

## MORTALITY AFTER THE TREATMENT OF HYPERTHYROIDISM WITH RADIOACTIVE IODINE

J.A. FRANKLYN, M.D., PH.D., P. MAISONNEUVE, PH.D., M.C. SHEPPARD, PH.D., F.R.C.P.,  
J. BETTERIDGE, R.G.N., AND P. BOYLE, PH.D.

### ABSTRACT

**Background** Hyperthyroidism affects many organ systems, but the effects are usually considered reversible. The long-term effects of hyperthyroidism on mortality are not known.

**Methods** We conducted a population-based study of mortality in a cohort of 7209 subjects with hyperthyroidism who were treated with radioactive iodine in Birmingham, United Kingdom, between 1950 and 1989. The vital status of the subjects was determined on March 1, 1996, and causes of death were ascertained for those who had died. The data on the causes of death were compared with data on age-specific mortality in England and Wales. The standardized mortality ratio was used as a measure of relative risk, and the effect of covariates on mortality was assessed by regression analysis.

**Results** During 105,028 person-years of follow-up, 3611 subjects died; the expected number of deaths was 3186 (standardized mortality ratio, 1.1; 95 percent confidence interval, 1.1 to 1.2;  $P < 0.001$ ). The risk was increased for deaths due to thyroid disease (106 excess deaths; standardized mortality ratio, 24.8; 95 percent confidence interval, 20.4 to 29.9), cardiovascular disease (240 excess deaths; standardized mortality ratio, 1.2; 95 percent confidence interval, 1.2 to 1.3), and cerebrovascular disease (159 excess deaths; standardized mortality ratio, 1.4; 95 percent confidence interval, 1.2 to 1.5), as well as fracture of the femur (26 excess deaths; standardized mortality ratio, 2.9; 95 percent confidence interval, 2.0 to 3.9). The excess mortality was most evident in the first year after radioiodine therapy and declined thereafter.

**Conclusions** Among patients with hyperthyroidism treated with radioiodine, mortality from all causes and mortality due to cardiovascular and cerebrovascular disease and fracture are increased. (N Engl J Med 1998;338:712-8.)

©1998, Massachusetts Medical Society.

**H**YPERTHYROIDISM is common, with a prevalence of approximately 2 percent in women and 0.2 percent in men.<sup>1</sup> It has widespread effects, among which those on the cardiovascular system are often prominent. Hyperthyroidism results in an increase in the heart rate, systolic blood pressure and pulse pressure,<sup>2</sup> and left ventricular contractility and mass,<sup>3,4</sup> and it increases the frequency of atrial arrhythmias, notably atrial fibrillation. All these changes are reversed by antithyroid treatment.<sup>2,4</sup> Subclinical hyperthyroidism, defined as low serum thyrotropin but

normal serum thyroid hormone concentrations, may also result in cardiovascular changes,<sup>4</sup> and low serum thyrotropin concentrations are a risk factor for the development of atrial fibrillation.<sup>5</sup> The effects of hyperthyroidism on other systems are less well documented, but it is associated with decreased bone mineral density<sup>6</sup> and an increased risk of osteoporotic fractures.<sup>7,8</sup>

There have been few population-based studies of the long-term effects of hyperthyroidism and its treatment on morbidity and mortality. Epidemiologic studies focused on the risk of cancer among patients with hyperthyroidism who were treated with radioiodine have not revealed consistent effects.<sup>9-12</sup> Studies of women with hyperthyroidism have, however, found increases in mortality from all causes and mortality from endocrine and cardiovascular diseases.<sup>12,13</sup>

In view of the prevalence of hyperthyroidism and its potential long-term effects, we examined the relation between hyperthyroidism and mortality in a population-based study with a long follow-up period. We used the Birmingham Thyroid Follow-up Register to identify a large cohort of subjects with hyperthyroidism who were treated with radioiodine between 1950 and 1989. We then compared data on death from all causes and from specific causes in this group of subjects with sex- and age-matched data on mortality in the general population of England and Wales.

### METHODS

#### Subjects

The study subjects were all patients who had been treated for hyperthyroidism with radioiodine in the West Midlands region of England during the years from 1950 through 1989. The date, dose, and number of radioiodine treatments, together with demographic data on the patients, had been recorded in the Birmingham Thyroid Follow-up Register,<sup>14,15</sup> which was established to ensure regular biochemical testing of patients and detection of hypothyroidism after treatment. The clinical features and underlying cause or severity of hyperthyroidism were not recorded consistently. Likewise, recording of details of subsequent thyroxine treatment and biochemical evidence of compliance with treatment was incomplete (2161 subjects were known to have become hypothyroid, 562 remained biochemically euthyroid, and the results in the remainder were unknown).

From the Department of Medicine, University of Birmingham, United Kingdom (J.A.F., M.C.S., J.B.); and the Division of Epidemiology and Biostatistics, European Institute of Oncology, Milan, Italy (P.M., P.B.). Address reprint requests to Dr. Franklyn at the Department of Medicine, University of Birmingham, Queen Elizabeth Hospital, Edgbaston, Birmingham B15 2TH, United Kingdom.

The initial cohort comprised 7772 subjects. Demographic data on these subjects were sent to the United Kingdom Office of National Statistics for tracing in the National Health Service Central Register. Of the 7772 subjects, 563 (7 percent) were excluded from the analysis, in the following categories: date of birth unknown (22 subjects), not found in the register (463), emigrated from the United Kingdom (30), residing in Northern Ireland (7), not registered with a primary care physician (34), and deceased but with no record of the cause of death (7). The characteristics of the 563 excluded subjects were similar to those of the rest of the cohort. The vital status of the 7209 remaining subjects (93 percent), who were included in the study, was determined as of March 1, 1996. For those who had died before that date, death certificates were obtained, and the reported causes of death were coded by the Office of National Statistics according to the ninth revision of the *International Classification of Diseases* (ICD-9).<sup>16</sup>

### Analysis of Mortality

The cause of death for each subject who had died was compared with age- and sex-specific mortality data for England and Wales, recorded in the World Health Organization data bank. Data from the cohort were compared with national data on mortality rather than with mortality data for the West Midlands region because the latter lacked detail and because approximately 20 percent of the subjects had moved from that region at some time before 1996. In view of the marked differences in the codes specified in successive revisions of the ICD used before 1980, the available data on annual mortality in England and Wales from 1979 through 1990, which were coded according to ICD-9, were used for comparison with data on the study cohort. Data from 1979 were applied to the years 1950 through 1979, year-specific data were applied to the years 1980 through 1989, and data from 1990 were applied to the years 1990 through 1995.

The number of person-years of risk was calculated from the date of first treatment with radioiodine until March 1, 1996, or the date of death. The expected number of deaths was calculated by multiplying the number of person-years in each stratum defined according to age, sex, and calendar year by the corresponding mortality rate for that age, sex, and period in England and Wales. To determine whether any bias was introduced by using imperfect age-specific rates for parts of the study, we repeated the analysis while restricting the calculation of expected deaths to the period for which appropriate age-specific rates of death were available. In this analysis, all the subjects in the cohort were included, but only person-years accumulated during 1979 through 1990 were considered; the expected number of deaths was compared with the observed number of deaths during the same period, as described above.

### Statistical Analysis

The standardized mortality ratio (the ratio of observed to expected deaths) was used as the estimate of relative risk. The 95 percent confidence intervals for the standardized mortality ratio were calculated on the assumption that the observed number of deaths followed a Poisson distribution.<sup>17</sup> Multivariate Poisson regression was used to assess the statistical significance of the difference in standardized mortality ratios between men and women and of trends in mortality according to time from treatment, age at treatment, and cumulative dose of radioiodine administered. Analyses were performed with adjustment for sex, age at first treatment (<50, 50 to 59, 60 to 69, or ≥70 years), time of treatment (1950 through 1959, 1960 through 1969, 1970 through 1979, or 1980 through 1989), cumulative dose of radioiodine (≤220, 221 to 480, or ≥481 MBq), and time since first treatment (1, 2 to 9, 10 to 19, or ≥20 years).<sup>17</sup> Observed survival was plotted against time by the Kaplan-Meier method in order to describe survival within the cohort.<sup>18</sup> Data were analyzed with use of SAS procedures,<sup>19</sup> and confidence intervals were calculated with confidence-interval analysis.<sup>20</sup>

## RESULTS

Characteristics of the 7209 subjects are shown in Table 1. Most (86 percent) received one dose of radioiodine, 12 percent received two doses, and 2 percent received three or more doses. The usual treatment protocol was the administration of fixed doses of radioiodine (185, 370, or 555 MBq).<sup>15</sup> The mean first dose administered was 266 MBq (range, 37 to 1851), with a mean cumulative dose of 314 MBq (range, 37 to 3959).

### Mortality from All Causes

Of the 7209 subjects, 3611 died before March 1, 1996. The expected number of deaths for the total number of person-years of risk (105,028 person-years) was 3186, leading to a relative risk of death of 1.1 (95 percent confidence interval, 1.1 to 1.2;  $P < 0.001$ ) (Table 2).

The risk of death due to endocrine and metabolic diseases and diseases of the circulatory system (which together accounted for 59 percent of deaths) was greater than that in the general population (Table 2). There were also increases in the risk of death due to injuries and poisonings, largely accounted for by an increase in deaths due to fracture. The risk of death from other major causes, including cancer and diseases of the respiratory and digestive systems, was not elevated. The pattern of results was the same when only person-years accumulated from 1979 through 1990 were included and when expected deaths were calculated on the basis of age-specific mortality data for the same period, although most standard mortality rates were smaller and an increase in the risk of death due to ischemic heart disease was no longer evident (data not shown).

When mortality among men and women in the cohort was considered separately, the increase in

**TABLE 1. DEMOGRAPHIC AND TREATMENT CHARACTERISTICS OF THE SUBJECTS WITH HYPERTHYROIDISM TREATED WITH RADIOIODINE IN 1950 THROUGH 1989.**

CHARACTERISTICS	ALL SUBJECTS (N=7209)	CUMULATIVE DOSE OF RADIOIODINE*		
		≤220 MBq (N=3440)	221-480 MBq (N=2559)	≥481 MBq (N=1194)
Female sex (%)	83	86	83	84
Mean age (yr)†	57	56	58	58
Mean cumulative dose (MBq)	314	—	—	—
Person-yr of follow-up	105,028	48,037	39,947	16,853

\*For 16 subjects, information about the cumulative dose of radioiodine was unavailable.

†The subjects ranged in age from 14 to 94 years.

**TABLE 2.** OBSERVED AND EXPECTED NUMBERS OF DEATHS AND STANDARDIZED MORTALITY RATIOS FOR CAUSES OF DEATH FOR WHICH THE RISK WAS ALTERED.\*

CAUSE OF DEATH	ICD-9 CODES	NO. OF DEATHS		SMR (95% CI)	P VALUE
		OBSERVED	EXPECTED		
Endocrine and metabolic disease	240–279	159	51	3.1 (2.6–3.6)	<0.001
Disease of the circulatory system	390–459	1955	1577	1.2 (1.2–1.3)	<0.001
All cardiovascular diseases		1258	1018	1.2 (1.2–1.3)	<0.001
Rheumatic heart disease		67	21	3.2 (2.5–4.2)	<0.001
Hypertensive disease		59	28	2.1 (1.6–2.7)	<0.001
Ischemic heart disease		867	812	1.1 (1.0–1.1)	0.03
Diseases of pulmonary circulation and other heart disease		265	157	1.8 (1.5–1.9)	<0.001
Cerebrovascular disease		605	446	1.4 (1.2–1.5)	<0.001
Other diseases of the circulatory system		92	112	0.8 (0.7–1.0)	0.03
Injuries and poisoning	800–999	100	61	1.6 (1.3–2.0)	<0.001
Fractures		50	26	1.9 (1.4–2.6)	<0.001
All causes		3611	3186	1.1 (1.1–1.2)	<0.001

\*ICD-9 denotes the ninth revision of the *International Classification of Diseases*,<sup>16</sup> SMR standardized mortality ratio, and CI confidence interval.

mortality from all causes was confined to women (observed deaths, 3009; expected deaths, 2544; standardized mortality ratio, 1.2; 95 percent confidence interval, 1.1 to 1.2). Among men, there were 602 observed deaths, whereas 641 were expected (standardized mortality ratio, 0.9; 95 percent confidence interval, 0.9 to 1.0;  $P < 0.001$  for the comparison between men and women).

When causes of death were grouped into categories, the pattern of results was generally similar to that described for the cohort as a whole (Table 2). There were excess deaths due to endocrine and metabolic disease in both sexes (women: standardized mortality ratio, 3.1; 95 percent confidence interval, 2.6 to 3.7; men: standardized mortality ratio, 3.0; 95 percent confidence interval, 1.9 to 4.5). There was also an excess of deaths due to cardiovascular disease among women but not among men (women: standardized mortality ratio, 1.3; 95 percent confidence interval, 1.2 to 1.4; men: standardized mortality ratio, 1.0; 95 percent confidence interval, 0.9 to 1.2;  $P < 0.001$  for the comparison between men and women). The pattern was similar for deaths due to injuries and poisonings (women: standardized mortality ratio, 1.7; 95 percent confidence interval, 1.4 to 2.1; men: standardized mortality ratio, 1.3; 95 percent confidence interval, 0.8 to 2.2).

#### Mortality Due to Endocrine Diseases, Cardiovascular and Cerebrovascular Diseases, and Fracture

Excess deaths due to endocrine and metabolic diseases were almost completely accounted for by disorders of the thyroid gland (106 excess deaths; standardized mortality ratio, 24.8; 95 percent confidence interval, 20.4 to 29.9). Excess deaths attrib-

uted to rheumatic heart disease were nearly always due to chronic disease, although two deaths were due to acute rheumatic fever. Excess deaths from hypertensive disease were due to hypertensive heart disease (31 excess deaths; standardized mortality ratio, 2.1; 95 percent confidence interval, 1.6 to 2.7) (Table 2), whereas excess deaths due to ischemic heart disease were related to chronic disease, not to acute myocardial infarction. Deaths due to heart failure, cardiac dysrhythmias, cardiomyopathy, and valvular disease accounted for the excess mortality in the category “diseases of pulmonary circulation and other forms of heart disease.” An excess of deaths due to cerebrovascular disease was related to increases in the risk of death from intracerebral and other intracranial hemorrhage (45 excess deaths), cerebral infarction (24 excess deaths), and acute but ill-defined cerebrovascular disease (84 excess deaths), whereas there was a significant reduction in deaths due to “other diseases of the circulatory system” (largely accounted for by “hemorrhage, unspecified,” and “circulatory disorders, unspecified”). An excess of deaths due to fractures was entirely accounted for by an increased risk of death from fracture of the femur (26 excess deaths; standardized mortality ratio, 2.9; 95 percent confidence interval, 2.0 to 3.9).

#### Mortality and Duration of Follow-up

When analyzed according to the length of follow-up after the first dose of radioiodine, mortality from all causes was increased at all time points; the standardized mortality ratio was greatest in the first year, with a decline thereafter (Table 3). The risk of death due to endocrine and metabolic diseases was also

greatest in the first year and then fell: an increase was no longer apparent among subjects followed for more than nine years. The pattern for cerebrovascular and cardiovascular diseases was similar. In contrast, the risk of death due to all fractures and to fracture of the femur was not significantly associated with time after treatment. There were no significant differences in the mean age at first treatment or the cumulative dose of radioiodine administered to the groups of subjects shown in Table 3 who were followed for 20 or more years (data not shown).

**Mortality and Age at Treatment**

Mortality from all causes according to age at the time of first treatment with radioiodine was increased for all age groups (Table 4). For death due to most cardiovascular causes (apart from rheumatic heart disease), as well as for death due to cerebrovascular disease, the risk was increased only in those who were older than 49 years of age at the time of treatment; there was a significant excess risk related to fracture confined to those who were more than 59 years old at the time of treatment, largely reflecting the increasing frequency of events with the aging of the cohort.

**Mortality and the Dose of Radioiodine**

Mortality from all causes increased (Table 5) and overall survival decreased (Fig. 1) with increasing cumulative doses of radioiodine. The relations between deaths from cardiovascular diseases and cerebrovascular disease and the cumulative dose of radioiodine were similar.

**DISCUSSION**

Among 7209 subjects with hyperthyroidism who were treated with radioiodine, mortality from all causes was 13 percent higher than in the general population of England and Wales. This finding agrees with the results of a study of 1762 women who were treated with radioiodine at the Massachusetts General Hospital Thyroid Unit between 1946 and 1964 and followed for an average of 14 years (standardized mortality ratio for all causes of death, 1.3)<sup>12</sup> and another in Sweden of 10,552 subjects who were followed for an average of 15 years after radioiodine treatment (standardized mortality ratio, 1.5 for women and 1.3 for men).<sup>13</sup>

We found significant increases in the risk of death attributed to thyroid disease, all forms of cardiovascular disease, cerebrovascular disease, and fracture of

**TABLE 3.** OBSERVED AND EXPECTED NUMBER OF DEATHS AND STANDARDIZED MORTALITY RATIOS FOR SELECTED CAUSES OF DEATH, ACCORDING TO THE TIME FROM THE FIRST DOSE OF RADIOIODINE.\*

CAUSE OF DEATH	≤1 Yr			2-9 Yr			10-19 Yr			≥20 Yr			P VALUE†
	OBSERVED	EXPECTED	SMR	OBSERVED	EXPECTED	SMR	OBSERVED	EXPECTED	SMR	OBSERVED	EXPECTED	SMR	
			(95% CI)			(95% CI)			(95% CI)			(95% CI)	
no.		no.		no.		no.		no.					
Endocrine and metabolic diseases	39	1.7	22.3 (15.8-30.5)	83	18.6	4.5 (3.6-5.5)	23	17.2	1.3 (0.8-2.0)	13	12.8	1.0 (0.5-1.7)	<0.001
All cardiovascular diseases	61	37.7	1.6 (1.2-2.1)	498	387	1.3 (1.2-1.4)	420	355	1.2 (1.1-1.3)	278	237	1.2 (1.0-1.3)	<0.001
Rheumatic heart disease	8	1.1	7.5 (3.2-14.8)	30	9.3	3.2 (2.2-4.6)	22	6.9	3.2 (2.0-4.8)	7	3.5	2.0 (0.8-4.1)	0.002
Hypertensive disease	3	1.2	2.5 (0.5-7.4)	28	11.4	2.5 (1.6-3.5)	18	9.9	1.8 (1.1-2.9)	10	5.7	1.8 (0.8-3.2)	0.07
Ischemic heart disease	37	30.2	1.2 (0.9-1.7)	335	310	1.1 (1.0-1.2)	286	282	1.0 (0.9-1.1)	209	189	1.1 (1.0-1.3)	0.42
Diseases of pulmonary circulation and other heart disease	13	5.3	2.4 (1.3-4.2)	105	56.5	1.9 (1.5-2.3)	94	55.8	1.7 (1.4-2.1)	52	39.2	1.3 (1.0-1.7)	<0.001
Cerebrovascular disease	33	14.9	2.2 (1.5-3.1)	220	160	1.4 (1.2-1.6)	223	155	1.4 (1.3-1.6)	129	117	1.1 (0.9-1.3)	<0.001
Fractures	2	1.0	2.0 (0.2-7.1)	16	9.8	1.6 (0.9-2.7)	19	8.7	2.2 (1.3-3.4)	13	6.1	2.1 (1.1-3.6)	0.17
All causes	219	121	1.8 (1.6-2.1)	1418	1225	1.2 (1.1-1.2)	1206	1097	1.1 (1.0-1.2)	763	742	1.0 (1.0-1.1)	<0.001

\*The whole cohort of 7209 was followed for the first year, 6390 subjects were followed for 2 to 9 years, 4671 for 10 to 19 years, and 1816 for 20 years or more. SMR denotes standardized mortality ratio, and CI confidence interval.

†P values are for the trend in results with time from treatment and were obtained from a multivariate Poisson regression model taking into account sex, age at treatment, period of treatment, and cumulative dose of radioiodine.

**TABLE 4.** OBSERVED AND EXPECTED NUMBER OF DEATHS AND STANDARDIZED MORTALITY RATIOS FOR SELECTED CAUSES OF DEATH, ACCORDING TO AGE AT THE FIRST DOSE OF RADIOIODINE.\*

CAUSE OF DEATH	<50 Yr (N=1938)			50-59 Yr (N=2266)			60-69 Yr (N=1821)			≥70 Yr (N=1184)			P VALUE†
	OBSERVED	EXPECTED	SMR	OBSERVED	EXPECTED	SMR	OBSERVED	EXPECTED	SMR	OBSERVED	EXPECTED	SMR	
			(95% CI)			(95% CI)			(95% CI)				
no.		no.		no.		no.							
Endocrine and metabolic diseases	15	6.1	2.5 (1.4-4.1)	37	15.5	2.4 (1.7-3.3)	51	15.7	3.2 (2.4-4.3)	56	13.2	4.2 (3.2-5.5)	0.90
All cardiovascular diseases	124	108	1.2 (0.9-1.4)	391	309	1.3 (1.1-1.4)	431	327	1.3 (1.2-1.5)	312	273	1.1 (1.0-1.3)	0.06
Rheumatic heart disease	14	3.3	4.2 (2.3-7.1)	26	7.6	3.4 (2.2-5.0)	19	6.2	3.1 (1.8-4.8)	8	3.7	2.2 (0.9-4.3)	0.04
Hypertensive disease	5	2.8	1.8 (0.6-4.1)	14	8.5	1.6 (0.9-2.8)	26	9.4	2.8 (1.8-4.1)	14	7.6	1.8 (1.0-3.1)	0.74
Ischemic heart disease	91	91.5	1.0 (0.8-1.2)	279	255	1.1 (1.0-1.2)	300	261	1.1 (1.0-1.3)	197	204	1.0 (0.8-1.1)	0.20
Diseases of pulmonary circulation and other heart disease	14	10.6	1.3 (0.7-2.2)	72	37.6	1.9 (1.5-2.4)	86	50.7	1.7 (1.4-2.1)	93	58	1.6 (1.3-2.0)	0.16
Cerebrovascular disease	48	37.1	1.3 (0.9-1.7)	169	120	1.4 (1.2-1.6)	206	144	1.4 (1.2-1.6)	182	146	1.2 (1.1-1.4)	0.02
Fractures	4	2.5	1.6 (0.4-4.0)	10	6.6	1.5 (0.73-2.8)	20	7.8	2.5 (1.6-3.9)	16	8.7	1.8 (1.0-3.0)	0.76
All causes	398	361	1.1 (1.0-1.2)	1087	962	1.1 (1.1-1.2)	1220	1006	1.2 (1.1-1.3)	906	857	1.1 (1.0-1.1)	0.001

\*SMR denotes standardized mortality ratio, and CI confidence interval.

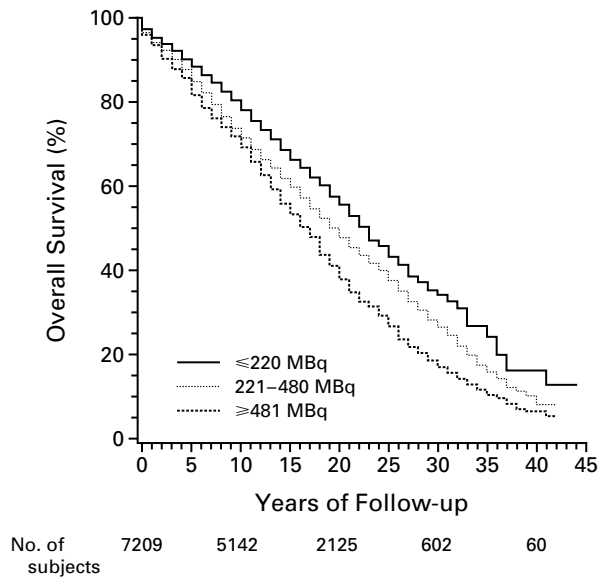
†P values are for the trend in results according to age at first treatment and were obtained from a multivariate Poisson regression model taking into account sex, time since treatment, period of treatment, and cumulative dose of radioiodine.

**TABLE 5.** OBSERVED AND EXPECTED NUMBER OF DEATHS AND STANDARDIZED MORTALITY RATIOS FOR SELECTED CAUSES OF DEATH, ACCORDING TO THE CUMULATIVE DOSE OF RADIOIODINE.\*

CAUSE OF DEATH	≤220 MBq (N=3440)			221-480 MBq (N=2559)			≥481 MBq (N=1194)			P VALUE†
	OBSERVED	EXPECTED	SMR	OBSERVED	EXPECTED	SMR	OBSERVED	EXPECTED	SMR	
			(95% CI)			(95% CI)			(95% CI)	
no.		no.		no.						
Endocrine and metabolic diseases	49	21	2.3 (1.7-3.1)	73	20	3.6 (2.8-4.5)	37	8.8	4.2 (3.0-5.8)	0.15
All cardiovascular diseases	442	402	1.1 (1.0-1.2)	515	423	1.2 (1.1-1.3)	299	191	1.6 (1.4-1.8)	<0.001
Rheumatic heart disease	23	8.3	2.7 (1.7-4.1)	23	8.6	2.7 (1.7-4.0)	21	3.8	5.6 (3.5-8.5)	0.12
Hypertensive disease	16	10.5	1.5 (0.9-2.5)	29	12	2.4 (1.6-3.5)	14	5.6	2.5 (1.3-4.2)	0.54
Ischemic heart disease	319	327	1.0 (0.9-1.1)	349	335	1.0 (0.9-1.2)	197	148	1.3 (1.1-1.5)	0.003
Diseases of pulmonary circulation and other heart disease	84	56	1.5 (1.2-1.8)	114	67	1.7 (1.4-2.0)	67	33	2.0 (1.6-2.6)	0.11
Cerebrovascular disease	207	1721	1.2 (1.1-1.4)	268	188	1.4 (1.3-1.6)	129	86	1.5 (1.3-1.8)	0.01
Fractures	18	9.6	1.9 (1.1-3.0)	19	10.9	1.7 (1.0-2.7)	13	5.1	2.5 (1.3-4.3)	0.29
All causes	1324	1265	1.0 (1.0-1.1)	1496	1317	1.1 (1.1-1.2)	775	598	1.3 (1.2-1.4)	<0.001

\*SMR denotes standardized mortality ratio, and CI confidence interval.

†P values are for the trend in results with cumulative dose of radioiodine administered and were obtained from a multivariate Poisson regression model taking into account sex, time since treatment, period of treatment, and age at first treatment.



**Figure 1.** Kaplan-Meier Survival Curves Showing the Relation between Survival and the Cumulative Dose of Radioiodine.

the femur. These findings agree with a reported increase in the standardized mortality ratio for death due to endocrine diseases and circulatory diseases in other studies.<sup>11,13</sup> In contrast to those studies, we did not find an increase in death due to respiratory diseases, but we confirmed the absence of an increase in deaths due to cancer.

The risk of death due to thyroid disease was increased in our cohort, but only in the first nine years after radioiodine treatment, and it was most marked in the first year. This finding is likely to be explained by an increased risk of death during the period of most severe hyperthyroidism (around the time of radioiodine therapy), although the attribution of death to thyroid disease is also likely to reflect knowledge of the diagnosis by the certifying doctor.

The major cause of excess mortality was circulatory disease (both cardiovascular and cerebrovascular). Mortality from cardiovascular disease was highest in the first year after radioiodine treatment and then declined. Hyperthyroidism is a cause of atrial fibrillation, which may in turn exacerbate rheumatic or nonrheumatic valvular disease, ischemic heart disease, or cardiac failure,<sup>21,22</sup> as may the other changes in cardiovascular function that occur in patients with hyperthyroidism.<sup>2,4</sup> The striking increase in mortality due to rheumatic heart disease may reflect the timing of investigations for hyperthyroidism and rheumatic heart disease in patients presenting with atrial fibrillation. Excess deaths due to hypertensive disease, ischemic heart disease, and other forms of heart disease were confined to subjects who were 50 years of age or older at the time of initial treatment; this pattern largely reflects increasing mortality from

heart disease with increasing age and the exacerbation of these disorders by hyperthyroidism.<sup>2,21,22</sup>

The relation between the cumulative dose of radioiodine and both mortality from all causes and mortality from cardiovascular disease may reflect a specific adverse influence of radioiodine (perhaps related to a short-term exacerbation of hyperthyroidism), but it is more likely to reflect the selection of subjects with cardiovascular disease or other serious illnesses for treatment with radioiodine. Because the likelihood that hyperthyroidism will be cured by radioiodine therapy is related to the dose administered,<sup>23</sup> as well as to the biochemical severity of the disease,<sup>24</sup> those with severe hyperthyroidism are more likely to receive a high dose. The view that the relation between the dose of radioiodine and mortality does not reflect a specific adverse effect of radioiodine is further supported by the observation that mortality from all causes was similar among groups of subjects with hyperthyroidism who were given radioiodine or other treatments.<sup>11</sup>

We do not know the influence of hypothyroidism or its treatment with thyroxine on mortality in this cohort. In our previous study of 1623 subjects in the same cohort, hypothyroidism developed in about half during a mean follow-up of 16 years.<sup>15</sup> Mortality from all causes was increased in a study of 710 women with idiopathic hypothyroidism,<sup>25</sup> a fact that may reflect increases in serum cholesterol concentrations in hypothyroid patients.<sup>26</sup> Hypothyroidism is also associated with diastolic hypertension and impaired myocardial contractility and may precipitate heart failure.<sup>27</sup> Furthermore, about half of persons with hypothyroidism have overt or subclinical thyroid dysfunction related to poor compliance with thyroxine therapy or inappropriate dosage.<sup>28,29</sup> Subclinical hyperthyroidism is a known risk factor for atrial fibrillation,<sup>5</sup> and it may cause an increase in left ventricular mass,<sup>4,30</sup> which is an independent risk factor for death from cardiovascular disease. Thus, in this cohort, hypothyroidism and subclinical hyperthyroidism secondary to thyroxine therapy may have contributed to excess cardiovascular mortality, but the contribution is likely to have been small because the excess deaths from cardiovascular disease, for the most part, occurred early after radioiodine treatment.

The excess mortality from cerebrovascular disease was also most marked in the first year and was confined to patients who were 50 years of age or older at the time of initial treatment. Approximately 15 percent of patients with hyperthyroidism who have atrial fibrillation have an arterial embolic event,<sup>31</sup> and it is likely that the increased risk of death due to cerebral infarction reflects embolic complications of cardiac dysrhythmias and other cardiovascular diseases. An increased risk of cerebral hemorrhage may reflect systolic hypertension in persons with hyperthyroidism and perhaps diastolic hypertension, with

subsequent hypothyroidism. The relation between the risk of cerebrovascular disease and the dose of radioiodine probably reflects a relation between the severity of the hyperthyroidism and risk of cerebrovascular disease.

We also found an increase in the risk of death due to fracture of the femur, presumably because hyperthyroidism induced a decrease in bone mineral density.<sup>6,32</sup> Our present finding of an almost 200 percent increase in the risk of death due to fractures of the femur is supported by a recent population-based study of elderly women, which found an increased risk of fracture in those with previous hyperthyroidism.<sup>8</sup>

In conclusion, we found increases in the risk of death due to cardiovascular disease, cerebrovascular disease, and fractures in subjects with hyperthyroidism who were treated with radioiodine. We do not know the influence of the severity or duration of hyperthyroidism on these findings, the direct role of radioiodine, or the role of hypothyroidism and its treatment. The findings suggest that further attention should be paid to the consequences of hyperthyroidism and its treatment with respect to the circulatory system and bone metabolism.

Supported by the Medical Research Council, United Kingdom, the BUPA Foundation, the Research Committee of the West Midlands Research and Development Directorate, the Endowment Fund of the former United Birmingham Hospitals, and the Associazione Italiana per la Ricerca sul Cancro.

*We are indebted to Dr. L. Somervaille for help in establishing the data set and to colleagues throughout the West Midlands who contributed to the Birmingham Thyroid Follow-up Register.*

## REFERENCES

1. Tunbridge WMG, Evered DC, Hall R, et al. The spectrum of thyroid disease in a community: the Wickham survey. *Clin Endocrinol (Oxf)* 1977;7:481-93.
2. Woeber KA. Thyrotoxicosis and the heart. *N Engl J Med* 1992;327:94-8.
3. Klein I, Ojamaa K. Cardiovascular manifestations of endocrine disease. *J Clin Endocrinol Metab* 1992;75:339-42.
4. Ching GW, Franklyn JA, Stallard TJ, Daykin J, Sheppard MC, Gammage MD. Cardiac hypertrophy as a result of long-term thyroxine therapy and thyrotoxicosis. *Heart* 1996;75:363-8.
5. Sawin CT, Geller A, Wolf PA, et al. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. *N Engl J Med* 1994;331:1249-52.
6. Auwerx J, Bouillon R. Mineral and bone metabolism in thyroid disease: a review. *QJM* 1986;232:737-52.
7. Bauer DC, Cummings SR, Tao JL, Browner WS. Hyperthyroidism increases the risk of hip fractures: a prospective study. *J Bone Miner Res* 1992;7:Suppl 1:121. abstract.
8. Cummings SR, Nevitt MC, Browner WS, et al. Risk factors for hip fracture in white women. *N Engl J Med* 1995;332:767-73.
9. Holm LE, Hall P, Wiklund K, et al. Cancer risk after iodine-131 therapy for hyperthyroidism. *J Natl Cancer Inst* 1991;83:1072-7.
10. Hall P, Boice JD Jr, Berg G, et al. Leukaemia incidence after iodine-131 exposure. *Lancet* 1992;340:1-4.
11. Hoffman DA, McConahey WM, Diamond EL, Kurland LT. Mortality in women treated for hyperthyroidism. *Am J Epidemiol* 1982;115:243-54.
12. Goldman MB, Maloof F, Monson RR, Aschengrau A, Cooper DS, Ridgway EC. Radioactive iodine therapy and breast cancer: a follow-up study of hyperthyroid women. *Am J Epidemiol* 1988;127:969-80.
13. Hall P, Lundell G, Holm LE. Mortality in patients treated for hyperthyroidism with iodine-131. *Acta Endocrinol (Copenh)* 1993;128:230-4.
14. Barber SG, Carter DJ, Bishop JM. System for long-term review of patients at risk of becoming hypothyroid: further experience. *Lancet* 1977;2:967-70.
15. Franklyn JA, Daykin J, Drolc Z, Farmer M, Sheppard MC. Long-term follow-up of treatment of thyrotoxicosis by three different methods. *Clin Endocrinol (Oxf)* 1991;34:71-6.
16. International classification of diseases: manual of the international classification of diseases, injuries, and causes of death: based on the recommendations of the Ninth Revision Conference, 1975, and adopted by the Twenty-ninth World Health Assembly. Vol. 1. Geneva: World Health Organization, 1977.
17. Breslow NE, Day NE. Statistical methods in cancer research. Vol. 2. The design and analysis of cohort studies. Lyon, France: International Agency for Research on Cancer, 1987. (IARC scientific publications no. 82.)
18. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-81.
19. SAS/STAT software, release 6.08. Cary, N.C.: SAS Institute, 1991.
20. Gardner MJ, Altman DG, eds. Statistics with confidence: confidence intervals and statistical guidelines. London: British Medical Journal, 1989.
21. Forfar JC, Muir AL, Sawers SA, Toft AD. Abnormal left ventricular function in hyperthyroidism: evidence for a possible reversible cardiomyopathy. *N Engl J Med* 1982;307:1165-70.
22. Iwasaki T, Naka M, Hiramatsu K, et al. Echocardiographic studies on the relationship between atrial fibrillation and atrial enlargement in patients with hyperthyroidism of Graves' disease. *Cardiology* 1989;76:10-7.
23. Smith RN, Wilson GM. Clinical trial of different doses of 131-I in treatment of thyrotoxicosis. *BMJ* 1967;1:129-32.
24. Franklyn JA, Daykin J, Holder R, Sheppard MC. Radioiodine therapy compared in patients with toxic nodular or Graves' hyperthyroidism. *QJM* 1995;88:175-80.
25. Goldman MB, Monson RR, Maloof F. Cancer mortality in women with thyroid disease. *Cancer Res* 1990;50:2283-9.
26. Kutty KM, Bryant DG, Farid NR. Serum lipids in hypothyroidism — a re-evaluation. *J Clin Endocrinol Metab* 1978;46:55-6.
27. Gammage MD, Franklyn JA. Hypothyroidism, thyroxine treatment, and the heart. *Heart* 1997;77:189-90.
28. Parle JV, Franklyn JA, Sheppard MC. Thyroxine replacement therapy. *Lancet* 1991;337:171.
29. Sawin CT, Gellar A, Hershman JM, Castelli W, Bacharach P. The aging thyroid: the use of thyroid hormone in older persons. *JAMA* 1989;261:2653-5.
30. Biondi B, Fazio S, Carella C, et al. Cardiac effects of long term thyrotropin-suppressive therapy with levothyroxine. *J Clin Endocrinol Metab* 1993;77:334-8.
31. Presti CF, Hart RG. Thyrotoxicosis, atrial fibrillation, and embolism, revisited. *Am Heart J* 1989;117:967-7.
32. Franklyn JA, Betteridge J, Holder R, Daykin J, Lilley J, Sheppard MC. Bone mineral density in thyroxine treated females with or without a previous history of thyrotoxicosis. *Clin Endocrinol (Oxf)* 1994;41:425-32.