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SECOND PRIMARY TUMORS FOLLOWING THYROID CANCER

A Swedish record-linkage study

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Abstract

The incidence of second primary tumors was studied through record-linkage in 2 968 thyroid cancer patients reported to the Swedish Cancer Registry during the period 1958–1975. The cohort was matched with the Swedish Cancer Registry between 1959 and 1984. A total of 283 second primary tumors were reported more than one year after thyroid cancer diagnosis, and the standardized incidence ratio (SIR) was 1.18 (95% confidence interval = 1.03–1.31). A significantly elevated risk of cancer of the kidney, endocrine glands, and nervous system was noted. Men had a higher risk (SIR = 1.37; 95% CI = 1.06–1.70) than women (SIR = 1.11; 95% CI = 0.96–1.28). Patients who were 36–45 years at the time of the thyroid cancer diagnosis were at highest risk of developing a second primary tumor (SIR = 1.35; 95% CI = 0.99–1.81). Significantly elevated risks were seen 5–9 years after the thyroid cancer diagnosis (SIR = 1.44; 95% CI = 1.14–1.69), and the SIR was close to unity after ⩾15 years of follow-up. Previously described elevated risks of subsequent leukemia and breast cancer were not confirmed in this study. Close medical surveillance, thyroid cancer treatment, hereditary factors, and a high frequency of autopsy could all contribute to the elevated risk of a second primary tumor in these patients.

Key words: Thyroid cancer, second primary tumor, cancer incidence, record-linkage.

Thyroid cancer is a relatively rare disease in most countries, the risk for women usually being twice as high as for men. In Sweden, 360 cases were reported to the Swedish Cancer Registry (SCR) in 1985 which corresponds to approximately 1% of all cancers reported (1). The prognosis for thyroid cancer is good, with an overall 5-year survival rate of approximately 75%. Age at the time of diagnosis, sex, stage and histopathology are all factors of prognostic value (2–4).

Ionizing radiation is the only established etiological factor for thyroid carcinoma although previous thyroid disorders, hormones, diet and hereditary factors have also been suggested as contributory factors (5–7).

In record-linkage studies thyroid cancer patients have been found to have increased risks of tumors of the connective tissue, breast, kidney (9, 10), nervous system and non-Hodgkin's lymphoma (10). None of these studies, except for that by Teppo et al. (11), have shown any increased risk of subsequent leukemia something which is contrary to other observations (12–14).

The purpose of the present study was to analyze the risks of second primary tumors in thyroid cancer patients registered in the SCR.

Material and Methods

The Swedish Cancer Registry, (SCR), started in 1958, collects nationwide data and receives notifications of newly diagnosed malignant tumors and leukemias. It is mandatory for clinicians, pathologists and cytologists to report to the SCR. Most diagnosed cases are thus reported by at least two independent sources and more than 95% of all cancers in Sweden are reported to the SCR (15).

Between 1958 and 1975, a total of 3 898 thyroid cancer patients (29% men and 71% women) less than 76 years of age were reported to the SCR. All patients who died within one year of diagnosis (n = 920) were excluded and 2 968 patients thus formed the study cohort. Their mean age at the time of the thyroid cancer diagnosis was 49 years (range 7–75 years) for the total cohort, 50 years for men and 49 years for women.

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The matching concept was the unique identification number which is assigned to all individuals in Sweden and is used in almost all Swedish population statistics. This number is composed of 10 digits and is not affected by changes in names.

The SCR contains data on name, identification number, diagnosis, date of diagnosis, basis for diagnosis, and date of death. It does not contain information on treatment, previous thyroid disorders, or the exact histologic diagnosis since the tumors are coded in accordance with ICD-7 (16).

The total cohort was matched with the SCR for reports of second primary tumors that occurred between 1959 and 1984. Basal cell carcinoma of the skin and carcinoma in situ were excluded.

The expected numbers of malignant tumors were calculated by indirect standardization with adjustment for calendar year-, sex-, and age-specific incidence data for the whole country as obtained from the SCR between 1959 and 1984. All patients were considered to be at risk from the time of thyroid cancer diagnosis until death or December 31, 1984. In calculating person-years at risk, the first year was excluded for each patient to reduce cancers present at the time of thyroid cancer diagnosis or thyroid cancer metastases to be part of the study. Cancers reported within the first year were excluded for the same reason.

The standardized incidence ratio (SIR) was calculated as the ratio between observed and expected numbers of tumors and 95% confidence intervals (CI) were determined by assuming the observed number of cases to be distributed as a Poisson variable.

Results

Between 1959 and 1984 a total of 526 second primary tumors were reported to the SCR. Of these, 157 were diagnosed prior to the thyroid cancer diagnosis and 86 were found less than one year after the thyroid cancer diagnosis and were therefore excluded. This left 283 second primary tumors reported more than one year after the thyroid cancer diagnosis in 269 patients. Fourteen of the patients had 2 second primary tumors. The age at diagnosis of the second primary tumor ranged from 32 to 90 years with a mean of 65 years. The number of person-years was 36 599 and the mean follow-up was 12 years.

Ninety-six percent of the second primary tumors were diagnosed after histopathological verification, of which 23% were first detected at autopsy. The rate of histopathologically verified diagnosis did not change much over time: 92% in 1958 and 96% in 1984. The rate of tumors found at autopsy decreased from 31% in 1958 to 15% at the end of the study period.

When the first person-year following the thyroid cancer diagnosis was excluded for each patient, the SIR for all cancers combined was 1.18 (95% CI = 1.03–1.31; Table 1). The risk was statistically significant for men (SIR = 1.37; 95% CI = 1.06–1.70) but not for women (SIR = 1.11; 95% CI = 0.95–1.28). The elevated SIRs for cancer of the nervous system and the endocrine glands other than the thyroid were statistically significant for both men and women. Of the 14 endocrine tumors found, 6 were pheocromocytomas and 5 parathyroid adenomas. The overall risk of kidney cancer was significantly elevated (SIR = 1.99; 95% CI = 1.14–3.25), with the highest risk for men. All 16 kidney cancers found were pelvic cancers.

The highest overall cancer risk was noted in patients 36–45 years of age (SIR = 1.35) and the lowest risk in patients younger than 35 years (SIR = 0.91) although none of the overall cancer risks differed statistically from unity in any of the different age groups (Table 2). SIRs were significantly increased for cancers of the endocrine glands excluding thyroid among patients 36–55 years of age, and

Table 1

Observed number of second primary tumors, and SIR with 95% CI, in relation to gender and cancer site

Cancer site	Male patients			Female patients			All patients		
	No. of cancers	SIR	95% CI	No. of cancers	SIR	95% CI	No. of cancers	SIR	95% CI
Digestive tract	26	1.34	0.75–1.78	43	0.92	0.67–1.24	69	1.05	0.91–1.46
Respiratory organs	5	0.63	0.21–1.48	6	0.88	0.32–1.92	11	0.75	0.37–1.33
Breast	0	0.00	0.00–36.89	45	0.99	0.72–1.33	45	0.99	0.72–1.32
Female genital organs				39	0.90	0.64–1.23	39	0.90	0.64–1.23
Male genital organs	16	1.17	0.67–1.90				16	1.77	0.76–1.90
Urinary tract	13	1.97	1.05–3.37	12	1.23	0.64–2.15	25	1.53	0.99–2.26
Nervous system	6	3.82	1.38–8.16	15	2.60	1.45–4.27	21	2.86	1.78–4.40
Endocrine glands	5	9.09	1.80–12.96	9	2.36	1.08–4.50	14	3.21	1.74–5.33
Lymphomas	1	0.52	0.01–2.93	6	1.29	0.47–2.78	7	1.07	0.43–2.18
Leukemias	2	1.13	0.13–4.01	6	1.53	0.46–3.35	8	1.41	0.61–2.77
Miscellaneous	9	1.31	0.60–2.49	19	0.93	0.56–1.46	28	1.03	0.68–1.49
Total	83	1.37	1.06–1.70	200	1.11	0.96–1.28	283	1.18	1.03–1.31

Table 2

Observed number of second primary tumors, and SIR with 95% CI, in relation to age at thyroid cancer diagnosis and cancer site

Cancer site	≤35 years (n = 634)			36–45 years (n = 502)			46–55 years (n = 683)			56–65 years (n = 645)			66–75 years (n = 504)		
	No. of cancers	SIR	95% CI	No. of cancers	SIR	95% CI	No. of cancers	SIR	95% CI	No. of cancers	SIR	95% CI	No. of cancers	SIR	95% CI
Digestive tract	1	0.54	0.01–3.00	4	0.65	0.18–1.68	21	1.36	0.84–2.08	18	0.79	0.47–1.24	25	1.25	0.81–1.85
Respiratory organs	0	0.00	0.00–6.96	0	0.00	0.00–1.99	2	0.50	0.06–1.81	4	0.79	0.21–2.01	5	1.46	0.48–3.43
Breast	3	0.75	0.15–2.19	12	1.37	0.70–2.38	10	0.75	0.36–1.38	11	0.92	0.46–1.64	9	1.19	0.55–2.28
Female genital organs	3	0.97	0.20–2.84	9	1.30	0.60–2.48	12	1.12	0.58–1.96	12	1.47	0.76–2.56	3	0.68	0.14–1.99
Male genital organs	0	0.00	0.00–19.42	1	1.56	0.04–8.71	5	2.23	0.74–5.21	5	0.96	0.42–2.51	5	0.91	0.30–2.12
Urinary tract	0	0.00	0.00–6.83	4	2.19	0.60–5.60	3	0.70	0.14–2.05	14	3.06	1.37–4.22	4	0.97	0.27–2.49
Nervous system	1	1.25	0.03–6.96	2	1.49	0.19–5.39	8	3.83	1.64–7.51	7	3.59	1.44–7.40	3	2.75	0.56–8.04
Endocrine glands	2	4.55	0.55–16.42	4	4.65	1.27–11.91	6	4.11	1.51–8.94	1	0.89	0.02–4.97	1	1.92	0.05–10.71
Lymphomas	0	0.00	0.00–7.38	3	3.61	0.77–10.56	1	0.59	0.01–3.28	1	0.49	0.01–2.72	2	1.36	0.16–4.91
Leukemias	0	0.00	0.00–11.18	2	3.13	0.38–11.29	1	0.73	0.02–3.98	2	1.08	0.13–3.88	3	1.97	0.41–5.77
Miscellaneous	3	1.47	0.30–4.30	4	1.13	0.31–2.86	8	1.19	0.51–2.34	8	0.97	0.44–1.84	7	0.60	0.16–1.54
Total	13	0.91	0.48–1.55	45	1.35	0.99–1.81	77	1.21	0.96–1.52	84	1.13	0.90–1.40	64	1.14	0.88–1.45
Person-years		9 792			7 792			9 029			6 655			3 455	

for tumors of the nervous system among patients 46–65 years old. Increased SIRs for cancer of the kidney were observed in the group 36–45 years of age (SIR = 3.92; 95% CI = 1.09–10.24) and 56–65 years (SIR = 4.91; 95% CI = 2.16–9.85).

When cancer risks were studied in relation to period of follow-up increased SIRs were observed for tumors of endocrine glands other than thyroid during years 1–9 of follow-up as well as for tumors of the nervous system during years 1–5 (Table 3). Kidneys, bladder and male genital organs had statistically significant increased SIR during years 5–9 of follow-up. Beyond 9 years of follow-up

Table 3

Observed number of second primary tumors, and SIR with 95% CI, in relation to time after thyroid cancer diagnosis and cancer site

Cancer site	1–4 years (n = 2 968)			5–9 years (n = 2 546)			10–14 years (n = 2 071)			≥15 years (n = 1 175)		
	No. of cancers	SIR	95% CI	No. of cancers	SIR	95% CI	No. of cancers	SIR	95% CI	No. of cancers	SIR	95% CI
Digestive tract	13	0.84	0.45–1.44	27	1.37	0.90–1.99	18	1.13	0.67–1.79	11	0.79	0.39–1.41
Respiratory organs	4	1.17	0.32–3.01	5	1.11	0.36–2.59	2	0.56	0.07–2.01	0	0.00	0.00–1.12
Breast	9	0.83	0.38–1.57	12	0.86	0.44–1.50	18	1.64	0.97–2.59	6	0.62	0.23–1.35
Female genital organs	8	0.89	0.38–1.75	17	1.64	0.96–2.64	6	0.79	0.29–1.72	8	1.31	0.57–2.58
Male genital organs	2	0.63	0.08–2.26	7	1.66	1.65–8.48	3	0.90	0.18–2.58	4	1.33	0.36–3.41
Urinary tract	0	0.00	0.00–0.97	16	3.24	1.86–5.27	3	0.77	0.16–2.25	6	1.68	0.62–3.66
Nervous system	9	4.84	2.17–8.99	4	1.78	0.47–4.45	5	2.91	0.95–6.86	3	2.00	0.41–5.84
Endocrine glands	4	4.44	1.21–11.38	5	3.79	1.25–8.98	4	3.54	0.99–9.31	1	0.99	0.02–5.57
Lymphomas	2	1.31	0.16–4.82	0	0.00	0.00–1.84	3	1.90	0.39–5.48	2	1.37	0.16–4.82
Leukemias	3	2.01	0.41–5.84	1	0.57	0.01–3.28	1	0.76	0.02–4.29	3	2.63	0.56–7.97
Miscellaneous	6	0.99	0.36–2.14	8	0.99	0.43–1.96	7	1.04	0.42–2.15	7	1.09	0.44–2.24
Total	60	1.06	0.80–1.34	102	1.44	1.14–1.69	70	1.25	0.94–1.53	51	1.02	0.71–1.26
Person-years		10 931			11 795			7 973			5 900	

no increased risk was observed for any site. SIRs for leukemia, malignant lymphoma or breast cancer were not significantly elevated during any of the follow-up periods.

Discussion

The risk of a second primary tumor following a thyroid cancer diagnosis was slightly but statistically significantly increased (SIR = 1.18) in this study using data from the SCR. It is possible that metastatic thyroid cancer in some cases was erroneously reported as a second primary tumor. This bias, however, was reduced by excluding the first person-year after the thyroid cancer diagnosis. The thyroid cancer patients were also likely to receive more medical surveillance than the general population, possibly leading to detection of tumors that would not otherwise have led to a clinically apparent disease.

Other factors such as the frequency of histopathological verifications at autopsy could explain the slight excess in the total number of second primary tumors. Twenty-three percent of the new cancers were found at autopsy. In 1985, 14% of all cancers diagnosed in Sweden were found incidentally at autopsy.

Previous studies have found increased risks of a second tumor in organs that are supposed to receive larger doses of ^{131}I, e.g. salivary gland, stomach, and bladder (14). In other studies an increased number of urinary tract tumors have been observed (8, 9). This was probably due to close medical surveillance since the tumors were found early in the follow-up period. In the present study SIR for cancer of the kidney was significantly elevated. The highest risk was observed after 5–9 years in patients 36–45 and 56–65 years of age. Iodine-131 and external radiotherapy cannot be ruled out as an explanation, although other factors such as screening for pheochromocytoma in thyroid cancer patients and smoking also could contribute to the elevated risk ratios. The excess was more pronounced in men and previous studies have shown increased risks of cancer of the renal pelvis but not of the renal parenchyma among smokers (17, 18). All of the 16 kidney cancers were pelvic cancers.

High risks of tumors of the endocrine system excluding thyroid were found for both men and women during the first 9 years after the thyroid cancer diagnosis. In 1961, Sipple (19) noted the coexistence of medullary thyroid carcinoma, pheochromocytoma and, later, carcinoma of the parathyroid gland. The entity was named multiple endocrine neoplasia type 2, or Sipple's syndrome. The ICD-7 code does not distinguish medullary carcinoma from other thyroid cancers but it is possible that such tumors occurred in our study since there were 6 pheochromocytomas and 5 parathyroid adenomas among the 14 second tumors of the endocrine glands.

Both sexes showed a significantly elevated risk of developing tumors of the nervous system with the highest risks 1–4 years after thyroid cancer diagnosis and among those who were 46–65 years old at diagnosis. This finding is in agreement with the results of a Danish study (10). The frequency of autopsies could not explain this increase since 35% of the patients with an intracranial tumor in our study were diagnosed at autopsy, compared to 37% of all intracranial tumors reported to the SCR (21). An increased risk of bladder cancer was seen 5–9 years after the thyroid cancer diagnosis, which argues against a radiation effect. The close medical surveillance could be part of the explanation.

Other studies have reported an increased risk of breast cancer in thyroid cancer patients suggesting common etiological factors (8). SIR for breast cancer was 0.99 in the present study with no significantly raised risk in any age category or during any follow-up period. An elevated risk of a subsequent leukemia has previously been described (11–13), but this was not confirmed in our study. Some other groups have also failed to observe any association between thyroid cancer and leukemia (8–10).

The present study suggests an association between thyroid cancer and cancers of kidney, endocrine glands other than thyroid and tumors of the nervous system. A high frequency of autopsy, hereditary factors and a closer medical surveillance increase the likelihood of diagnosing preclinical tumors and could explain the slight risk increment. In addition it is possible that tumors in these sites share common etiological factors. Thyroid cancer treatment could contribute to the elevated incidence, but the SCR does not contain information on type of treatment. The follow-up period is still short and a continued study is needed to confirm the present results.

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REFERENCES

1. Cancer incidence in Sweden 1985. Stockholm: National Board of Health and Welfare, The Cancer Registry, 1989.
2. Franssila KO. Prognosis in thyroid carcinoma. Cancer 1975; 36: 1138–46.
3. Tubiana M, Schlumberger M, Rougier P, et al. Long-term results and prognostic factors in patients with differentiated thyroid carcinoma. Cancer 1985; 55: 794–804.
4. Halnan KE. Influence of age and sex on the incidence and prognosis of thyroid cancer. Cancer 1986; 19: 1534–6.

5. Ron E, Modan B. Thyroid. In: Schottenfeld D, Fraumeni JF Jr, eds. Cancer epidemiology and prevention. Philadelphia: W.B. Saunders Company, 1982: 837–54.
6. Committee on the Biological Effects of Ionizing Radiations. The effects on populations of exposure to low levels of ionizing radiation. Washington, DC: Natl Acad Press, 1980.
7. United Nations Scientific Committee on the Effects of Atomic Radiation. 1988 Report to the General Assembly, with annexes. Sources, effects and risks of ionizing radiation. New York: United Nations, 1988.
8. Ron E, Curtis R, Hoffman DA, Flannary JT. Multiple primary breast and thyroid cancer. Br J Cancer 1984; 49: 87–92.
9. Tucker MA, Boice JD Jr, Hoffman DA. Second cancer following cutaneous melanoma and cancers of the brain, thyroid, connective tissue, bone, and eye in Connecticut, 1935–82. Natl Cancer Inst Monogr 1985; 68: 161–89.
10. Østerlind A, Olsen JH, Lynge E, Evertz M. Second cancer following cutaneous melanoma and cancers of the train, thyroid, connective tissue, bone, and eye in Denmark, 1943–80. Natl Cancer Inst Monogr 1985; 68: 361–88.
11. Teppo L, Pukkala E, Saxén E. Multiple cancer — an epidemiologic exercise in Finland. JNCI 1985; 75: 207–17.
12. Pochin EE. Long term hazards of radioiodine treatment of thyroid carcinoma. In: Hedinger CE, ed. Thyroid cancer. UICC Monograph Series, vol. 12. Berlin: Springer-Verlag, 1969: 293–304.
13. Brincker H, Hansen HS, Andersen AP. Induction of leukaemia by ^{131}I treatment of thyroid carcinoma. Br J Cancer 1973; 28: 232–7.
14. Edmonds CJ, Smith T. The long-term hazards of the treatment of thyroid cancer with radioiodine. Br J Radiol 1986; 59: 45–51.
15. Mattsson B, Wallgren A. Completeness of the Swedish Cancer Register. Non-notified cancer cases recorded on death certificates in 1978. Acta Radiol Oncol 1984; 23: 305–13.
16. International Classification of Diseases (ICD-7). Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death. 7th revision 1955. Geneva: World Health Organization, 1957.
17. McCredie M, Stewart JH, Ford JM. Analgesics and tobacco as risk factors for cancer of the ureter and renal pelvis in men. J Urol 1983; 130: 28–30.
18. McCredie M, Ford JM, Stewart JH. Risk factors for cancer of the renal parenchyma. Int J Cancer 1988; 42: 13–6.
19. Sipple JH. The association of pheochromocytoma with carcinoma of the thyroid gland. Am J Med 1961; 31: 163–6.
20. Adami H-O, Bergkvist L, Krusemo U, Persson I. Breast cancer as a risk factor for other primary malignant diseases. A nationwide cohort study. JNCI 1984; 73: 1049–55.