

THYROID CANCER RISK AFTER THYROID EXAMINATION WITH ^{131}I : A POPULATION-BASED COHORT STUDY IN SWEDEN

Paul W. DICKMAN^{1*}, Lars-Erik HOLM², Göran LUNDELL³, John D. BOICE, JR.^{4,5} and Per HALL¹

¹Department of Medical Epidemiology, Karolinska Institutet, Stockholm, Sweden

²Swedish Radiation Protection Board, Stockholm, Sweden

³Department of Oncology, Karolinska University Hospital, Stockholm, Sweden

⁴International Epidemiology Institute, Rockville, MD, USA

⁵Vanderbilt University, School of Medicine, Nashville, TN, USA

Ionizing radiation is the only established cause of thyroid cancer, though the effect of diagnostic administration of ^{131}I on thyroid cancer risk appears minimal. The annual number of thyroid examinations using radioiodine is currently 5 per 1,000 individuals worldwide, so this issue is of public health importance. Our objective was to evaluate the excess risk of thyroid cancer following a range of known doses of ^{131}I administered for diagnostic purposes. We conducted a nationwide, population-based cohort study in Sweden including all 36,792 individuals who received ^{131}I for diagnostic purposes during 1952–1969 and were alive and free of thyroid cancer 2 years after exposure. Accrual of person-time at risk commenced 2 years after the first ^{131}I administration. Follow-up for cancer was to the end of 1998. Standardized incidence ratios (SIRs) were calculated as the ratio between the observed and expected numbers of thyroid cancers. Estimates were stratified by previous exposure to external radiation therapy to the neck, reason for thyroid examination, ^{131}I dose, sex, age at exposure and time since exposure. Thyroid cancers ($n = 129$) were diagnosed during 886,618 person-years at risk. Excess thyroid cancers were observed only among the 1,767 patients who reported previous external radiation therapy to the neck [SIR = 9.8, 95% confidence interval (CI) 6.3–14.6] and among those originally referred due to suspicion of a thyroid tumor (SIR = 3.5, 95% CI 2.7–4.4 for 11,015 patients without previous external radiation therapy). The 24,010 patients without previous exposure to external radiation therapy to the neck who were referred for a reason other than suspicion of a thyroid tumor received an estimated dose to the thyroid of 0.94 Gy. Among these patients, 36 thyroid cancers were observed compared to 39.5 expected (SIR = 0.91, 95% CI 0.64–1.26). We found no evidence that administration of ^{131}I for diagnostic purposes increases risk of thyroid cancer. However, our study included few patients under age 20, so the results apply primarily to exposure among adults. Our data suggest that protraction of dose may result in a lower risk than brief X-ray exposure of the same total dose.

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In light of reports of an increased risk of thyroid cancer in patients treated with therapeutic doses of ^{131}I for hyperthyroidism^{1,2} and the extensive number of childhood thyroid cancers diagnosed in the republics adjacent to the Chernobyl nuclear power plant,³ we conducted an extended follow-up of 36,792 Swedes who received ^{131}I for diagnostic purposes during 1952–1969. Results based on this cohort have previously been reported in 1988⁴ and 1996.⁵ The current study extends the follow-up by 8 years, meaning that the majority of subjects have moved into the age range where thyroid cancers are more common. The current study includes an additional 1,767 patients who were exposed to external radiation therapy to the neck prior to the administration of ^{131}I , thereby providing a unique opportunity to study the combined effect of the 2 exposures.

Thyroid carcinomas are heterogeneous with respect to histology, clinical presentation, treatment response and prognosis. Their malignant potential ranges from slow-growing microcarcinomas, nor-

mally found incidentally at goiter surgery or autopsy, to fast-growing and highly malignant anaplastic thyroid carcinomas. Thyroid carcinomas are more aggressive in children than in adults, but paradoxically, the prognosis is better in children.⁶

Several risk factors for thyroid cancer have been proposed, though a causal association has been shown only for ionizing radiation.³ A history of benign nodules, miscarriages, iodine deficiency or excess and elevated levels of thyroid-stimulating hormones have been evaluated as possible causative factors; but the evidence is inconsistent.^{7–9} The childhood thyroid gland is one of the most radiosensitive organs in the body,³ others being red bone marrow and the premenopausal female breast. In a pooled analysis of children exposed to external photon radiation,¹⁰ the excess relative risk of 7.7 Gy⁻¹ [95% confidence interval (CI) 2.1–28.7] for thyroid cancer was the highest excess relative risk found for any organ. Among survivors of the atomic bombings, the most pronounced risk of thyroid cancer was found among those exposed before the age of 10 years; the highest risk was seen 15–29 years after exposure and was still increased 40 years after exposure.¹¹ There is little evidence, however, that exposures after age 20 increase the risk of thyroid cancer except, perhaps, when they are very large.³

The carcinogenic effect of ^{131}I is less understood, the radiation being delivered during a protracted period of 6–7 weeks, which might allow for repair to any DNA damage. Further, the distribution of ^{131}I within the thyroid gland is such that the relatively weak β particle emitted during radioactive decay will not uniformly irradiate the thyroid gland and, thus, not always penetrate to the cells at risk of transformation. The effects of ^{131}I administered to children in a medical setting have not been studied in detail since medical examinations or treatments rarely include children.⁵

Knowledge of the effect of ^{131}I after medical administration is of clinical importance, and the finding of increased mortality due to thyroid cancer after treatment for hyperthyroidism in 2 studies^{1,2} is somewhat surprising since it contrasts with previous findings.¹² Because of the extremely short latency and lack of a significant dose response, it is possible that the thyroid cancers existed at the time of therapy for hyperthyroidism.

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*Correspondence to: Department of Medical Epidemiology, Karolinska Institutet, Box 281, 171 77 Stockholm, Sweden. Fax: +46-8-314-975. E-mail: paul.dickman@mep.ki.se

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Studies of thyroid cancer risk after diagnostic procedures using ¹³¹I are important since the annual number of thyroid examinations using radioiodine was 5 per 1,000 individuals worldwide during 1991–1996.³ Since approximately 45% of patients examined are below the age of 40 years at examination and the annual collective dose (in the world) is 33,500 person-Sv, even a slight increase in risk could have an important detrimental effect on a population basis.

The present study is an extended follow-up of patients who received ¹³¹I for diagnostic purposes, and our aim was to study more fully thyroid cancer risk in relation to age at exposure, thyroid absorbed dose, reason for referral, time after exposure and previous exposure to external radiation therapy to the neck.

MATERIAL AND METHODS

Our study was based on 40,535 patients examined with ¹³¹I before age 75 years in Sweden during 1952–1969. During this period, use of ¹³¹I as a diagnostic tool was restricted to 7 university hospitals. We abstracted information from the medical records of all patients examined with ¹³¹I at these 7 hospitals. Thyroid scintigrams were performed on the majority of patients. Thyroid doses are 10–20 times higher for scintigrams than for thyroid uptake tests. Excluded from the analysis were patients followed for less than 2 years (*n* = 3,083), patients who died prior to 1958 [the first year for which data from the Swedish Cancer Registry (SCR) are available, *n* = 114] and patients for whom absorbed dose could not be determined due to missing information on 24 hr thyroid uptake (*n* = 546). Among the 546 patients excluded due to missing information on uptake, one thyroid cancer was diagnosed during follow-up compared to 0.9 expected. Table I summarizes the characteristics of the patients.

The absorbed thyroid dose from ¹³¹I depends on the amount of ¹³¹I administered, the physical and biologic half-lives of ¹³¹I, the ¹³¹I uptake in the thyroid gland and the size of the thyroid gland. We estimated the total absorbed thyroid dose for each individual based on the administered ¹³¹I activity and the 24 hr uptake at each administration by applying appropriate conversion factors, as published.¹³ Patients were grouped into 4 absorbed ¹³¹I dose categories: <0.25, 0.25–0.50, 0.50–1.00 and >1.00 Gy.

Estimated thyroid weight, based on information abstracted from patient records (primarily the results of scintigrams), was available for 48% of patients. The relationship between the size of the thyroid gland and the absorbed ¹³¹I dose is approximately linear; *i.e.*, when the gland weight is doubled, the absorbed dose is reduced by a factor of 2. When the thyroid mass was not known, the dose was estimated under the assumption that the thyroid was of normal mass (*i.e.*, <30 g).¹³

The follow-up period commenced at the date of first ¹³¹I administration or 1 January 1958 if the patient was first exposed prior to 1958. Accumulation of person-time at risk began 2 years after the date of first ¹³¹I administration; *i.e.*, the first 2 years following exposure were excluded since we considered it unlikely that tumors diagnosed in this period would be due to administration of ¹³¹I. It is most probable that tumors diagnosed in this early period existed at the time of ¹³¹I administration. Consequently, to be eligible for the study, an individual was required to be alive and free of thyroid cancer 2 years after first administration of ¹³¹I. Person-time at risk was accumulated until the date of diagnosis of thyroid cancer, date of death, date of emigration or 31 December 1998, whichever occurred first.

A unique personal identity number is assigned to all Swedish residents and used to index almost all registers in Sweden, including the mortality register, cancer register, register of total population (from which emigrants are identified) and hospital medical records.¹⁴ The personal identity number, which was introduced in 1947, consists of 10 digits, 6 digits representing date of birth, 2 additional digits previously used to identify birth region, 1 digit representing gender and a check digit.

Using the unique personal identity number, the cohort was matched to the national mortality register to identify all deaths during 1952–1998 and to the SCR to identify all thyroid cancers diagnosed during 1958–1998. The population-based SCR commenced in 1958 and receives notification of all newly diagnosed cancers from both pathologists/cytologists and physicians. Reporting is mandatory, and most cancers are reported from more than one source. It is estimated that >96% of all incident cancers are reported to the SCR, and 98% of those reported are histologically verified.¹⁵ The SCR does not register cancers where information is based on death certificate only. Information on histology was obtained from the records of the SCR. The SCR uses the same code for papillary and follicular carcinomas and the same code for anaplastic and medullary carcinomas, so it is not possible to distinguish between these histologies. Thyroid cancer incidence rates among males were approximately 2 per 1,000,000 person-years during the 1960s, rose to a peak of 3 during 1975–1985 and fell back to 2 during the 1990s. Corresponding rates for females were 5, 6.5 and 5 per 1,000,000 person-years.¹⁵

The expected number of thyroid cancers in the cohort was calculated using the EPICURE software package¹⁶ with incidence data from the SCR and indirect standardization with adjustment for sex, attained age and calendar period. Standardized incidence ratios (SIRs) were calculated as the ratio between observed and expected numbers of thyroid cancers along with exact 95% CIs.¹⁷ We do not report the expected number of cases (*E*) in any of the tables presented here; but when the observed number of cases is 0,

TABLE I—CHARACTERISTICS OF PATIENTS EXPOSED TO ¹³¹I CLASSIFIED ACCORDING TO PRIOR EXPOSURE TO EXTERNAL RADIATION THERAPY (XRT) TO THE NECK AND REASON FOR REFERRAL

| | No prior exposure to XRT | | | Prior exposure to XRT | | |
|--|----------------------------|-----------|------------|----------------------------|----------------|----------------|
| | Reason for referral | | | Reason for referral | | |
| | Suspicion of thyroid tumor | Other | All | Suspicion of thyroid tumor | Other | All |
| Number of patients at risk ¹ | 11,015 | 24,010 | 35,025 | 608 | 1,159 | 1,767 |
| Observed number of thyroid cancers | 69 | 36 | 105 | 12 | 12 | 24 |
| Percentage male | 14 | 23 | 20 | 18 | 25 | 22 |
| Mean age at first exposure (range, years) | 44 (0–74) | 43 (0–74) | 43 (0–74) | 53 (16–74) | 51 (8–74) | 52 (8–74) |
| Patients <20 years of age at exposure, (%) | 6 | 7 | 7 | 0 | 2 | 1 |
| Mean follow-up period (range, years) | 27 (2–47) | 27 (2–47) | 27 (2–47) | 20 (2–44) | 20 (2–47) | 20 (2–47) |
| Mean number of administered doses (range) | 1.3 (1–10) | 1.3 (1–9) | 1.3 (1–10) | — ₂ | — ₂ | — ₂ |
| Mean total administered activity ³ (MBq) | 2.5 | 1.6 | 1.9 | 3.5 | 3.1 | 3.2 |
| Mean 24 hr thyroid uptake (%) | 39 | 38 | 39 | 36 | 36 | 36 |
| Mean total absorbed ¹³¹ I dose to thyroid ⁴ (Gy) | 1.37 | 0.94 | 1.07 | 1.75 | 1.74 | 1.74 |

¹Number of patients alive and free of thyroid cancer 2 years after first exposure. ²Only total administered activity was recorded. ³Mean over all patients of total administered activity (summed over all administrations) for each patient. ⁴Mean over all patients of total absorbed dose to thyroid (summed over all administrations) for each patient.

this quantity can be calculated from the upper limit (denoted U) of the CI and the observed number of cases (O) using the formula $E = \chi^2_{2(O+1),0.975}/2U$, where $\chi^2_{2(O+1),0.975}$ is the 97.5th percentile of the χ^2 distribution with $2(O+1)$ degrees of freedom. This can be implemented in, e.g., Microsoft Excel using the formula $\text{CHIINV}[0.025,2*(O+1)]/(2*U)$.

Results based on this cohort were previously reported in 1988⁴ and 1996.⁵ The major additions in this report are the inclusion of individuals previously exposed to external radiation therapy to the neck region and the assessment of risk as early as 2 years after exposure (the previous reports excluded the first 5 years following exposure). In addition, follow-up has been extended by 8 years compared to the previous publication. Unlike previous studies based on this cohort, we excluded individuals exposed in 1950 and 1951 since it is not possible to ascertain whether these individuals died prior to 1952 (the first year for which mortality data are available).

Information on prior external radiation therapy to the neck was obtained from patients prior to examination with ^{131}I and recorded in the medical record. We abstracted this information from the medical records, a process which was simplified by the fact that each of the treating hospitals utilizes a standardized form for recording information related to ^{131}I administration. One of the items on this form is a check box for prior external radiation therapy to the neck. Information on the reason for, date of and dose of external radiation therapy was not recorded. Previous reports on this cohort excluded patients who reported prior external radiation therapy to the neck. With the exception of thyroid cancer, patients previously treated with external radiation therapy for both benign and malignant conditions were included. Results for patients previously exposed to external radiation therapy are always reported separately.

A total of 7,915 individuals were first exposed during 1952–1957, of whom 7,405 were alive on 1 January 1958 (when cancer registration commenced). Similar to previous reports, we assumed that these 7,405 individuals were free of thyroid cancer on 1 January 1958. To study whether this assumption may have induced bias, we conducted an analysis restricted to patients first exposed during 1958–1969.

It is possible that patients with high uptake ($T_{24} \geq 50\%$) were considered hyperthyroid and referred for surgery, in which case they would be at reduced risk of thyroid cancer. We therefore estimated SIRs separately for individuals with uptake in the ranges 0–30%, 30–50% and $\geq 50\%$.

Poisson regression models¹⁸ were fitted to determine whether the SIR varied across categories of age at first exposure, time since first exposure, absorbed ^{131}I dose to the thyroid gland and gender while simultaneously adjusting for each of these factors. The models were estimated in the framework of generalized linear models using SAS (Cary, NC) PROC GENMOD, where the outcome was the observed number of cases, the error structure Poisson and the link logarithmic and the logarithm of the expected number of cases was an offset. Separate models were fitted for each combination of reason for referral and prior exposure to external radiation therapy. The likelihood ratio test was used to determine whether statistically significant differences in the SIR existed according to the factors of interest.

Cox proportional hazards models¹⁹ were fitted to the data for patients diagnosed with thyroid cancer, to learn whether latency time (time from first administration of ^{131}I to diagnosis of thyroid cancer) or time from diagnosis of thyroid cancer to death due to thyroid cancer was associated with prior exposure to external radiation therapy to the neck while adjusting for the other factors of interest.

RESULTS

The most common reasons for diagnostic administration of ^{131}I were suspected thyroid tumor (32%), hyperthyroidism (42%), hy-

pothyroidism (17%) and hypercalcemia (8%). Excess thyroid cancers were observed only among the 1,767 patients who received prior external radiation therapy to the neck (SIR = 9.8, 95% CI 6.3–14.6) and among patients referred because of a suspicion of thyroid tumor (SIR = 3.5, 95% CI 2.7–4.4 for 11,015 patients without previous external radiation therapy).

Evidence suggests that exposure to ionizing radiation may increase the risk of papillary thyroid carcinoma but not other types of thyroid cancer (at least in individuals exposed at young ages). For example, 105 of 107 cases of childhood thyroid cancer diagnosed in Belarus following the Chernobyl accident were papillary carcinomas.²⁰ Of the 129 thyroid cancers diagnosed during follow-up in our study (*i.e.*, from 2 years subsequent to the first ^{131}I administration), 96 were papillary or follicular, 27 were anaplastic or medullary, 1 was a sarcoma and 5 were of unclear histology. Among patients who did not report previous exposure to external radiation therapy to the neck, 72% had thyroid cancers classified as papillary or follicular compared to 83% who reported previous exposure to external radiation therapy. As mentioned previously, the SCR does not record detailed information on histology. We have, however, abstracted information on histology from medical records for all patients diagnosed during 1958–1987: 38% were classified as papillary, 30% follicular, 5% medullary, 14% anaplastic and 12% mixed follicular/papillary.

Patients without prior exposure to external radiation therapy to the neck

The absorbed dose to the thyroid gland was estimated to be 1.37 Gy among patients referred due to suspicion of a thyroid tumor and 0.94 Gy among patients referred for other reasons (Table I). Patients referred because of a suspected thyroid tumor had relatively larger glands (Table II), which resulted in a relatively lower estimated dose when thyroid weight was taken into account.

Differences exist between the dose estimates presented in this report and those presented previously.⁵ This is partly due to our use of a more refined method of dose estimation (we estimated the dose separately for each administration for an individual and adjusted for age). The main difference, however, is that the previous report presented the unadjusted dose estimates for all patients along with the adjusted dose estimates based on only those patients for whom thyroid weight was available. Since the patients with a known thyroid weight received lower doses, these estimates are not comparable. In Table II, we present the adjusted and unadjusted estimates for the same patients (*i.e.*, those for whom information on thyroid mass was available). Unadjusted estimates for all patients are presented in Table I.

Excess thyroid cancers were observed among the 11,015 patients referred because of a suspected thyroid tumor (SIR = 3.48, 95% CI 2.71–4.41), though not for the 24,010 patients referred for other reasons (SIR = 0.91, 95% CI 0.64–1.26) (Table III).

There was no evidence of a dose–response relationship for either of the 2 classifications of reason for referral among patients without prior exposure to external radiation therapy (Table III). Neither was an association observed between the estimated SIR and time since first administration of ^{131}I (Table III) for these individuals. Although the estimated SIRs were slightly higher during the first 2 periods of follow-up, 2–10 years after exposure, they were of similar magnitude within each of the 4 classifications of follow-up time; *i.e.*, a statistically significant excess risk of thyroid cancer was observed among individuals referred due to suspicion of thyroid cancer, an excess risk that did not vary with time since first ^{131}I exposure. There was no evidence of excess risk of thyroid cancer among individuals referred for other reasons, a finding which was consistent for each of the 4 classifications of time since first ^{131}I exposure. There were no discernible trends in risk among patients with prior exposure to external radiation therapy, though the data are more difficult to interpret due to the lower number of thyroid cancers diagnosed.

TABLE II – DISTRIBUTION OF THYROID WEIGHT AND THYROID DOSE ACCORDING TO PRIOR EXPOSURE TO EXTERNAL RADIATION THERAPY (XRT) TO THE NECK AND REASON FOR REFERRAL

| | Reason for referral | | |
|---|----------------------------|-------|------|
| | Suspicion of thyroid tumor | Other | All |
| No prior exposure to XRT | | | |
| Percent with weight available | 52 | 46 | 48 |
| Distribution of thyroid weight | | | |
| <30 g | 31 | 62 | 51 |
| 30–60 g | 57 | 35 | 43 |
| >60 g | 12 | 3 | 6 |
| Unadjusted mean dose to thyroid gland ¹ (Gy) | 1.06 | 0.80 | 0.89 |
| Adjusted mean dose to thyroid gland ² (Gy) | 0.81 | 0.67 | 0.72 |
| Prior exposure to XRT | | | |
| Percent with weight available | 70 | 44 | 53 |
| Distribution of thyroid weight | | | |
| <30 g | 45 | 65 | 56 |
| 30–60 g | 45 | 32 | 38 |
| >60 g | 9 | 3 | 6 |
| Unadjusted mean dose to thyroid gland ¹ (Gy) | 1.53 | 1.77 | 1.66 |
| Adjusted mean dose to thyroid gland ² (Gy) | 1.24 | 1.53 | 1.40 |
| All patients³ | | | |
| Percent with weight available | 53 | 45 | 48 |
| Distribution of thyroid weight | | | |
| <30 g | 32 | 62 | 52 |
| 30–60 g | 56 | 35 | 42 |
| >60 g | 12 | 3 | 6 |
| Unadjusted mean dose to thyroid gland ¹ (Gy) | 1.09 | 0.84 | 0.93 |
| Adjusted mean dose to thyroid gland ² (Gy) | 0.84 | 0.71 | 0.75 |

¹ Mean absorbed dose without adjusting for thyroid weight (among patients with known thyroid weight). ² Mean absorbed dose after adjusting for thyroid weight (among patients with known thyroid weight). ³ All patients, irrespective of prior exposure to external radiation therapy.

There was no evidence of an association between age at first exposure and subsequent excess risk of thyroid cancer (Table IV), though only 7% of patients were younger than 20 years at the time of first administration of ¹³¹I. Among the 2,367 individuals younger than 20 years at first exposure, 3 had thyroid cancer observed during follow-up compared to 3.0 expected.

The SIR for males was higher than that for females among individuals referred due to suspicion of thyroid cancer (Table IV). This difference was statistically significant ($p < 0.0001$) based on the likelihood ratio test in the Poisson regression model, which controlled for ¹³¹I dose, time since first exposure and age at first exposure. This was the only factor (of gender, ¹³¹I dose, time since first exposure and age at first exposure) for which a statistically significant difference (*i.e.*, $p < 0.1$) in SIRs was observed for any of the combinations of reasons for referral and exposure to prior external radiation therapy. Among patients referred for other reasons, the estimated SIR was lower for males than females, though the difference was not statistically significant ($p = 0.11$).

The SIR is a measure of the multiplicative risk associated with exposure. Since the baseline risk of thyroid cancer differs considerably between males and females, it is of interest to also estimate the additive (or absolute) excess risk. The estimated SIR for females (all reasons for referral) was 1.62 ($O = 88, E = 54.20, Y = 704,332$), while the corresponding estimate for males was 3.29 ($O = 17, E = 5.17, Y = 151,127$) (Table IV), where O, E and Y represent the observed and expected numbers of thyroid cancers diagnosed during Y person-years at risk. The estimated additive excess risk, given by $(O - E)/Y$, was 0.783 excess thyroid cancers per 10,000 person-years for males compared to 0.480 excess thyroid cancers per 10,000 person-years for females; *i.e.*, the

estimated excess risk associated with exposure to ¹³¹I was higher for males than females on both the absolute and relative scales. Excess risk was, again, restricted to patients referred due to suspicion of a thyroid tumor. Among patients who did not report previous exposure to external radiation therapy, the estimated numbers of excess thyroid cancers per 10,000 person-years were 0.0, 0.7, 0.3 and 1.0 for the dose categories <0.25, 0.25–0.50, 0.50–1.00 and >1.00 Gy, respectively.

There was no evidence of an association between excess risk and 24 hr uptake. Among individuals referred due to suspicion of a thyroid tumor, the estimated SIRs were 3.7, 3.5 and 3.3 based on 15, 39 and 15 observed thyroid cancers for patients with uptakes in the ranges 0–30%, 30–50% and >50%, respectively. Among patients referred for other reasons, the corresponding estimates were 0.6, 1.2 and 0.8 based on 6, 21 and 9 observed thyroid cancers.

Patients previously exposed to external radiation therapy to the neck

Only 1,767 patients reported previous external radiation therapy to the neck compared to 35,022 who did not (Table I). Among these 1,767 patients, 24 thyroid cancers were diagnosed during follow-up compared to 2.4 expected, giving an estimated SIR of 9.8 (95% CI 6.3–14.6) (Table III). Although the estimated SIRs were considerably higher, the pattern of estimates according to other factors was similar to that observed among patients who did not report previous exposure to external radiation therapy; *i.e.*, the excess risk of thyroid cancer was higher among the 608 patients referred due to suspicion of a thyroid cancer, but there was no evidence of an association between excess risk and ¹³¹I dose (Table III), time since exposure to ¹³¹I (Table III) and age at first exposure to ¹³¹I (Table IV). The estimated SIR was higher for males than females for both classifications of reason for referral (Table IV), but the differences were not statistically significant (based on a Poisson regression model).

There was evidence that patients previously exposed to external radiation therapy to the neck had shorter latency times (time from first ¹³¹I exposure to diagnosis of thyroid cancer) and shorter survival times (time from diagnosis of cancer to death due to thyroid cancer), though the effects were not statistically significant. In a Cox proportional hazards model fitted to the data for the 129 patients diagnosed with thyroid cancer with latency time as the outcome, the estimated hazard ratio for patients previously exposed to external radiation therapy compared to those who were not was 1.48 (95% CI 0.92–2.37). When survival time was the outcome, the estimated hazard ratio was 1.49 (95% CI 0.67–3.28). Both estimates were adjusted for reason for referral, age at first exposure and gender. In the latency analysis, all 129 observations ended in an “event” (diagnosis of thyroid cancer), whereas in the analysis of survival time following diagnosis, only the 32 deaths classified as being due to thyroid cancer were considered events.

Similar estimates were obtained when the analyses were restricted to the 29,720 patients first exposed to ¹³¹I during 1958–1969 (1958 being the year that population-based cancer registration commenced). A total of 104 thyroid cancers were diagnosed among these patients, giving an estimated SIR of 2.13 (*cf.* 2.09 for the 36,792 patients first exposed during 1952–1969). In the restricted analysis, the SIR for patients without prior exposure to external radiation therapy to the neck who were referred due to suspicion of a thyroid tumor was 3.37 (*cf.* 3.48), and for those referred for other reasons it was 0.87 (*cf.* 0.91).

DISCUSSION

We found no evidence of an increased risk of thyroid cancer due to exposure to ¹³¹I among 36,792 Swedes who received ¹³¹I for diagnostic purposes. Increased risks were confined to patients previously exposed to radiotherapy toward the neck region and/or those referred for examination due to suspicion of a thyroid tumor.

TABLE III - OBSERVED NUMBER OF THYROID CANCERS (O), SIR AND ASSOCIATED 95% CI STRATIFIED ACCORDING TO ¹³¹I DOSE, PRIOR EXPOSURE TO EXTERNAL RADIATION THERAPY (XRT) TO THE NECK REGION, REASON FOR REFERRAL, ESTIMATED THYROID DOSE AND NUMBER OF YEARS SINCE FIRST ADMINISTRATION OF ¹³¹I

| | Years after first administration of ¹³¹ I | | | | | | | | | | | | | | |
|--|--|-------|-------------|------|-------|-------------|-------|-------|-------------|-----|-------|-------------|-----|-------|-------------|
| | 2-5 | | | 5-10 | | | 10-20 | | | ≥20 | | | All | | |
| | O | SIR | 95% CI | O | SIR | 95% CI | O | SIR | 95% CI | O | SIR | 95% CI | O | SIR | 95% CI |
| Patients who did not report previous XRT to the neck region | | | | | | | | | | | | | | | |
| Referred for suspicion of a thyroid tumor | | | | | | | | | | | | | | | |
| ≤0.25 | 0 | 0.00 | 0.00-17.46 | 2 | 5.22 | 0.63-18.85 | 2 | 2.48 | 0.30-8.97 | 4 | 5.29 | 1.44-13.55 | 8 | 3.71 | 1.60-7.31 |
| 0.25-0.50 | 0 | 0.00 | 0.00-12.71 | 5 | 9.34 | 3.03-21.80 | 4 | 3.51 | 0.96-9.00 | 3 | 2.52 | 0.52-7.35 | 12 | 3.80 | 1.96-6.64 |
| 0.50-1.00 | 0 | 0.00 | 0.00-11.27 | 0 | 0.00 | 0.00-5.94 | 3 | 2.23 | 0.46-6.53 | 7 | 4.57 | 1.84-9.41 | 10 | 2.62 | 1.25-4.81 |
| >1.00 | 11 | 12.00 | 5.99-21.46 | 8 | 4.60 | 1.99-9.06 | 7 | 1.85 | 0.75-3.82 | 13 | 3.07 | 1.63-5.24 | 39 | 3.65 | 2.60-5.00 |
| All | 11 | 6.30 | 3.15-11.27 | 15 | 4.58 | 2.56-7.55 | 16 | 2.27 | 1.30-3.68 | 27 | 3.50 | 2.30-5.09 | 69 | 3.48 | 2.71-4.41 |
| Referred for other reasons | | | | | | | | | | | | | | | |
| ≤0.25 | 1 | 1.01 | 0.03-5.61 | 2 | 1.08 | 0.13-3.90 | 1 | 0.26 | 0.01-1.43 | 1 | 0.23 | 0.01-1.27 | 5 | 0.45 | 0.15-1.05 |
| 0.25-0.50 | 2 | 3.55 | 0.43-12.83 | 0 | 0.00 | 0.00-3.48 | 2 | 0.89 | 0.11-3.21 | 3 | 1.13 | 0.23-3.31 | 7 | 1.07 | 0.43-2.21 |
| 0.50-1.00 | 0 | 0.00 | 0.00-5.41 | 1 | 0.72 | 0.02-4.01 | 2 | 0.66 | 0.08-2.38 | 5 | 1.19 | 0.39-2.77 | 8 | 0.86 | 0.37-1.69 |
| >1.00 | 1 | 1.10 | 0.03-6.15 | 6 | 3.18 | 1.17-6.92 | 3 | 0.73 | 0.15-2.14 | 6 | 1.05 | 0.39-2.29 | 16 | 1.27 | 0.73-2.06 |
| All | 4 | 1.27 | 0.35-3.26 | 9 | 1.45 | 0.66-2.76 | 8 | 0.60 | 0.26-1.19 | 15 | 0.88 | 0.50-1.46 | 36 | 0.91 | 0.64-1.26 |
| All reasons for referral | | | | | | | | | | | | | | | |
| ≤0.25 | 1 | 0.83 | 0.02-4.63 | 4 | 1.79 | 0.49-4.58 | 3 | 0.64 | 0.13-1.87 | 5 | 0.97 | 0.31-2.26 | 13 | 0.98 | 0.52-1.67 |
| 0.25-0.50 | 2 | 2.34 | 0.28-8.47 | 5 | 3.13 | 1.02-7.31 | 6 | 1.77 | 0.65-3.85 | 6 | 1.56 | 0.57-3.40 | 19 | 1.96 | 1.18-3.06 |
| 0.50-1.00 | 0 | 0.00 | 0.00-3.65 | 1 | 0.50 | 0.01-2.77 | 5 | 1.14 | 0.37-2.67 | 12 | 2.09 | 1.08-3.65 | 18 | 1.37 | 0.81-2.17 |
| >1.00 | 12 | 6.58 | 3.40-11.50 | 14 | 3.86 | 2.11-6.48 | 10 | 1.27 | 0.61-2.33 | 19 | 1.91 | 1.15-2.99 | 55 | 2.36 | 1.78-3.08 |
| All | 15 | 3.07 | 1.72-5.06 | 24 | 2.53 | 1.62-3.77 | 24 | 1.18 | 0.76-1.76 | 42 | 1.70 | 1.23-2.30 | 105 | 1.77 | 1.45-2.14 |
| Patients who reported previous XRT to the neck | | | | | | | | | | | | | | | |
| Referred for suspicion of a thyroid tumor | | | | | | | | | | | | | | | |
| ≤0.25 | 0 | 0.00 | 0.00-477.05 | 0 | 0.00 | 0.00-299.91 | 1 | 50.28 | 1.27-280.13 | 0 | 0.00 | 0.00-259.81 | 1 | 18.48 | 0.47-102.95 |
| 0.25-0.50 | 0 | 0.00 | 0.00-252.56 | 0 | 0.00 | 0.00-182.52 | 0 | 0.00 | 0.00-114.23 | 1 | 43.71 | 1.11-243.56 | 1 | 11.11 | 0.28-61.92 |
| 0.50-1.00 | 1 | 43.91 | 1.11-244.63 | 0 | 0.00 | 0.00-101.44 | 1 | 15.27 | 0.39-85.07 | 0 | 0.00 | 0.00-60.00 | 2 | 10.75 | 1.30-38.82 |
| >1.00 | 1 | 15.00 | 0.38-83.59 | 3 | 27.15 | 5.60-79.36 | 4 | 21.28 | 5.80-54.49 | 0 | 0.00 | 0.00-20.17 | 8 | 14.60 | 6.30-28.77 |
| All | 2 | 17.89 | 2.17-64.64 | 3 | 16.73 | 3.45-48.88 | 6 | 19.63 | 7.20-42.73 | 1 | 3.55 | 0.09-19.80 | 12 | 13.66 | 7.06-23.87 |
| Referred for other reasons | | | | | | | | | | | | | | | |
| ≤0.25 | 0 | 0.00 | 0.00-99.07 | 0 | 0.00 | 0.00-58.93 | 2 | 19.76 | 2.39-71.39 | 0 | 0.00 | 0.00-41.79 | 2 | 6.91 | 0.84-24.97 |
| 0.25-0.50 | 0 | 0.00 | 0.00-121.37 | 0 | 0.00 | 0.00-75.43 | 0 | 0.00 | 0.00-48.07 | 0 | 0.00 | 0.00-63.00 | 0 | 0.00 | 0.00-17.19 |
| 0.50-1.00 | 0 | 0.00 | 0.00-120.96 | 0 | 0.00 | 0.00-69.69 | 0 | 0.00 | 0.00-41.12 | 1 | 14.34 | 0.36-79.90 | 1 | 4.12 | 0.10-22.94 |
| >1.00 | 0 | 0.00 | 0.00-46.99 | 2 | 13.42 | 1.63-48.50 | 4 | 14.75 | 4.02-37.77 | 3 | 9.41 | 1.94-27.50 | 9 | 11.01 | 5.03-20.90 |
| All | 0 | 0.00 | 0.00-20.88 | 2 | 6.38 | 0.77-23.05 | 6 | 11.14 | 4.09-24.24 | 4 | 7.47 | 2.04-19.13 | 12 | 7.67 | 3.96-13.40 |
| All reasons for referral | | | | | | | | | | | | | | | |
| ≤0.25 | 0 | 0.00 | 0.00-82.04 | 0 | 0.00 | 0.00-49.26 | 3 | 24.78 | 5.11-72.40 | 0 | 0.00 | 0.00-36.00 | 3 | 8.74 | 1.80-25.53 |
| 0.25-0.50 | 0 | 0.00 | 0.00-81.97 | 0 | 0.00 | 0.00-53.37 | 0 | 0.00 | 0.00-33.83 | 1 | 12.28 | 0.31-68.42 | 1 | 3.28 | 0.08-18.29 |
| 0.50-1.00 | 1 | 18.77 | 0.48-104.59 | 0 | 0.00 | 0.00-41.31 | 1 | 6.44 | 0.16-35.90 | 1 | 7.62 | 0.19-42.46 | 3 | 6.99 | 1.44-20.44 |
| >1.00 | 1 | 6.89 | 0.17-38.38 | 5 | 19.27 | 6.26-44.97 | 8 | 17.43 | 7.52-34.34 | 3 | 5.98 | 1.23-17.48 | 17 | 12.45 | 7.25-19.93 |
| All | 2 | 6.93 | 0.84-25.05 | 5 | 10.15 | 3.29-23.68 | 12 | 14.21 | 7.34-24.82 | 5 | 6.12 | 1.99-14.29 | 24 | 9.83 | 6.30-14.62 |

TABLE IV - OBSERVED NUMBER OF THYROID CANCERS (O), SIR AND ASSOCIATED 95% CI STRATIFIED ACCORDING TO PRIOR EXPOSURE TO EXTERNAL RADIATION THERAPY (XRT) TO THE NECK, REASON FOR REFERRAL, GENDER AND AGE AT FIRST ADMINISTRATION OF ¹³¹I

| Age (years) | Males | | | Females | | | All | | |
|---|-------|-------|--------------|---------|-------|--------------|-----|-------|--------------|
| | O | SIR | 95% CI | O | SIR | 95% CI | O | SIR | 95% CI |
| No prior XRT | | | | | | | | | |
| Referred for suspicion of a thyroid tumor | | | | | | | | | |
| 0-20 | 0 | 0.00 | 0.00-121.96 | 1 | 1.18 | 0.03-6.60 | 1 | 1.14 | 0.03-6.37 |
| 21-50 | 7 | 9.95 | 4.00-20.50 | 30 | 2.55 | 1.72-3.64 | 37 | 2.96 | 2.09-4.09 |
| 51+ | 9 | 17.07 | 7.80-32.40 | 22 | 3.71 | 2.33-5.62 | 31 | 4.80 | 3.26-6.82 |
| All | 16 | 12.69 | 7.25-20.60 | 53 | 2.86 | 2.14-3.74 | 69 | 3.48 | 2.71-4.41 |
| Referred for other reasons | | | | | | | | | |
| 0-20 | 0 | 0.00 | 0.00-19.37 | 2 | 1.05 | 0.13-3.81 | 2 | 0.96 | 0.12-3.46 |
| 21-50 | 0 | 0.00 | 0.00-1.55 | 23 | 0.98 | 0.62-1.47 | 23 | 0.89 | 0.57-1.34 |
| 51+ | 1 | 0.75 | 0.02-4.16 | 10 | 0.97 | 0.46-1.77 | 11 | 0.94 | 0.47-1.68 |
| All | 1 | 0.26 | 0.01-1.43 | 35 | 0.98 | 0.68-1.37 | 36 | 0.91 | 0.64-1.26 |
| All reasons for referral | | | | | | | | | |
| 0-20 | 0 | 0.00 | 0.00-16.72 | 3 | 1.09 | 0.23-3.20 | 3 | 1.01 | 0.21-2.96 |
| 21-50 | 7 | 2.27 | 0.91-4.69 | 53 | 1.51 | 1.13-1.97 | 60 | 1.57 | 1.20-2.02 |
| 51+ | 10 | 5.35 | 2.57-9.85 | 32 | 1.96 | 1.34-2.77 | 42 | 2.31 | 1.67-3.13 |
| All | 17 | 3.29 | 1.92-5.27 | 88 | 1.62 | 1.30-2.00 | 105 | 1.77 | 1.45-2.14 |
| Prior XRT | | | | | | | | | |
| Referred for suspicion of a thyroid tumor | | | | | | | | | |
| 0-20 | 0 | 0.00 | 0.00-6847.24 | 0 | 0.00 | 0.00-2135.59 | 0 | 0.00 | 0.00-1627.87 |
| 21-50 | 1 | 34.96 | 0.89-194.77 | 3 | 7.06 | 1.46-20.65 | 4 | 8.82 | 2.40-22.60 |
| 51+ | 1 | 20.71 | 0.52-115.39 | 7 | 18.70 | 7.52-38.52 | 8 | 18.93 | 8.17-37.30 |
| All | 2 | 25.83 | 3.13-93.30 | 10 | 12.49 | 5.99-22.97 | 12 | 13.66 | 7.06-23.87 |
| Referred for other reasons | | | | | | | | | |
| 0-20 | 0 | 0.00 | 0.00-1386.10 | 1 | 65.89 | 1.67-367.09 | 1 | 56.06 | 1.42-312.33 |
| 21-50 | 2 | 22.50 | 2.72-81.28 | 5 | 7.15 | 2.32-16.70 | 7 | 8.89 | 3.57-18.31 |
| 51+ | 1 | 10.14 | 0.26-56.52 | 3 | 4.55 | 0.94-13.28 | 4 | 5.27 | 1.44-13.50 |
| All | 3 | 15.78 | 3.25-46.11 | 9 | 6.55 | 3.00-12.43 | 12 | 7.67 | 3.96-13.40 |
| All reasons for referral | | | | | | | | | |
| 0-20 | 0 | 0.00 | 0.00-1152.75 | 1 | 59.15 | 1.50-329.58 | 1 | 49.74 | 1.26-277.12 |
| 21-50 | 3 | 25.53 | 5.27-74.62 | 8 | 7.12 | 3.07-14.03 | 11 | 8.86 | 4.42-15.86 |
| 51+ | 2 | 13.62 | 1.65-49.19 | 10 | 9.67 | 4.64-17.78 | 12 | 10.16 | 5.25-17.75 |
| All | 5 | 18.69 | 6.07-43.61 | 19 | 8.74 | 5.26-13.64 | 24 | 9.83 | 6.30-14.62 |

No dose-response relationship or variation in risk with age was noted, though our study included very few patients under age 20.

The thyroid gland is highly susceptible to ionizing radiation, presumably due to its superficial location, high level of oxygenation and high cell turnover rate during childhood and adolescence. In studies of children who received external radiation therapy for tinea capitis,²¹ doses as low as 0.1 Sv were found to increase the risk of thyroid cancer and the dose-response relationship appeared to be linear below 4 Sv. At doses above 4 Sv, cell killing probably outweighs carcinogenic transformation.³

Age at exposure

A striking feature of radiation-associated thyroid cancers is the profound age dependence, which suggests that the thyroid gland is especially sensitive to ionizing radiation during periods of rapid cell proliferation. Atomic bomb survivor data underline the strong modifying effect of age at exposure, with no excess risk seen in individuals older than 20 years at exposure.¹¹ A pooled analysis of 7 studies revealed that thyroid cancer was induced by brief external radiation in childhood but rarely developed after adult exposure.¹⁰

Although screening programs around Chernobyl likely affect the findings, the geographic distribution of childhood thyroid cancers in the Chernobyl area suggests a relationship with the ionizing radiation from the radionuclides released from the accident. Thyroid doses, including not only ¹³¹I but an additional unknown fraction of short-lived radioiodines, resulted in estimated thyroid doses of 2-5 Gy.³ A total of 1,800 childhood thyroid cancers have been identified in the most heavily contaminated areas of southern Belarus, northern Ukraine and the southwest of Russia. One peculiarity with the Chernobyl childhood cancers is the short latency period, not previously described elsewhere, which may, in part, reflect the advancement in time of diagnosis due to the intense screening that followed the accident. It is also possible, however, that this finding is a general phenomenon, which could not be observed in other cohorts due to lack of statistical power.

Our previous follow-up report⁵ excluded the first 5 years after exposure. In light of the Chernobyl data,³ we included the 2-5 years after exposure without observing any increase in risk during this period. Only 3 thyroid cancers (SIR = 1.01) were found among the 2,367 individuals who were first exposed while aged less than 20 years without prior exposure to radiation therapy. One of the 3 cases was diagnosed in a patient referred for ¹³¹I examination because of a suspicion of thyroid cancer. One possible reason that we did not observe an increase in risk for this age group is that only about 300 individuals were younger than 10 years at examination. One case of thyroid cancer (expected 0.02) was diagnosed among the 20 individuals who were first exposed while aged less than 20 years and previously exposed to external radiation therapy.

Protraction of dose and dose distribution

Protracted or fractionated exposure is less carcinogenic than brief γ exposure,³ but the results are not entirely consistent. The half-life of ¹³¹I is approximately 1 week, and most of the absorbed dose to the thyroid is delivered in about 6 weeks. It is conceivable that a low dose rate allows repair of DNA damage to occur or that the ability to detoxify free radicals and repair DNA is saturated at higher dose rates, thereby producing more profound negative effects on the cell. Alternatively, the distribution of dose from decay of ¹³¹I in the thyroid gland might be such that critical cells are spared. However, it could also be that a nonuniform distribution, particularly for those with an enlarged thyroid gland, leads to hot spots, which could partly explain the higher risk in the group referred due to a suspected thyroid cancer. Nonuniformity of dose and lack of information on thyroid weight for some individuals introduce uncertainties. However, we have exact information on the amount of ¹³¹I administered and the 24 hr thyroid uptake for all patients and have taken into account all parameters available. We therefore believe that the relative magnitudes of the estimated doses are reasonably accurate.

Although our patients received relatively large diagnostic doses (approx. 1.0 Gy), protracted radiation exposures would be expected to be less carcinogenic than if the same dose was experienced over a brief period. The evidence in humans for a reduced risk of thyroid disease after protracted exposure is sparse. Lifetime exposure to elevated levels of natural background radiation in China has not been associated with an increase in the number of thyroid tumors.²² A French study of childhood irradiation for skin hemangiomas suggested a sparing effect with protracted exposure.²³ A pooled analysis of 7 major studies of thyroid irradiation concluded that spreading dose over time may lower the risk of subsequent thyroid cancer.¹⁰

Thyroid condition

The relationship between benign thyroid disorders and thyroid cancer is methodologically difficult to investigate. Although a number of studies have related thyroid adenoma, goiter and thyroiditis with an excess risk for thyroid carcinoma, other studies have failed to support these findings.^{1,2,8} Few report an increased risk of thyroid cancer in patients with previous hypothyroidism or hyperthyroidism, though some studies have indicated an increased risk in hyperthyroid patients treated with ¹³¹I.^{1,2,8} In a pooled analysis of 12 case-control studies including 2,519 thyroid cancer cases, a strong relationship between previous goiter, benign adenomas and nodules was observed, with odds ratios as high as 38 for men with a previous history of goiter.⁸

As with other endocrine glands, it is clinically problematic to distinguish between hyperplasia, benign thyroid tumors and malignant thyroid tumors. In analogy with thyroid carcinomas, the classification of benign thyroid disorders is complex and has been the focus of several reassessments following the availability of thyroid uptake tests, scintigraphy, ultrasound and fine needle aspiration biopsies.

We addressed these issues by excluding all thyroid cancers diagnosed within 2 years of the initial ¹³¹I administration, to reduce the effect of increased medical surveillance. However, comparison to general population rates is inappropriate if the condition studied, *i.e.*, benign thyroid conditions, is strongly associated with thyroid cancer and the exposure under study since it leads to an overestimate of the excess risk associated with exposure to ¹³¹I. Internal comparisons based on dose response are, however, free of the difficulties associated with external comparisons.

External radiation therapy

Radiation treatment was used mainly until the 1960s for benign disorders such as cervical lymphadenopathy, tonsillitis, enlarged thymus, tinea capitis and skin disorders. Such treatment is likely to have caused the sharp increase in thyroid cancer incidence first noticed in the 1950s, reaching a plateau in the 1980s.^{24–26} In a birth cohort analysis, Pottern *et al.*²⁶ reported that the incidence of thyroid cancer for those born during 1870–1910 was low, increased for birth cohorts 1910–1950 and declined for those born thereafter, a pattern which was consistent with increases in risk due to the widespread use of radiation therapy for benign conditions of the head and neck among children and adolescents from the early 1920s to the late 1950s.

Information on previous external radiation therapy to the neck was obtained from the patients, and some misclassification is possible. We believe that if this exposure were misclassified, it is more likely that individuals who received external radiotherapy

were classified as unexposed rather than *vice versa*. It could be that the patient provided erroneous information because he or she was too young to remember or the treating physician neglected to ask. Since we did not observe excess thyroid cancers among those individuals classified as having no previous radiation therapy and referred for reasons other than suspicion of thyroid cancer, we are reasonably confident that there are no serious problems with misclassification of this exposure.

We do not believe that the 10-fold increased risk of thyroid cancer observed among individuals exposed to both ¹³¹I and external radiotherapy is causally associated with administration of ¹³¹I since the excess risks are unaffected by age at exposure or absorbed ¹³¹I dose to the thyroid. It is most likely that the absorbed doses from external radiotherapy were received at higher dose rates and during earlier years of life. Unfortunately, we have no information on reason for treatment with external radiotherapy, date of treatment or dose delivered.

Strengths and limitations

The strengths of the present study are the size of the cohort and the almost complete information on the amount of iodine administered and thyroid gland uptake. The findings underscore the crucial need for information on reason for referral and previous exposure to radiotherapy. Without this information, the interpretation of the results could be very misleading. The complete follow-up through the population-based cancer, mortality and population registers facilitates estimation of SIRs through accurate data on observed number of cancers and person-years at risk.

Potential weaknesses of the study are the comparison of a patient cohort with the country as a whole since there is always a reason for an individual to be examined. Lack of dosimetry for the external radiation therapy prevented a dose–response analysis for the 1,767 individuals who reported this exposure. Our study gives only limited information on the possible risks of ¹³¹I to children because relatively few patients were administered ¹³¹I prior to age 10, when the thyroid gland is thought to be especially vulnerable to the carcinogenic effect of radiation.

Among the 608 patients referred due to suspicion of a thyroid tumor who reported previous exposure to external radiotherapy, 1 in 50 of those who were determined to be free of thyroid cancer at the time of examination were diagnosed with a thyroid cancer 2 or more years later. Many of these cancers would have been present and could probably have been detected at the first examination. Among those who did not report prior exposure to external radiotherapy, the corresponding figures were 1 in 167 for the 11,105 patients referred for suspicion of a thyroid tumor and 1 in 687 for the 24,007 patients referred for other reasons. It should be emphasized that this is a selected group of individuals who were referred to clinics specializing in thyroid disorders.

Most clinicians have 2 concerns regarding the adverse effects of radioiodine, the carcinogenic and the teratogenic effects. The carcinogenic effect of ¹³¹I after thyroid uptake tests and scintigrams appears to be negligible for exposure during adulthood. The teratogenic effect will be addressed in a future report.

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