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Thyroid Cancer after Diagnostic Administration of Iodine-131[1]

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To provide quantitative data on the risk of thyroid cancer after exposure to ^{131}I, 34,104 patients administered ^{131}I for diagnostic purposes were followed for up to 40 years. The mean thyroid dose was estimated as 1.1 Gy, and 67 thyroid cancers occurred in contrast to 49.7 expected (standardized incidence ratio = 1.35; 95% confidence interval 1.05–1.71). Excess cancers were apparent only among patients referred because of a suspected thyroid tumor, and no increased risk was seen among those referred for other reasons. Further, risk was not related to radiation dose to the thyroid gland, time since exposure or age at exposure. The slight excess of thyroid cancer thus appeared to be due to the underlying thyroid condition and not radiation exposure. Among those under age 20 years when ^{131}I was administered, a small excess risk (3 cancers compared to 1.8 expected) was about 2–10 times lower than that predicted from data for the A-bomb survivors. These data suggest that protraction of dose may result in a lower risk than an acute X-ray exposure of the same total dose.

INTRODUCTION

The correlation between ionizing radiation and thyroid cancer was first suggested more than 40 years ago *(1, 2).* Thyroid cancer has been linked convincingly to ionizing radiation only after childhood exposure *(3–7).* Despite some reports that adult exposure might increase the risk, the evidence is weak *(8–10).* In the most recent follow-up of A-bomb survivors, thyroid cancer risk was increased significantly only among individuals under age 20 years at exposure *(11).* Other than radiation dose, age at exposure appears to be the most important determinant of future risk, and differences in reported risk estimates might merely reflect differences in age distribution.

Increased cancer risks after exposure to ^{131}I in humans have not been demonstrated convincingly. The thyroid dose from radioactive decay of ^{131}I is absorbed gradually over time with an effective half-life of 7 days. The distribution of dose within the gland is not uniform, and critical follicular cells may receive lower effective exposure than reflected by a mean thyroid dose to the entire gland. In contrast, the non-uniform dose distribution, particularly in patients with nodular glands, could lead to higher doses. No excess risk of thyroid cancer has been found among hyperthyroid patients treated with high-dose ^{131}I *(12–14).* The advanced age of patients with hyperthyroidism and the predominance of cellular destruction over cell transformation at average organ doses greater than 60 Gy are likely reasons for the low risk observed after therapeutic doses of ^{131}I.

Fallout from nuclear weapons tests has resulted in an increased risk of thyroid cancer among Marshall Islanders, but most of the dose was delivered from γ rays and short-lived radioiodines and not ^{131}I *(15).* In an extended follow-up of 4,800 children exposed to fallout from nuclear devices at the Nevada Test Site, a small but nonsignificant excess of thyroid cancer was reported after a mean thyroid dose of 0.17 Gy *(16).* Biases related to selection and dietary recall, however, could not be discounted entirely *(17).* A dramatic increase in thyroid cancer has been reported among children in Belarus within 5 years after the Chernobyl accident *(18, 19),* but the extent to which ^{131}I was involved remains unclear *(17, 18).* No childhood study has found an excess of thyroid cancer within 5 years of exposure, even after high-dose radiotherapy *(5, 20).* The short latency is also at odds with an analytical study which found no excess thyroid abnormalities among populations living in contaminated areas around Chernobyl *(21).* The remarkable and rapid increase seen in Belarus within 5 years of the accident probably reflects, to some extent, increased screening procedures and increased awareness as seen in other radiation studies *(20, 22).* Ongoing studies with estimated thyroid doses to individuals should help clarify the causal factors associated with the increase.

Against this background, we extended the follow-up of a large series of patients administered ^{131}I diagnostically *(23).*

[1] This study was conducted in cooperation with L-E. Holm, National Institute of Public Health; G. Lundell, Department of General Oncology, Radiumhemmet, Karolinska Hospital; M. Lidberg, Department of Hospital Physics, South Hospital; A. Hallquist, Stockholm's Sjukhem, Stockholm; G. Berg, Department of General Oncology, Sahlgren's Hospital, Gothenburg; G. Bjelkengren, Department of General Oncology, and U-B. Ericsson, Department of Internal Medicine, Malmö General Hospital, Malmö; and J. Tennvall, Department of General Oncology, University Hospital, Lund, Sweden.

TABLE I
Characteristics of Patients Exposed to ^{131}I in Relation to Reason for Referral

	Reason for referral		
	Suspicion of thyroid tumor	Other reasons	All
Number of patients	10,785	23,319	34,104
Males/females, %	14/86	22/78	20/80
Mean age at exposure (range), years	44 (1–75)	42 (1–75)	43 (l–75)
Patients <20 years of age at exposure, %	6	8	7
Mean follow-up period (range), years	23 (5–38)	24 (5–39)	24 (5–39)
Mean 24-h thyroid uptake (range), %	40 (0–96)	40 (0–96)	40 (0–96)
Mean administered activity (range), MBq	2.4 (0.04–37)	1.6 (0.04–37)	1.9 (0.04–37)

Note. The first 5 years after exposure were excluded

Each individual's radiation dose to the thyroid was computed for the first time based on information available in the clinical records. The aim was to provide quantitative data on the risk of thyroid cancer after relatively low-dose and low-dose-rate exposures.

MATERIALS AND METHODS

The patients were recruited from seven university hospitals; their characteristics have been described elsewhere *(23, 24).* Patients were under 75 years of age when examined with ^{131}I during the period 1950–1969. Excluded were patients lost to follow-up because of insufficient information on name or date of birth *(n* = 782), individuals dying within the first 5 years of follow-up *(n* = 2,594) and those who had received external radiotherapy to the head and neck region *(n* = 2,545).

Intensive searches revealed that 975 of the patients included in our previous investigation died during the 1950s within 5 years of exposure. They were excluded in the present analyses. The cohort thus consisted of 34,104 patients (80% women and 20% men) with a mean age of 43 years (range 1–75 years) at first exposure and a mean follow-up of 24 years (range 5–39 years, Table I). A total of 2,408 individuals were exposed before 20 years of age and 316 before the age of 10 years.

A total of 10,785 (32%) patients were referred when a thyroid tumor was suspected and 23,319 patients for other reasons (mainly possible hypo- or hyperthyroidism). Patients examined because of a suspicion of thyroid tumor were administered higher levels of ^{131}I than patients examined for other reasons (Table I). The mean administered activity was 2.4 MBq and 1.6 MBq, respectively.

The absorbed thyroid dose from ^{131}I depends on the amount of ^{131}I administered, the physical half-life of ^{131}I, the ^{131}I uptake in the thyroid gland and the size of the thyroid gland. We estimated absorbed thyroid dose for individuals taking into account actual administered ^{131}I activity and 24-h thyroid uptake of ^{131}I and applying appropriate conversion factors as published in tables in ICRP Publication 53 *(25).* Patients were grouped into four dose categories: <0.25 Gy, 0.25–0.50 Gy, 0.51–1.00 Gy and >1.00 Gy.

Thyroid weight was estimated based on information abstracted from patient records and on scintigrams which were available for 48% of the patients. The relationship between the size of the thyroid gland and absorbed dose is approximately linear; i.e., when the gland weight is doubled, the absorbed dose is reduced by a factor of 2. The influence of thyroid weight on cancer risk was evaluated only for the 48% of the cohort with this information.

The follow-up period started at the time of first ^{131}I administration or, if the patient was examined prior to 1958, at January 1, 1958. The end of follow-up was the date of thyroid cancer diagnosis, death or emigration or December 31, 1990. Thyroid cancers occurring during the first 5 years of follow-up were excluded because any thyroid cancer occurring shortly after examination would likely be related to referral or increased medical surveillance and not ^{131}I exposure. Further, there is no evidence that radiation causes excess thyroid cancer within 5 years of exposure *(20).*

A personal identification number is used for nearly all population registers in Sweden and consists of 6 digits for year, month and day of birth, supplemented with 4 digits related to where the individual was born, sex and a check digit. When the 10-digit personal identification number was not found in the medical records, patients were traced through local parishes and population registers. The personal identification number was not found in 1.6% of the cases.

The cohort was matched with the Swedish Cancer Register (SCR), using the personal 10-digit identification number, for the period 1958–1990 to identify thyroid carcinomas. The SCR was started in 1958 and receives notifications on newly diagnosed cancers from both pathologists/cytologists and physicians. Reporting to the register is mandatory, and most cancers are reported from more than one source. Over 96% of all cancers in Sweden are reported to the register *(26).* The expected number of thyroid cancers was calculated using incidence data from the SCR and indirect standardization with adjustment for sex, attained age and calendar period.

Standardized incidence ratios (SIR) were calculated as the ratio between observed and expected numbers of thyroid cancers. The 95% confidence intervals (CI) were calculated assuming that the distribution of the observed number of cancers was Poisson. Trends for SIR were calculated using the formulas suggested by Breslow and Day *(27).*

RESULTS

The absorbed dose to the thyroid gland was estimated to be 1.3 Gy among patients referred because a thyroid tumor was suspected and 0.9 Gy among those examined for other reasons (Table II). Patients referred under the suspicion of a thyroid tumor had relatively large glands, which resulted in a lower estimated thyroid dose when thyroid weight was taken into consideration (Table II).

The 34,104 patients administered ^{131}I accrued 653,093 person-years of observation. Of these, 54,480 occurred among those under age 20 when exposed. Between 1958 and 1990, 67 thyroid cancers were identified more than 5 years after ^{131}I administration. Forty-two of the 67 patients who developed thyroid cancer were referred because of clinical indications that a thyroid tumor might be present. The mean time after ^{131}I administration to the diagnosis of thyroid cancer was 15 years. Overall, 21 thyroid cancers were diagnosed 5–9 years after exposure, 22 after 10–19 years and 24 thereafter. There were 36 papillary, 18 follicular and 11 anaplastic or giant cell

TABLE II
Thyroid Dose Adjusted for Gland Size and Weight among Patients Exposed to ^{131}I

	Reason for referral		
	Suspicion of thyroid tumor	Other reasons	All
Mean dose to the thyroid (range), Gy	1.3 (0.0–25.7)	0.9 (0.0–40.5)	1.1 (0.0–40.5)
Distribution of thyroid weight (%), g[a]			
<30	31	62	51
30–60	58	35	43
>60	11	3	6
Adjusted mean dose to the thyroid (range), Gy[b]	0.9 (0.0–25.7)	0.7 (0.0–29.2)	0.8 (0.0–29.2)

Note. The first 5 years after exposure were excluded.
[a] Available for 48% of the patients.
[b] After correction for thyroid weight.

thyroid cancers found and one sarcoma of the thyroid gland. In one case the exact histopathology was not given.

The overall risk for thyroid cancer more than 5 years after exposure was 1.35 (95% CI 1.05–1.71; Table III). A significantly higher risk was seen for the 10,785 patients referred when a thyroid tumor was suspected (SIR = 2.86; 95% CI 2.06–3.86) compared to those referred for other reasons (SIR = 0.75; 95% CI 0.48–1.10).

No dose–response relationship was noticed regardless of the reason for referral *(P* = 0.48 for suspected tumor; *P* = 0.76 for other reasons). The highest risks were seen during the period 5 to 9 years after ^{131}I administration (Table III).

Thirty-three thyroid cancers werw observed among the patients for whom there was information on gland size. The inclusion of estimated thyroid size in the dose calculations resulted in relatively minor changes in the computed SIRs (Table IV).

Only 3 thyroid cancers occurred among the 2,408 patients exposed before the age of 20 years (SIR = 1.69; 95% CI 0.35–4.93; Table V). Each of the three individuals who developed thyroid cancer had been administered ^{131}I between the age of 15–19 years. Among the 1,764 children not referred when a thyroid tumor was suspected, 2 thyroid cancers occurred (SIR = 1.38; 95% CI 0.17–4.98).

TABLE III
Observed Number of Cases (Obs.) and Thyroid Cancer Risk (SIR) in Relation to Estimated Thyroid Dose and Years after ^{131}I Administration

	Years after ^{131}I administration											
	5–9			10–19			>=20			All		
Dose,Gy[a]	Obs.	SIR	95% CI	Obs.	SIR	95% CI	Obs.	SIR	95% CI	Obs.	SIR	95% CI
						All						
<=0.25	4	1.72	0.47–4.40	4	0.77	0.21–1.97	3	0.93	0.19–2.73	11	1.03	0.51–1.83
0.26–0.50	5	2.67	0.87–6.24	6	1.41	0.52–3.07	5	1.93	0.63–4.51	16	1.84	1.05–2.98
0.51–1.00	1	0.50	0.01–2.77	4	0.86	0.23–2.20	4	0.95	0.26–2.44	9	0.46	0.38–1.57
>1.00	11	2.95	1.47–5.28	8	0.93	0.40–1.84	12	1.70	0.88–2.98	31	1.60	1.09–2.27
All	21	2.11	1.31–3.23	22	0.97	0.61–1.47	24	1.41	0.90–2.10	67	1.35	1.05–1.71
						Referred for suspicion of a thyroid tumor						
<=0.25	2	4.88	0.59–17.62	2	2.17	0.26–7.85	2	5.71	0.69–20.64	6	3.57	1.3–7.77
0.26–050	5	7.94	2.48–18.52	4	2.78	0.76–7.11	3	4.17	0.86–12.18	12	4.30	2.22–7.51
0.51–1.00	0	0.00	0.03–6.15	3	2.14	0.44–6.26	1	1.14	0.03–6.33	4	1.39	0.38–3.56
>1.00	7	3.87	1.55–7.97	6	2.17	0.79–4.71	7	2.53	1.02–5.21	20	2.72	1.66–4.20
All	14	4.06	2.22–6.81	15	2.30	1.29–3.79	13	2.75	1.47–4.71	42	2.86	2.06–3.86
						Referred for other reasons						
<=0.25	2	1.04	0.13–3.76	2	0.47	0.06–l.69	1	0.35	0.01–1.95	5	0.55	0.18–1.29
0.26–0.50	0	0.00	0.00–2.97	2	0.71	0.09–2.57	2	1.07	0.13–3.86	4	0.68	0.18–1.73
0.51–1.00	1	0.71	0.02–3.95	1	0.31	0.01–1.71	3	0.90	0.19–2.64	5	0.47	0.20–1.46
>1.00	4	2.08	0.57–5.33	2	0.46	0.06–l.65	5	1.17	0.38–2.73	11	1.04	0.52–1.86
All	7	1.08	0.43–2.22	7	0.48	0.19–0.98	11	0.89	0.45–1.60	25	0.75	0.48–1.10

Note. The first 5 years after exposure were excluded.
[a] Estimated without considering thyroid weight.

TABLE IV
Observed Number of Cases (Obs.) and Thyroid Cancer Risk (SIR) in Relation to Estimated Thyroid Dose for 48% of the Population in the Study with Information on Gland Size

	With thyroid weight			Without thyroid weight		
Dose, Gy	Obs.	SIR	95% CI	Obs.	SIR	95% CI
<=0.25	8	0.96	0.41–1.89	6	0.93	0.64–2.65
0.26–0.50	10	1.88	0.90–3.46	10	1.76	0.84–3.24
0.51–1.00	3	0.73	0.15–2.13	5	1.17	0.38–2.73
>1.00	12	2.12	1.10–3.70	12	1.71	0.88–2.99

Note. The first 5 years after exposure were excluded.

Men had a significantly higher relative risk than women among those with a suspicion of a thyroid tumor (Table V). No cases of thyroid cancer were found among men referred for other reasons.

DISCUSSION

Age at Exposure

The thyroid gland of children appears to be one of the organs most susceptible to radiation carcinogenesis with estimates of relative risk (RR) at 1 Gy ranging from 4 to 12 *(17)*. Substantial excesses of thyroid cancer have been reported among children exposed to ionizing radiation because of tinea capitis *(4)*, enlarged thymus glands *(28)*, skin hemangioma *(29)*, enlarged tonsils *(6)* and cancer *(5)*, and among A-bomb survivors *(11)*. In contrast, no dose–response relationship has been reported after adult exposure. Small excesses have been seen among Chinese medical X-ray workers *(30)*, cervical cancer patients *(8)* and young adults with Hodgkin's disease *(10)*. No increased risk of a thyroid cancer was found among A-bomb survivors exposed over age 20 years *(11)*.

Since 93% of our 34,104 patients were over age 20 years when ^{131}I was administered, the apparent absence of an overall effect might be attributable in part to the lower sensitivity of the adult thyroid gland. Among the 2,408 patients <20 years of age in our series, however, only 3 thyroid cancers developed and the SIR of 1.69 was not statistically significant. Two of these cancers developed in children (n = 1,764) not referred under the suspicion of a thyroid tumor, giving an SIR of 1.38 (95% CI 0.17–4.98). Assuming for the sake of argument that the latter risk estimate was the true risk associated with ^{131}I exposure in childhood and adolescence, then the computed excess relative risk (ERR) of 0.25 per Gy (range 0–2.7) can be compared to an ERR of 4.5 per Gy reported among A-bomb survivors aged 10–19 at exposure *(17)*.

Protraction of Dose and Dose Distribution

Iodine-131 delivers nearly all its radiation dose within the first 6 weeks of exposure, and the radioactivity is also lost. It is conceivable that this dose rate allows the repair of DNA damage to occur. Alternatively, the distribution of dose from decay of ^{131}I in the thyroid gland might be such

TABLE V
Observed Number of Cases (Obs.) and Thyroid Cancer Risk (SIR) among Patients Administered ^{131}I in Relation to Age at Exposure and Sex

	Men			Women			All		
Age, years	Obs.	SIR	95% CI	Obs.	SIR	95% CI	Obs.	SIR	95% CI
				All					
≤20	0	0.00	0.00–23.06	3	1.85	0.38–5.41	3	1.69	0.35–4.93
21–50	6	2.33	0.86–5.08	34	1.23	0.85–1.72	40	1.32	0.94–1.80
>50	6	3.14	1.15–6.84	18	1.17	0.69–1.84	24	1.38	0.88–2.05
				Referred for suspicion of a thyroid tumor					
≤20	0	0.00	0.00–184.85	1	3.24	0.08–17.97	1	3.04	0.08–16.88
21–50	6	10.71	3.93–23.32	19	2.13	1.28–3.32	25	2.63	1.70–3.88
>50	6	11.54	4.23–25.11	10	1.81	0.87–3.33	16	2.65	1.51–4.30
				Referred for other reasons					
≤20	0	0.00	0.00–26.35	2	1.53	0.18–5.52	2	1.38	0.17–4.98
21–50	0	0.00	0.00–1.84	15	0.80	0.45–1.32	15	0.72	0.40–1.19
>50	0	0.00	0.00–2.65	8	0.81	0.35–1.59	8	0.71	0.31–1.39

Note. The first 5 years after exposure were excluded.

that critical cells were spared. On the other hand, the non-uniformity of dose distribution in the gland, particularly in patients with a thyroid neoplasm, might lead to higher doses, which could explain in part the higher risk in the group referred for a suspected thyroid cancer. A non-uniformity of dose and the lack of information on thyroid weight for all individuals introduce uncertainties. However, we have taken into account all the parameters available, and we know exactly how much ^{131}I was administered and also the 24-h thyroid uptake. We therefore believe that the relative magnitude of dose is reasonably accurate.

Although our patients received relatively large diagnostic doses (~1.0 Gy), protracted radiation exposures would be expected to be less carcinogenic than when the same exposure is given over a brief period *(17)*. 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 thyroid tumors *(30)*. A French study of childhood irradiation for skin hemangiomas suggested a sparing effect with protracted exposure *(31)*. A recent parallel analysis of most major studies of thyroid irradiation concluded that spreading dose over time may lower the risk of subsequent thyroid cancer *(20)*.

Thyroid Condition

The influence of the underlying thyroid condition, real or suspected, could influence the observations in several ways. Comparisons with general population rates would be inappropriate if the condition were strongly associated with thyroid cancer, or if persons under surveillance for a suspected thyroid condition were more likely to have a thyroid cancer detected because of increased medical surveillance. Both situations would lead to an overestimation of the possible risk associated with ^{131}I. We attempted to address these possibilities by excluding all thyroid cancers that were reported within 5 years of the initial ^{131}I administration. This seemed a reasonable period since no excess thyroid cancers have been reported within 5 years of exposure *(20)*. The decreasing risk of thyroid cancer with time after ^{131}I examination is consistent with the possibility that the underlying condition and medical screening contributed to some of the early thyroid cancers. On the other hand, exclusion of individuals who had been examined because of a suspected thyroid tumor may have depleted the exposure group of persons who would have been likely to develop thyroid cancer. If so, comparisons with the general population would underestimate risk, at least during the early years of exposure. To address this possibility, we examined dose– and time–response relationships. No trend of increasing risk with increasing dose was suggested, nor was an increasing risk seen with time since exposure; i.e., no risk was apparent after 10 years, arguing against a strong relationship for ^{131}I and thyroid cancer in this series.

A recent report from cancer registry data in Belarus purports high rates of thyroid cancer to be associated with radioactive fallout, mainly radioactive iodine, including ^{131}I from the Chernobyl accident *(32)*. This opinion was shared by an expert panel formed by the Commission of the European Communities, although they emphasized that the influence of screening should be considered carefully in assessing the results *(33)*. The time between exposure and appearance of the thyroid cancer is remarkably short and the dramatic increase in thyroid cancers most likely is related at least in part to the intense screening, increased awareness and changed referral routines *(22)*. Further, it appears that iodine deficiency and other environmental or familial factors might have contributed to an unusual sensitivity of the thyroid gland of children exposed to short-lived isotopes of iodine and ^{131}I. Although the bone marrow doses were apparently much lower than those to the thyroid, it is interesting to note that the incidence of childhood leukemia in Belarus, an entity known to be increased 2–3 years after exposure to ionizing radiation, was not highcr during the period 1986–1991 than the preceding period 1979–1985 *(34)*.

Strengths and Limitations

The strengths of this investigation include the unbiased and exceptionally complete ascertainment of thyroid cancers. The use of national cancer registration files coupled with a 10-digit personal identification number for each citizen allowed a comprehensive ascertainment of cancer incidence in a large population followed for up to 40 years. Second, the amount of ^{131}I administered to each of the 34,000 patients was readily available from their medical records. Based on reasonable assumptions, organ doses to the thyroid gland could be computed with some precision. Third, the doses to the thyroid were substantial and covered a wide range, enabling an examination of the dose–response relationship. Fourth, this is the largest analytical study of thyroid cancer and radiation in terms of person-dose (the number of persons times the estimated dose to the thyroid gland) reported so far.

Limitations include the relatively small number of individuals <20 years of age, restricting the inferences that could be made concerning childhood exposures. Nonetheless, 2,408 children and adolescents received an average of 1.5 Gy to the thyroid gland, and this dose is equivalent to that reported in studies where increased risks have been seen after external radiation exposure *(20)*. The influence of the underlying condition on risk could also operate in several ways. Patients with an underlying thyroid disorder probably have a slightly increased probability of the detection of thyroid cancer due to a closer thyroid surveillance. These conditions, however, would lead to an overestimation of risk, whereas none was found.

Thyroid gland size is an important determinant of thyroid dose, and we had information on 48% of the population in the study. Using thyroid gland size in calculating risk in relation to dose did not alter the dose–response relationship in any significant way.

Because of the high risk of thyroid cancer found among persons who received ^{131}I because of a suspected thyroid tumor, it is important that any similar studies of medical uses of ^{131}I be able to address the reason for the ^{131}I examination. Further, we found that a substantial number of patients referred for ^{131}I examination had previously received external radiotherapy to the head and neck region. If we had failed to obtain information on prior radiotherapy or whether a suspicion of a thyroid tumor was the reason for the ^{131}I scan, a relatively high rate of thyroid cancer would have been incorrectly correlated with ^{131}I exposures.

In conclusion, it is reassuring that the careful examination of over 34,000 patients who received substantial radiation doses to their thyroid glands from ^{131}I did not reveal a radiation-related risk of thyroid cancer. While it is impossible to exclude the existence of a low risk associated with this exposure, it appears clear that exposures in adult life are associated with minimal risk. Contrasting studies of childhood exposures, ^{131}I appears considerably less (2 to 10 times) effective in inducing thyroid cancer than brief exposures to external radiation.

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