

	Years Between Study Entry and Cancer Death							
	0-4 (n = 33 748)†		5-9 (n = 29 581)†		≥10 (n = 25 285)†		Total (N = 33 748)†	
Type of Malignancy	Observed/ Expected	SMR (95% CI)‡	Observed/ Expected	SMR (95% CI)‡	Observed/ Expected	SMR (95% CI)‡	Observed/ Expected	SMR (95% CI)‡
All malignancies	479/366.40	1.31 (1.19-1.43)	402/389.84	1.03	2069/2101.39	0.98	2950/2857.64	1.03
All solid cancers	443/338.59	1.31 (1.19-1.44)	358/358.15	1.00	1893/1913.39	0.99	2694/2610.13	1.03
Buccal cavity	9/6.26	1.44	6/6.85	0.88	36/34.50	1.04	51/47.60	1.07
Digestive tract	143/121.32	1.18	118/126.04	0.94	610/612.52	1.00	871/859.88	1.01
Esophagus	1/4.84	0.21	6/5.40	1.11	30/30.33	0.99	37/40.57	0.91
Stomach	35/26.31	1.33	24/24.24	0.99	82/83.16	0.99	141/133.72	1.05
Colorectal	66/55.73	1.18	73/59.90	1.22	313/312.46	1.00	452/428.09	1.06
Liver	10/14.85	0.67	5/13.84	0.36 (0.12-0.84)	45/48.91	0.92	60/77.59	0.77 (0.59-1.00)
Pancreas	25/16.64	1.50	8/19.50	0.41 (0.18-0.81)	128/116.99	1.09	161/153.13	1.05
Larynx	2/2.08	0.96	1/2.27	0.44	5/11.65	0.43	8/16.00	0.50 (0.22-0.99)
Lung	54/33.84	1.60 (1.20-2.08)	55/42.87	1.28	391/374.83	1.04	500/451.53	1.11 (1.01-1.21)
Breast	80/55.44	1.44 (1.14-1.80)	68/58.01	1.17	312/279.94	1.11	460/393.37	1.17 (1.06-1.28)
Uterus	34/38.48	.088	19/34.04	0.56 (0.34-0.87)	64/101.71	0.63 (0.48-0.80)	117/174.23	0.67 (0.56-0.80)
Ovary§	22/19.08	1.15	26/19.99	1.30	104/98.09	1.06	152/137.16	1.11
Prostate	9/7.31	1.23	8/8.95	0.89	43/65.90	0.65 (0.47-0.88)	60/82.16	0.73 (0.56-0.94)
Bladder	10/7.96	1.26	5/8.78	0.57	49/47.05	1.04	64/63.79	1.00
Kidney	17/5.94	2.86 (1.67-4.58)	7/6.57	1.07	42/37.77	1.11	66/50.28	1.31 (1.02-1.67)
Brain, nervous system	5/7.24	0.69	9/7.48	1.20	41/37.57	1.09	55/52.29	1.05
Thyroid	13/1.74	7.47 (3.97-12.78)	2/1.76	1.14	14/6.97	2.01 (1.10-3.37)	29/10.47	2.77 (1.85-3.98)
All hematopoietic and lymphoproliferative	36/27.81	0.77	44/31.69	1.39 (1.01-1.86)	176/188.00	0.94	256/247.50	1.03
Lymphoma	16/13.39	1.24	13/14.46	0.90	69/75.28	0.92	98/103.13	0.95
Leukemia	15/12.55	1.19	22/13.59	1.62 (1.01-2.45)	81/73.16	1.11	118/99.29	1.19

*Data exclude British patients.
†The number of person-years for 0 to 4 years between study entry and cancer death is 158 654; for 5 to 9 years, 137 290; for 10 or more years, 420 715; and the total number of person-years is 716 659.
‡SMR indicates standardized mortality ratio; CI, confidence interval. Confidence intervals are shown for SMRs significant at 5% level.
§Data include other and unspecified female genital cancers.

3.95) cancer mortality was observed. A deficit of mortality from cancers of the uterus (corpus and cervix) also was seen (SMR, 0.67; 95% CI, 0.55-0.80). Five or more years after study entry, only mortality from lung and thyroid cancer remained in excess, but the deficit of deaths from cancer of the uterus was still observed. For men, the overall risk of cancer mortality was lower than expected (SMR, 0.92; 95% CI, 0.86-0.99). Based on only 5 deaths, the risk of thyroid cancer was elevated (SMR, 3.51; 95% CI, 1.13-8.18), largely because of a 14-fold excess (95% CI, 2.35-33.72) during the first 4 years of follow-up. Deficits of laryngeal (SMR, 0.29; 95% CI, 0.006-0.83) and prostate (SMR, 0.73; 95% CI, 0.56-0.94) cancer mortality were evident.

Patients With Graves Disease and Toxic Nodular Goiter.—An increase in overall cancer mortality was not associated with Graves disease (SMR, 1.02; 95% CI, 0.98-1.06), but was 16% higher than expected among patients with toxic nodular goiter (SMR, 1.16; 95% CI, 1.03-1.30) (Table 4). Among Graves disease patients, mortality from cancers of the breast, kidney, and thyroid was elevated, but again the excess risks were observed only during the first 4 years of follow-up. Deaths from cancers of the liver, larynx, uterus, and prostate as well as multiple myeloma were lower than expected. Among patients with toxic nodular goiter, excess deaths from lung, breast, and thyroid malignancies were observed and were seen 5 or more years after study entry (SMR for lung cancer, 1.46 [95% CI, 1.01-2.06]; for breast cancer, 1.45 [95% CI, 1.03-1.98]; and for thyroid cancer, 4.3 [95% CI, 1.16-11.01]).

Table 4.—Cancer Mortality Among US Hyperthyroid Patients by Thyroid Disease*

Type of Malignancy	Graves Disease (n = 30 725)† Observed/ Expected	Graves Disease (n = 30 725)† SMR (95% CI)‡	Toxic Nodular Goiter (n = 2694)† Observed/ Expected	Toxic Nodular Goiter (n = 2694)† SMR (95% CI)‡
All	2617/2574.70	1.02	298/257.19	1.16 (1.03-1.30)
Buccal cavity	48/43.36	1.11	2/3.86	0.52
Digestive tract	777/759.06	1.02	81/92.01	0.88
Esophagus	31/37.10	0.84	6/3.17	1.89
Stomach	117/116.26	1.01	19/15.97	1.19
Colorectal	411/377.40	1.09	34/46.25	0.74
Liver	51/67.39	0.76 (0.56-1.00)	8/9.29	0.86
Pancreas	149/137.03	1.09	12/14.69	0.82
Larynx	6/14.84	0.40 (0.15-0.88)	2/1.06	1.88
Lung	453/422.09	1.07	43/26.60	1.62 (1.17-2.18)
Breast	405/355.22	1.14 (1.03-1.26)	48/34.48	1.39 (1.03-1.85)
Uterus	98/154.76	0.63 (0.51-0.77)	19/17.65	1.08
Ovary§	139/123.85	1.12	12/12.03	1.00
Prostate	51/74.77	0.68 (0.51-0.90)	9/6.74	1.34
Bladder	59/56.01	1.05	5/7.12	0.70
Kidney	61/45.46	1.34 (1.03-1.72)	3/4.38	0.68
Brain	49/48.80	1.00	6/3.13	1.92
Thyroid	19/9.12	2.08 (1.25-3.25)	8/1.23	6.53 (2.80-12.82)
CLL	26/22.84	1.14	5/3.02	1.66
Non-CLL	80/65.95	1.21	6/6.72	0.89
Lymphoma	86/93.28	0.92	10/8.96	1.12
Myeloma	25/38.53	0.65 (0.42-0.96)	5/3.47	1.44

*Data exclude British patients. SMR indicates standard mortality ratio; CI, confidence interval; CLL indicates chronic lymphatic leukemia and includes chronic and unspecified lymphocytic leukemia (*International Classification of Diseases, Eighth Revision*, codes 204.1, 204.9); non-CLL includes acute lymphocytic leukemia, all myeloid and monocytic leukemia, and other and unspecified leukemia (*International Classification of Diseases, Eighth Revision*, codes 204.0, 205, 206, 207).

†The 329 patients whose disease type is unknown are excluded from the analyses. The number of person-years for those with Graves disease is 669 231; and for toxic nodular goiter, 42 465.

‡Confidence intervals are shown for SMRs significant at 5% level.

§Data include other and unspecified female genital cancer.

^{131}I Treatment

Cancer mortality relative to treatment was evaluated excluding the first year of follow-up (Table 5). Although almost 21 000 people with over 385 000 person-years of follow-up were studied, the overall cancer risk for patients treated with ^{131}I was close to that expected using national cancer mortality rates (SMR, 1.02; 95% CI, 0.98-1.07). Mortality from thyroid cancer (SMR, 3.94; 95% CI, 2.52-5.86) was raised, but mortality from cancers of the uterus and prostate was below expectation. Among the 8054 patients treated with ^{131}I only, findings were similar. To ensure that the elevated thyroid cancer mortality was not due to the 4 patients who had thyroid cancer prior to entering the study, we also analyzed the data excluding them. The SMR was still substantially increased (SMR, 3.28).

Between 1 and 5 years after follow-up, significantly elevated SMRs (Table 6) were observed for all cancer mortality (SMR, 1.24; 95% CI, 1.10-1.40) and mortality from colorectal cancer (SMR, 1.42; 95% CI, 1.04-1.90). Deaths from lung cancer (SMR, 1.44; 95% CI, 1.13-1.81) and non–chronic lymphatic leukemia (non-CLL) (SMR, 1.88; 95% CI, 1.18-2.84) were in excess within the first 9 years. After 10 years of follow-up only thyroid cancer mortality remained significantly increased. There were no observed or expected thyroid cancer deaths among the 365 patients treated with ^{131}I before age 20 years.

Among patients with Graves disease treated with ^{131}I (Table 7), thyroid cancer mortality was increased (SMR, 2.84; 95% CI, 1.62-4.61), but it was not significantly elevated 5 or more years after follow-up (SMR, 1.88; 95% CI, 0.86-3.57). An excess of total cancer deaths (SMR, 1.31; CI, 1.07-1.58) and mortality from cancers of the esophagus, uterus (particularly corpus uteri), and thyroid were observed among toxic nodular goiter patients receiving ^{131}I therapy (Table 7). Mortality from cancers of the esophagus (SMR, 5.26; CI, 1.42-13.5), corpus uteri (SMR, 3.0; CI, 1.09-6.53), and thyroid (SMR, 11.1; CI, 2.26-32.5) remained high in patients with toxic nodular goiter more than 5 years after study entry.

Significant relationships between the number of ^{131}I treatments and overall cancer mortality (SMR, 1.00, 1.09, and 0.99 for 1, 2-4, and ≥5 treatments, respectively) or individual cancer sites, except thyroid cancer, were not observed (data not shown). Restricting the analysis to either 5 years or 10 or more years after study entry did not modify these conclusions. The SMRs for thyroid cancer deaths increased with increasing number of treatments during the study period (2.74, 6.21, and 6.61 for 1, 2-4, and ≥5 treatments, respectively), as well as for the period beginning 10 years after study entry (2.66, 4.48, and 5.43 for 1, 2-4, and ≥5 treatments, respectively).

Table 7 provides some evidence of a relationship between administered ^{131}I activity and total cancer mortality, as well as mortality from lung and thyroid cancer. However, at 10 or more years after study entry, the relationship with administered activity was less notable; the SMRs for less than 7 mCi, 7-15 mCi, and 15 mCi or more administered activity were 0.90, 1.03, and 1.06, respectively, for all cancer mortality; 0.83, 1.03, and 1.21, respectively, for lung cancer mortality; and 1.85, 4.11, and 1.59, respectively, for thyroid cancer mortality (data not shown). An evaluation of ^{131}I activity by type of hyperthyroidism indicated that thyroid cancer mortality increased with increasing administered activity for patients with Graves disease. Among

Table 5.—Cancer Mortality Among US Hyperthyroid Patients by Treatment Group*

	Treatment Group							
	Any Iodine 131 (n = 20 949)†		Iodine 131 Only (n = 8054)†		Surgery With or Without Drugs (n = 10 876)†		Drugs Only (n = 1177)†	
Type of Malignancy	Observed Mortality	SMR (95% CI)‡	Observed Mortality	SMR (95% CI)‡	Observed Mortality	SMR (95% CI)‡	Observed Mortality	SMR (95% CI)‡
All	1742	1.02	659	1.04	1005	0.99	95	1.31 (1.06-1.60)
Buccal cavity	32	1.12	12	1.12	13	0.79	5	4.16 (1.34-9.72)
Digestive tract	537	1.05	207	1.09	286	0.95	26	1.19
Esophagus	25	1.00	11	1.15	10	0.74	1	0.99
Stomach	82	1.05	28	0.97	42	0.90	7	1.95
Colorectal	282	1.11	108	1.15	154	1.02	12	1.12
Liver	39	0.87	16	0.97	19	0.69	2	0.97
Pancreas	99	1.07	38	1.10	56	1.05	3	0.79
Larynx	4	0.41	2	0.54	3	0.56	0	0
Lung	295	1.06	96	0.91	182	1.17 (1.01-1.35)	10	0.94
Breast	248	1.10	90	1.08	172	1.17 (1.00-1.36)	18	1.69
Uterus	68	0.69 (0.54-0.88)	22	0.61 (0.38-0.93)	36	0.57 (0.40-0.79)	4	0.83
Ovary§	86	1.09	31	1.07	54	1.06	5	1.37
Prostate	36	0.67 (0.47-0.93)	10	0.50 (0.24-0.91)	21	0.82	2	1.09
Bladder	42	1.08	14	0.97	17	0.78	2	1.30
Kidney	37	1.23	16	1.43	21	1.19	2	1.61
Brain	30	0.98	18	1.60	20	1.05	5	3.71 (1.19-8.64)
Thyroid	24	3.94 (2.52-5.86)	11	4.91 (2.45-8.79)	4	1.07	0	0
CLL	19	1.23	6	1.05	12	1.30	0	0
Non-CLL	53	1.22	18	1.12	30	1.14	1	0.54
Lymphoma	52	0.85	26	1.16	39	1.06	4	1.53
Myeloma	21	0.81	10	1.02	7	0.48 (0.40-0.79)	2	1.95

*Data exclude British patients. SMR indicates standardized mortality ratio; CI confidence interval; CLL indicates chronic lymphatic leukemia and includes chronic and unspecified lymphocytic leukemia (*International Classification of Diseases, Eighth Revision*, codes 204.1, 204.9); non-CLL includes acute lymphocytic leukemia, all myeloid and monocytic leukemia, and other and unspecified leukemia (*International Classification of Diseases, Eighth Revision*, codes 204.0, 205, 206, 207).
†The number of person-years for any iodine 131 treatment is 385 468; for iodine 131 only, 141 543; for surgery with or without drugs, 275 963; and for drugs only, 21 415.
‡Confidence intervals are shown for SMRs significant at 5% level.
§Data include other and unspecified female genital cancers.

patients with toxic nodular goiter, there was no relationship with amount of activity, but the number of cancers was small and the CIs were wide.

The Poisson regression analyses of the relationship between administered activity and subsequent thyroid cancer mortality, taking type of hyperthyroidism into account, excluded patients treated surgically (because their risk of thyroid cancer is reduced by decreasing the volume of tissue) and patients who had cancer before study entry, leaving 16 thyroid cancer deaths (Table 8). The RR in the highest administered activity group was 2.3 (95% CI, 0.97-9.5), but the exposure-response trend was not statistically significant ($P = .12$). Similarly, the excess RR point estimate result (excess RR at 1 mCi = 0.12) was positive, but not significant. Five or more years after study entry, no relationship was seen between administered activity and subsequent thyroid cancer mortality.

No relationship between level of ^{131}I administered activity or estimated bone marrow dose and CLL, non-CLL, Hodgkin disease, non–Hodgkin lymphoma, or multiple myeloma was demonstrated (Table 9). Because the latency period for radiation-induced non-CLL is short, we also analyzed the non-CLL data for only the first 10 years of follow-up, but again, no association with estimated bone marrow dose was seen ($P = .46$). For multiple myeloma, the RRs were increased in the 2 highest administrated activity and estimated bone marrow dose groups, but the numbers were small and the dose-response trend was not significant.

Surgical Treatment

Among the 10 876 patients receiving surgical treatment without ^{131}I, the SMR for total cancer mortality was 0.99 (Table 5). Excluding the first year of follow-up, lung and breast cancer mortality was significantly elevated among surgical patients, but not thyroid cancer mortality (SMR, 1.07). A 50% reduction in multiple myeloma mortality (SMR, 0.48; 95% CI, 0.19-0.99) was observed.

Antithyroid Drug Treatment

One year or more after study entry, there was a significant increase in the number of cancer deaths from all causes, as well as buccal and brain cancer among patients treated with antithyroid drugs (Table 5). Because patients treated with antithyroid drugs had an especially high rate of cancers diagnosed before study entry, an SMR analysis excluding patients with cancers diagnosed prior to study entry was performed. In this analysis, only brain cancer deaths remained elevated; however, excluding patients with cancers prior to study entry will underestimate the SMR.

COMMENT

We evaluated cancer mortality following 3 treatment modalities for hyperthyroidism. We put special emphasis on ^{131}I therapy because it is the treatment of choice in the United States, and the role of ^{131}I in carcinogenesis remains unclear. The investigators of the first evaluation of the Cooperative Thyrotoxicosis Therapy Follow-up Study cohort reported no increased risk of either leukemia or thyroid cancer incidence among patients treated with ^{131}I compared with patients treated by other methods.[5,6,10,16] In contrast, Williams[28] interpreted the thyroid data as showing a slight excess of anaplastic thyroid cancer among the group treated with ^{131}I, which he hypothesized might be caused by radiation-induced progression from undetected differentiated carcinomas to undifferentiated carcinomas. Additional follow-up of 2 subgroups of female patients from the original cohort suggested that there might be a slight increased risk of cancers occurring in organs known to concentrate ^{131}I[11,13] or of breast cancer incidence.[14]

In the present follow-up, ^{131}I treatment did not result in a larger-than-expected

number of deaths due to cancer when compared with US age-, sex-, and calendar-year–specific mortality rates. No excess mortality was observed when cancer in organs that concentrate ^{131}I (salivary, esophagus, stomach, colon, rectum, liver, bladder, and kidney) were grouped together (SMR, 1.03). A detailed analysis of hematopoietic malignancies revealed that neither ^{131}I administered activity nor estimated bone marrow dose were associated with mortality from non-CLL. This lack of positive results is not unexpected because the mean doses to all organs, except for the thyroid gland, which received extremely large doses, were below 200 mGy. At such low doses the statistical power to detect effects is limited. Because the study population was almost entirely adult, the results, however, cannot be generalized to childhood exposure.

Mortality studies are not well suited for studying thyroid cancer. Nonetheless, we did observe a significantly increased rate of thyroid cancer mortality among men and women and among patients with toxic nodular goiter or Graves disease. The elevated risk of thyroid cancer mortality was seen only for patients treated with ^{131}I. Using either an external (SMR analysis) or internal (Poisson analysis) comparison, the risk appeared to increase with increasing amounts of ^{131}I administered activity. The trend was not significant more than 10 years after study entry, or in the analysis using the internal comparison.

Several points should be noted in interpreting these results. The correlation between the amount of administered activity and thyroid radiation dose generally is poor in patients with hyperthyroidism[22]; patients receiving higher ^{131}I activity generally had more severe disease and frequently had relapses; patients dying from thyroid cancer were more likely to have had toxic nodular goiter than Graves disease (30% vs 8%); the major increase in mortality was seen in the first 5 years after treatment; goiter, particularly nodular goiter, has been reported as a risk factor for thyroid cancer[29-31]; and some of the patients with toxic nodular goiter may have had an undiagnosed preexisting thyroid cancer when they entered the study.

If it is assumed that the observed excess of thyroid cancer is causal, the risk would be smaller than the risks observed following external radiation. Some of the difference may be explained by ^{131}I therapy-induced cell killing. Although thyroid doses could not be estimated directly, the aim of ^{131}I treatment for hyperthyroidism is to destroy the thyroid.[32] The effectiveness of ^{131}I in killing thyroid cells presumably reduces the likelihood of malignant cell transformation. Another explanation may be related to age at exposure. Since the risk of developing thyroid cancer after external irradiation decreases with increasing age at exposure, with little risk demonstrated after age 20 years, data from this study of adults are insufficient to allow relevant comparisons between ^{131}I and external radiation. To date, almost all human data on ^{131}I are from populations exposed as adults,[15,33-37] whereas most data from external radiation exposure to the thyroid are from individuals treated during childhood.[38,39] Finally, some patients treated with ^{131}I in this study had full or partial thyroidectomies later, which might have lowered the risk of subsequent thyroid cancer by removing radiation-damaged tissue.

Compared with our study, the patients in a Swedish mortality series[15] were slightly older, had 4 fewer years of follow-up, and had a higher percentage of patients with toxic nodular goiter and consequently a larger mean total ^{131}I administered activity. The SMR for total cancer mortality was close to expected in both studies and, with the exception of thyroid cancer, the SMRs for other cancers were between 0.8 and 1.3. Although the increased risk of digestive tract and respiratory cancer mortality reached significance in the Swedish study, the risks were only 10% and 30% higher than expected, respectively. In our study, we did observe an increased risk of respiratory cancer mortality among patients with toxic nodular goiter treated with ^{131}I. Differences between the 2 studies easily could be caused by the higher proportion of Swedish patients with toxic nodular goiter or due to chance.

This study is unique because of its large size and its inclusion of patients not treated with ^{131}I. In the present follow-up, small but significant increases in breast, lung, and kidney cancer mortality were observed in the entire cohort of hyperthyroid patients compared with the general population. Smoking, lifestyle, and reproductive histories were not known, and these factors could confound the results. Because much of the elevated mortality occurred during the first few years of follow-up, underlying disease may be responsible for some of the excess. Although the group of patients treated with antithyroid drugs was small, the observed cancer mortality for several sites (total cancer, buccal, stomach, breast, and brain) was higher than expected compared with national rates. Analyses excluding patients with previous cancers suggested that some, but not all, of the excess could be attributed to the selection of patients for drug therapy. Patients

Table 6.—Cancer Mortality Among US Hyperthyroid Patients Treated With Iodine 131 by Latency*

	Years Between Study Entry and Cancer Death					
	1-4 (n = 20 949)†		5-9 (n = 18 245)†		≥10 (n = 14 997)†	
Type of Malignancy	Observed Mortality	SMR (95% CI)‡	Observed Mortality	SMR (95% CI)‡	Observed Mortality	SMR (95% CI)‡
All	258	1.24 (1.10-1.40)	278	1.05	1206	0.98
Buccal cavity	6	1.65	2	0.42	24	1.19
Digestive tract	83	1.21	83	0.97	371	1.04
Esophagus	0	0	5	1.31	20	1.09
Stomach	14	0.98	17	1.07	51	1.06
Colorectal	45	1.42 (1.04-1.90)	49	1.20	188	1.03
Liver	6	0.74	4	0.45	29	1.04
Pancreas	16	1.62	6	0.44 (0.16-0.96)	77	1.11
Larynx	1	0.82	0	0	3	0.43
Lung	31	1.49 (1.01-2.12)	44	1.41 (1.02-1.89)	220	0.97
Breast	39	1.26	36	0.93	173	1.11
Uterus	18	0.89	16	0.74	34	0.61 (0.42-0.85)
Ovary§	8	0.75	18	1.35	60	1.09
Prostate	5	1.14	5	0.78	26	0.61 (0.40-0.89)
Bladder	6	1.30	2	0.33	34	1.21
Kidney	6	1.75	4	0.88	27	1.22
Brain	3	0.75	6	1.20	21	0.98
Thyroid	12	12.32 (6.38-21.61)	1	0.86	11	2.78 (1.38-4.97)
CLL	2	0.93	5	1.96	12	1.12
Non-CLL	8	1.61	14	2.10 (1.14-3.52)	31	0.98
Lymphoma	5	0.62	10	1.02	37	0.85
Myeloma	3	1.35	4	1.23	14	0.68

*Data exclude British patients. SMR indicates standardized mortality ratio; CI, confidence interval; CLL indicates chronic lymphatic leukemia and includes chronic and unspecified lymphocytic leukemia (*International Classification of Diseases, Eighth Revision*, codes 204.1, 204.9); non-CLL includes acute lymphocytic leukemia, all myeloid and monocytic leukemia, and other and unspecified leukemia (*International Classification of Diseases, Eighth Revision*, codes 204.0, 205, 206, 207).

†The number of person-years for 1 to 4 years between study entry and cancer death is 78 372; for 5 to 9 years, 83 190; and for 10 or more years, 223 906.

‡Confidence intervals are shown for SMRs significant at 5% level.

§Data include other and unspecified female genital cancers.

Table 7.—Cancer Mortality Among Iodine 131–Treated US Hyperthyroid Patients by Type of Hyperthyroidism and Iodine 131 Administered Activity*

	Type of Hyperthyroidism				Administered Activity (mCi)					
	Graves Disease (n = 19 625)†‡		Toxic Nodular Goiter (n = 1089)†‡		<7 (n = 8085)†		7-14 (n = 9062)†		≥15 (n = 3802)†	
Type of Malignancy	Observed Mortality	SMR (95% CI)§	Observed Mortality	SMR (95% CI)§	Observed Mortality	SMR (95% CI)§	Observed Mortality	SMR (95% CI)§	Observed Mortality	SMR (95% CI)§
All	1615	1.01	104	1.31 (1.07-1.58)	637	0.94	763	1.04	342	1.18 (1.06-1.31)
Buccal cavity	30	1.10	1	0.85	14	1.23	15	1.21	3	0.61
Digestive tract	501	1.05	30	1.07	211	1.07	216	0.98	110	1.18
Esophagus	21	0.88	4	4.06 (1.10-10.45)	9	0.91	9	0.83	7	1.62
Stomach	75	1.04	6	1.28	28	0.97	38	1.12	16	1.05
Colorectal	265	1.12	13	0.92	114	1.15	114	1.04	54	1.18
Liver	36	0.87	2	0.73	16	0.95	14	0.72	9	1.05
Pancreas	95	1.09	4	0.87	40	1.09	37	0.93	22	1.37
Larynx	4	0.42	0	0	0	0	4	0.93	0	0
Lung	281	1.05	11	1.29	108	0.94	129	1.08	58	1.33 (1.01-1.72)
Breast	229	1.08	13	1.20	85	0.92	120	1.25 (1.04-1.49)	43	1.18
Uterus	57	0.62 (0.47-0.81)	11	2.05 (1.02-3.67)	14	0.36 (0.20-0.61)	31	0.73	23	1.34
Ovary‖	81	1.09	4	1.06	32	0.98	39	1.16	15	1.19
Prostate	34	0.67 (0.46-0.93)	2	1.00	14	0.69	14	0.60	8	0.81
Bladder	41	1.14	1	0.46	15	1.02	16	0.95	11	1.51
Kidney	35	1.23	1	0.74	16	1.33	19	1.46	2	0.39
Brain	27	0.92	3	3.05	13	1.01	12	0.92	5	1.09
Thyroid	16	2.84 (1.62-4.61)	7	18.88 (7.58-38.98)	7	3.01 (1.20-6.19)	9	3.42 (1.56-6.50)	8	7.05 (3.05-13.95)
CLL	19	1.33	0	0	8	1.36	8	1.20	3	1.04
Non-CLL	50	1.22	2	0.96	25	1.44	18	0.96	10	1.35
Lymphoma	49	0.85	2	0.72	17	0.69	24	0.92	11	1.08
Myeloma	18	0.73	2	1.76	6	0.57	11	0.99	4	0.94

*Data exclude British patients. SMR indictes standardized mortality ratio; CI, confidence interval; CLL indicates chronic lymphatic leukemia and includes chronic and unspecified lymphocytic leukemia (*International Classification of Diseases, Eighth Revision*, codes 204.1, 204.9); non-CLL includes acute lymphocytic leukemia, all myeloid and monocytic leukemia, and other and unspecified leukemia (*International Classification of Diseases, Eighth Revision*, codes 204.0, 205, 206, 207).

†The number of person-years for those with Graves disease is 368 934; for those with toxic nodular goiter, 13 088; for less than 7 years of administered activity, 160 563; for 7 to 14 years, 165 666; and for 15 or more years, 59 239.

‡Disease type is unknown for 253 patients.

§Confidence intervals are shown for SMRs significant at 5% level.

‖Data include other and unspecified female genital cancer.

Table 8.—Thyroid Cancer Mortality Among Iodine 131–Treated Patients by Administered Activity*

	Thyroid Cancer Deaths			Thyroid Cancer Deaths ≥5 Years After Study Entry		
Administered Activity, mCi	PYR	Deaths	RR	PYR	Deaths	RR
<7	146 494	4	1.00†	112 832	3	1.00†
7-14	145 700	6	1.24	109 679	6	1.67
≥15	52 786	6	2.28	38 162	1	0.57
P value for trend			.12			>.5
Excess RR at 1 mCi			0.12			0.009

*Data include 18 633 patients from the United States and England who did not undergo partial or full thyroidectomy and who did not have a cancer prior to study entry. PYR indicates person-years of follow-up; RR, relative risk.

†Reference category.

treated with drugs mainly received thiourea derivatives, iodine compounds, or a combination of the 2, but sometimes received various other drugs. The type, quantity, and dates of drug use generally were not available from the medical charts and could not be taken into consideration in the analysis. Because the quality of the drug data in this study is clearly limited, long-term effects of antithyroid drugs need to be evaluated further.

Although the study has several strengths, it also has limitations. First, thyroid doses could not be estimated and exposure response was based on ^{131}I administered activity. Second, mortality is not the ideal study end point. Causes of death, as listed on death certificates, frequently are inaccurate and rarely mention the histological type of cancer. In addition, information on cancers with high survival rates such as thyroid and breast is limited. Third, about 20 cancer sites were evaluated by latency, type of hyperthyroidism, treatment group, and for patients treated with ^{131}I, amount of administered activity. By conducting multiple comparisons, the probability of incorrectly rejecting a null hypothesis increases and suggests cautious interpretation of these data. On the other hand, the small number of patients and deaths in many of the subgroup analyses and the low radiation doses to most organs, other than the thyroid, limit the power to detect significant risks. Finally, patients are selected for a specific treatment based on their medical condition. For example, patients undergoing surgery were less likely to have had a previous cancer (except of the thyroid) than patients treated with drugs or ^{131}I. Thus, comparing risks related to treatment is problematic.

In summary, in a large series of hyperthyroid patients followed up for nearly a lifetime, cancer mortality was not significantly elevated. High-dose therapeutic ^{131}I administration, the most frequent treatment, also was not linked to an excess of total cancer mortality. Although a small number of thyroid cancer deaths might be attributed to ^{131}I therapy, overall, it appears to be a safe therapy.

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Table 9.—Mortality From Hematopoietic Malignancies Among Hyperthyroid Patients by Iodine 131 Dose Groups*

Administered Activity	PYR	Leukemia†				Lymphoma†				Multiple Myeloma	
		CLL		Non-CLL		Hodgkin		Non–Hodgkin			
		Deaths	RR	Deaths	RR	Deaths	RR	Deaths	RR	Deaths	RR
Administered iodine 131 activity, mCi											
0	321 698	12	1.00	31	1.00	6	1.00	31	1.00	8	1.00
>0-6	177 360	5	0.61	25	1.19	3	0.77	15	0.66	4	0.81
7-14	176 279	4	0.44	17	0.76	1	0.17	20	0.89	12	2.23
≥15	63 494	3	0.83	10	1.12	2	1.36	8	0.95	4	1.73
P value for trend			>.5		>.5		>.5		>.5		.3
Excess RR at 1 mCi			−0.008		0.001		−0.008		−0.003		0.038
Bone marrow dose, cGy											
0	313 021	12	1.00	31	1.00	6	1.00	31	1.00	8	1.00
>0-4.9	331 955	8	0.50	38	0.92	4	0.56	34	0.80	16	1.69
≥5	90 279	3	0.63	13	1.11	2	1.00	9	0.79	4	1.36
P value for trend			>.5		>.5		>.5		>.5		.3
Excess RR at 1 cGy			−0.01		−0.01		−0.01		0.006		0.11

*CLL indicates chronic lymphocytic leukemia; PYR, person-years of follow-up; and RR, relative risk.
†Data include patients from England, but exclude patients with cancers diagnosed before study entry.

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