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Incidence, detection and outcome of differentiated thyroid cancer in Western Sweden

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Abstract

Background: It is unclear whether the increasing incidence of thyroid cancer (TC) due to increased diagnosis of small and indolent tumours might mask a real increase of clinically significant cancers. The aim of this study was to correlate surgery, pathology and outcome data of individual patients to the mode of primary detection (palpation, by imaging or incidental) to assess if TC incidence has increased.

Methods: The Swedish Cancer Registry identified all patients with TC in Västra Götaland County representing approximately 1.6 million inhabitants. Clinical information was retrieved from medical records of patient cohorts from three study intervals (2001–2002, 2006–2007 and 2011–2014) comprising 60 per cent of all TC patients. Data were also obtained from the NORDCAN registry to compare of TC incidence with other Nordic countries.

Results: Between 2001 and 2014, the annualized standard incidence rate/100 000 population (ASR) of TC increased from 3.14 to 10.71 in women and from 1.12 to 3.77 in men. This was higher than the mean incidence for Sweden but similar to that in Norway and Finland. Differentiated TC (DTC) increased more than threefold. The majority of tumours (64 per cent) were detected by palpation. Larger tumours (10–20, 21–40 and greater than 40 mm) increased as much as microcarcinomas (less than 10 mm). Only 5 per cent of the tumours were detected by imaging. All disease-specific deaths (8.5 per cent of DTC in the first two cohorts) and most patients with recurrent or persistent disease (6.6 per cent of DTC cases) were diagnosed due to tumour-related symptoms.

Conclusion: DTC in Western Sweden gradually increased between 2001 and 2014. The majority of tumours were detected by palpation suggesting a real increase in the incidence of clinically significant thyroid malignancies.

Introduction

Thyroid cancer (TC), especially papillary thyroid carcinoma (PTC), has been increasing in incidence, which is often attributed to the greater use of neck ultrasonography that identifies small asymptomatic cancers[1]. Ultrasound screening in Korea led to a dramatic increase in diagnosis of papillary microcarcinomas (tumours 10 mm or less)[2,3]. It has been suggested that small TCs might be being 'over-diagnosed' with this approach[4–9], although this strategy also increases the diagnosis of larger thyroid tumours[10–15]. It is currently unknown whether increased radiological imaging might mask a real increase in TC. Most previous studies are registry based and without consideration of individual patient and tumour characteristics. This is further complicated by contradictory data regarding thyroid-cancer-specific deaths, showing both stable and increasing rates[16–18].

Thyroid screening with ultrasonography has not been used in Sweden or in the other Nordic countries, and ultrasonography was not routinely used in Sweden among clinicians until recently. A study based on the NORDCAN registry demonstrated an increased TC incidence in the Nordic countries since 1970, accelerating further after 2006[19], but lacked information on tumour size and stage.

The present study was based on cumulative registry data obtained from the Swedish Cancer Registry (SCR) between 2001 and 2014. This was combined with individual clinical data obtained from medical records of patients diagnosed with TC in Västra Götaland (VG) county, comprising 17 per cent of the Swedish population. The aim of this study was to correlate surgery, pathology and outcome data of individual patients to the mode of primary detection (palpation, imaging or incidental) to assess if TC incidence has increased.

Methods

Data sources and population cohorts

Patients diagnosed with primary TC (ICD-10 code C73) in VG County were identified in the SCR administered by the National Board of Health and Welfare (http://www.socialstyrelsen.se). SCR registers all new cancer cases in the country independently reported by both clinicians and cytopathologists; under-reporting

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is considered to be negligible. The coverage of SCR was reported to exceed 95 per cent[20,21]. The NORDCAN registry collects the official data on cancer incidence for comparison between the Nordic countries (https://nordcan.iarc.fr/en). The Western Region of Sweden defined in the NORDCAN registry comprises VG County (1.6 million inhabitants) and northern part of Halland (30 000 inhabitants). Although there is a small discrepancy in individual numbers, both populations can be considered to be nearly identical. All calculations of TC incidence and statistical analysis refer to the population of VG County.

The population of VG County increased from 1.5 million in 2001 to 1.6 million in 2014 corresponding to approximately 17 per cent of the Swedish population. Information on tumour characteristics, means of detection, treatment and follow-up until 31 March 2016 was retrieved from medical records in six hospitals of all patients identified in the SCR and living in VG County at the time of diagnosis. Cohorts from three representative time intervals were chosen for detailed review of individual patient data: in the beginning, 2001–2002, in the middle, 2006–2007 and at the end, 2011–2014. The last interval was extended to 4 years corresponding to the highest TC incidence reported by NORDCAN[19].

Health care organization and clinical management

All thyroid and parathyroid surgery in VG County was performed at five public hospitals located in Gothenburg (Sahlgrenska University Hospital), Borås, Skövde, Trollhättan and Kungälv, and one private hospital in Gothenburg (Carlanderska Hospital). No hospitals outside the county managed TC patients in the present cohorts. Standardized regional treatment protocols comprised total thyroidectomy and central lymph node dissection (CLND) for patients with a malignant thyroid tumour according to preoperative fine-needle aspiration cytology (FNAC). Lobectomy with ipsilateral CLND was performed in cases of FNAC indicating suspicion of malignancy. The remaining thyroid tissue was removed with contralateral CLND in a second operation if TC was confirmed histopathologically. Lateral dissection was performed when enlarged lymph nodes suggesting metastatic spread were found. National guidelines for management of TC in accordance with European Thyroid Association (ETA) and American Thyroid Association (ATA) guidelines[22,23] were introduced in 2011. This did not alter the surgical protocol, but a weekly multidisciplinary video conference was implemented to ensure uniform management. In addition, all FNAC and histopathological specimens were reviewed at Sahlgrenska University Hospital. Before 2011, both FNAC and routine histopathological analyses were performed at each hospital unless a second opinion was requested. The Bethesda system for reporting thyroid FNAC was described in the national guidelines in 2011 and was gradually introduced in the region during subsequent years.

Tumour detection

Medical records from all TC patients in the three cohorts were available and complete. Reviews were performed by three of the authors in close collaboration to ensure consistent assessment. Three separate patient groups were distinguished by means of initial means of tumour detection.

The palpation group was patients referred to surgery due to a palpable nodule in the neck with FNAC suggesting TC or with symptoms from distant metastasis in which a thyroid tumour was revealed by physical examination.

The incidental group was patients diagnosed with TC after histopathological examination of surgical specimens when treated for benign thyroid conditions, or when FNAC showed follicular neoplasia which proved to be benign, but histopathology revealed a previously undetected occult carcinoma in addition. This group also included patients with hyperparathyroidism (HPT) in which intraoperative findings of a thyroid tumour led to lobectomy with further management in accordance with guidelines when TC was confirmed histopathologically.

The imaging group was patients with thyroid nodules detected by ultrasonography, CT, 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) or MRI primarily conducted for a non-thyroid indication. Preoperative FNAC indicated neoplasia in all these cases.

Tumour diagnosis and staging

Palpation-guided FNAC was performed by cytologists or surgeons while ultrasound-guided FNAC was performed by radiologists. Tumour diameters were measured from specimens or by imaging in the small number of cases not subjected to surgery. *TNM*

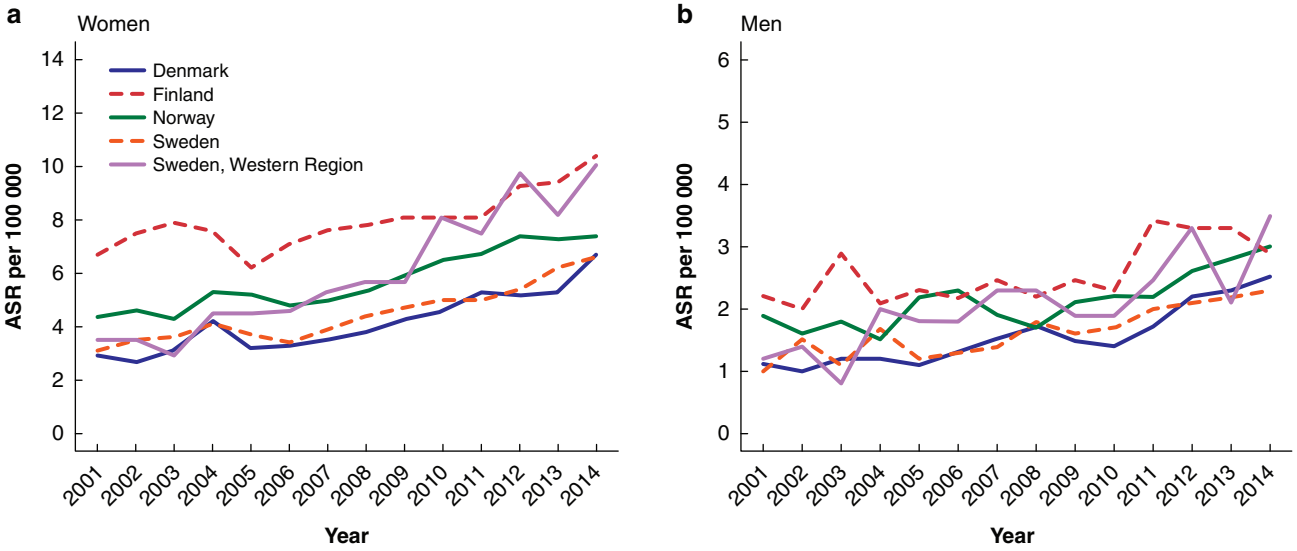

Fig. 1 Annual incidence of thyroid cancer in Denmark, Finland, Norway, Sweden and the Western Region of Sweden in 2001–2014
a for women and b for men. The world standard population was used for calculation of the age-standardized rates (ASRs).

Classification of Malignant Tumours, 7th edition[24], was used as it was the classification which applied to most patients during the entire study interval. N0 was defined as lack of tumour spread when six or more investigated lymph nodes were investigated and found negative. M0/1 status was based on imaging findings, occasionally confirmed microscopically after biopsy.

Tumours were classified as one of four distinct TC subgroups: papillary (PTC), follicular (FTC), medullary (MTC) or anaplastic carcinomas (ATC). Further subclassification of PTC and FTC variants were inconsistently reported over time and between participating hospitals and therefore not monitored for further evaluation in this study. Poorly differentiated thyroid carcinomas (PDTC) featured signs of tumour progression from PTC or FTC and were therefore classified as (originating from) differentiated thyroid carcinoma (DTC) in the outcome evaluation of treatment.

Statistical analysis

The programming language R (version 3.5.3) was used to calculate age-standardized incidence rates (ASRs) per 100 000 person-years using the direct method correlating to the world standard population divided in 5-year age classes, the highest being 85 years and older. The population at risk in VG County based on crude incidence rates was estimated using the mid-year population for each investigated cohort.

The estimated annual percentage change (EAPC) for the entire study interval was obtained by monitoring the yearly change in trend after fitting a linear regression model with the log of the ASR being the response. Errors of the EAPC calculations were assumed to have constant variance.

ASRs were calculated separately for means of detection, type, size and T stage of tumours using the binomial method for standard error calculations. ASR differences between cohorts were considered significantly different at a 5 per cent significance level by calculating the standardized rate ratio with 95 per cent confidence intervals[25].

Ethics

The regional board of ethics for human studies ('Regionala etikprövningsnämnden i Göteborg') approved the study with reference to VGFOUREG—154331/Dnr: 261–11.

Results

Data on patients with thyroid cancer diagnosed and treated in Västra Götaland County 2001–2014

TC rates retrieved from the NORDCAN registry between 2001 and 2014 showed a higher incidence in the Western Region of Sweden than in the whole of Sweden and Denmark but similar to that in Norway and Finland for both sexes (*Fig. 1*). Based on data retrieved from SCR, 1230 patients with TC were diagnosed in VG County during the entire study interval. ASR of TC in this population increased from 3.1 to 10.7 in women and from 1.1 to 3.8 in men, corresponding to an EAPC of +10.4 (95 per cent c.i. 8.1 to 12.8) per cent and +8.0 (95 per cent c.i. 4.3 to 11.7) per cent respectively.

Review of medical records from the three time intervals (2001–2002, 2006–2007 and 2011–2014) involved 736 (60 per cent) of all patients with TC. Subsequent data presentation and graphs refer to comparison of these cohorts. Mean age was 53 (range 6–92) years and did not change significantly between the cohorts. FNAC was conducted for 664 (90 per cent) of the patients out of which 466 (70 per cent) were guided by palpation. Ultrasound-guided FNAC increased from 5 (11 per cent) patients in 2001 to 69 (52 per cent) in 2014. False benign preoperative FNAC occurred in 142 patients (21 per cent) in total and for tumours larger than 10 mm in 76 patients (15 per cent) with no changing trend over the years. In tumours larger than 10 mm (531 patients), cytology was non-diagnostic in three patients and was not performed for 23 patients, altogether comprising less than 5 per cent of this tumour group. DTC occurred in 686 (93 per cent) patients, out of which 583 (85 per cent) were PTC and 103 (15 per cent) were FTC. Most patients (72 per cent) with DTC were women. Six patients did not have surgery (one male patient with a 6-mm PTC declined surgery and five patients had inoperable ATC).

Both PTC and FTC increased significantly in incidence between 2001–2002 and 2011–2014 (*Fig. 2*). ASR calculation demonstrated that PTC increased three-fold from 1.53 to 4.84 and FTC increased fivefold from 0.13 to 0.73. These changes are statistically significant. Nine DTC cases (1.3 per cent) were subclassified as PDTC due to histological signs of tumour progression from PTC (8 patients) and FTC (1 patient). All patients with PDTC presented with a palpable thyroid tumour and were evenly distributed between the investigated cohorts (data not shown). The incidence of MTC (22 patients; 2.9 per cent) and ATC (28 patients; 3.8 per cent) remained low and stable (*Fig. 2*) and all were detected by palpation.

Differentiated thyroid carcinoma rates by means of tumour detection

The majority of patients with DTC (441 patients, 64 per cent) were referred to surgery due to clinical signs or symptoms, mostly a palpable thyroid nodule (*Table 1* and *Fig. 3*); six patients presented with symptoms of distant metastases (primary tumour diameters ranged from 20–70 mm). Tumour detection by palpation of DTC increased almost three-fold from ASR 1.20 in 2001–2002 to 3.48 in 2011–2014 (*Fig. 3* and *Table 2*). Mean age of patients with palpable DTC subjected to surgery decreased from 58.2 to 50.7 years between the first and last cohorts (*Table 1*). In patients with palpable tumours the number of PTCs increased progressively whereas FTCs increased predominantly between the first and second cohorts (*Table 1*).

Incidental tumours comprised 208 (30 per cent) of the patients with DTC (*Table 1*), being diagnosed after surgery for non-toxic

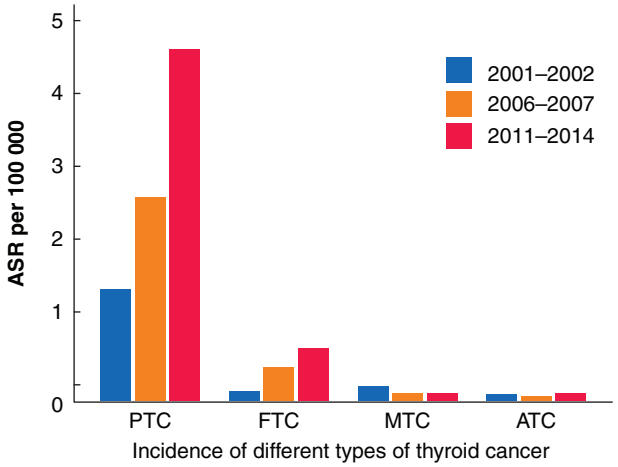

Fig. 2 Incidence of different types of thyroid cancer in Västra Götaland County.

Age-standardized rate (ASR) per 100 000 person-years adjusted to world age. PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; MTC, medullary thyroid carcinoma; ATC, anaplastic thyroid carcinoma.

Table 1 Relationship between methods of tumour detection and tumour type and size in patients with differentiated thyroid cancer

	Palpation			Incidental			Imaging		
	2001–2002	2006–2007	2011–2014	2001–2002	2006–2007	2011–2014	2001–2002	2006–2007	2011–2014
Age at diagnosis	58.2(19.2)	53.6(19.8)	50.7(18.2)	50.1(11.9)	49.1(15.0)	50.7(14.1)	–	43.0(25.5)	60.3(16.1)
Tumour size (mm)	31.8(20.6)	36.2(26.2)	30.1(18.9)	13.6(25.0)	12.2(13.4)	13.9(17.3)	–	17.5(6.4)	17.7(11.5)
PTC	$n=53$	$n=70$	$n=235$	$n=16$	$n=41$	$n=135$	$n=0$	$n=2$	$n=31$
ASR	1.12	1.71	2.90	0.41	1.03	1.64	0.00	0.06	0.29
FTC	$n=4$	$n=22$	$n=57$	$n=2$	$n=3$	$n=11$	$n=0$	$n=0$	$n=4$
ASR	0.08	0.41	0.58	0.05	0.06	0.11	0.00	0.00	0.04

Values in parentheses are standard deviation. PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; ASR,age standardized rate per 100 000 person-year.

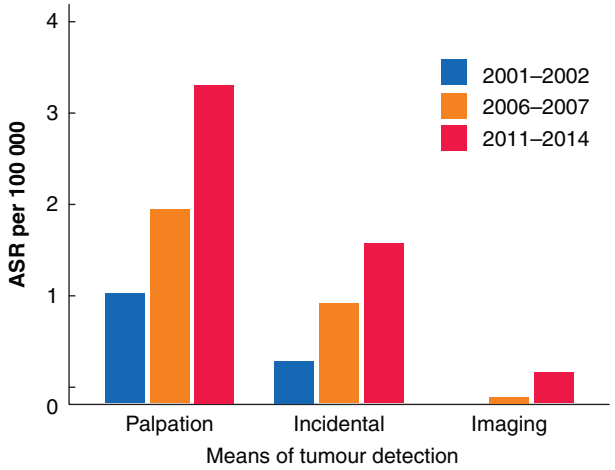

Fig. 3 Differentiated thyroid cancer incidence in Västra Götaland County based on means of tumour detection by palpation, incidentally at surgery or neck imaging for non-thyroid reasons.

ASR, age-standardized rate per 100 000 person-years.

nodular goitre (125 patients), toxic goitre (56), follicular adenoma (13) and HPT (14 patients). DTC discovered incidentally increased significantly 3.8-fold with an ASR of 0.46 in 2001–2002 and 1.75 in 2011–2014 (*Fig. 3* and *Table 2*). Most incidentally detected tumours were microcarcinomas (135 cases; 65 per cent) but also larger tumours were encountered in this group (*Table 3*). The vast majority of incidental tumours were PTCs (*Table 1*).

Imaging revealed unexpected thyroid lesions in 37 (5 per cent) patients with DTC (*Tables 1* and *3*). The tumours were discovered by CT (13 patients), ultrasonography (11 patients), FDG-PET (10 patients) and MRI (3 patients). ASR of DTC detected by imaging increased from none in the first to 0.06 in the second and to 0.33 in the last study interval (*Fig. 3*), corresponding to 1.9 and 5.6 per cent respectively, of the total DTC diagnoses. Patients with DTC discovered by imaging in the most recent cohort had a mean age of 60 years—some 10 years older than in the corresponding palpation and incidental groups (*Table 1*).

Tumour size and T stage of differentiated thyroid carcinoma

The ASR of DTC tumours increased 3.5-fold for tumours larger than 10 up to 20 mm, 3.9-fold for tumours larger than 20 up to 40 mm and 2.8-fold for tumours larger than 40 mm (*Table 2*). Tumours less than 10 mm increased 3.3 times (*Fig. 4*). Mean tumour size for all DTC tumours was 25 mm and varied on a yearly basis between 21 and 30 mm with no trend towards smaller tumours at the end of the study interval.

Table 2 Statistical significance of changes in tumour size, T stage and means of detection for differentiated thyroid cancer

	2001–2002 ASR	2011–2014 ASR	Standardized rate ratio*
Tumour size (mm)			
≤10	0.52	1.69	3.25 (2.24, 4.71)
>10–20	0.33	1.14	3.44 (2.16, 5.46)
>20–40	0.45	1.75	3.86 (2.62, 5.67)
>40	0.35	0.98	2.79 (1.73, 4.50)
T stage			
T1a	0.52	1.58	3.02 (2.07, 4.43)
T1b	0.25	0.89	3.57 (2.10, 6.07)
T2	0.40	1.44	3.57 (2.35, 5.41)
T3	0.42	1.51	3.60 (2.37, 5.45)
T4	0.06	0.14	2.21 (0.89, 5.50)
Means of detection			
Palpation	1.20	3.48	2.91 (2.25, 3.77)
Incidental	0.46	1.75	3.79 (2.60, 5.54)

*Values in parentheses are 95 per cent confidence intervals. Standardized rate ratio is $ASR_{2011-2014}/ASR_{2001-2002}$.

Table 3 Means of detection correlated to tumour size in patients with differentiated thyroid cancer

Primary tumour size (mm)	Total	Palpation	Incidental	Imaging
≤10	202	53	135	14
>10–20	135	97	30	8
>20–40	206	169	23	14
>40	143	122	20	1

Similar results were obtained when examined by T staging of DTC (*Fig. 5*). ASR of stages T1a–T3 increased significantly 3.0–3.6 times between 2001–2002 and 2011–2014 (*Table 2*). ASR of DTC stage T4 (33 cases) doubled from the first to the last time interval (*Fig. 5*) although this increase was not statistically significant (*Table 2*).

Only patients with PTC (583 patients) were evaluated for regional lymph node metastases. Of these, some 190 were node positive (141 N1a and 49 N1b). The relative proportions of N1a to N1b were similar across the three time intervals, as was the case for N0 and Nx. The numbers of patients with DTC with distant metastases at diagnosis (M1) were five in 2001–2002, 10 in 2006–2007 and 14 in 2011–2014, corresponding to two to five cases annually throughout the study interval.

Follow-up of the investigated differentiated thyroid carcinoma cohorts

Follow-up data as of 31 March 2016 showed that the first cohort of patients with DTC (2001–2002, 75 patients) with mean observation time of 14 years, had eight disease-specific deaths (11 per

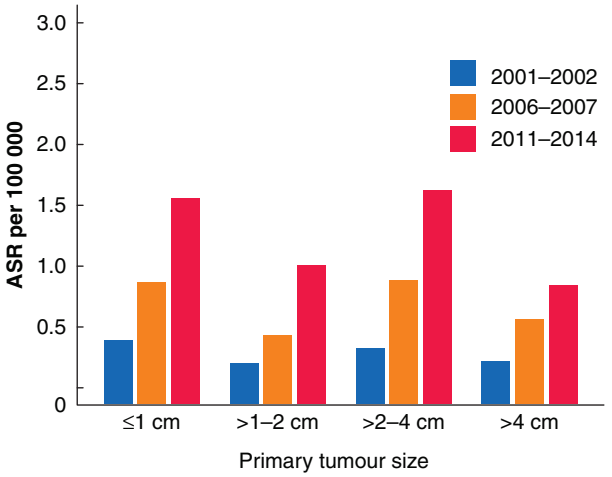

Fig. 4 Primary tumour size of differentiated thyroid cancer diagnosed in three cohorts of 686 patients diagnosed and treated in Västra Götaland County

ASR, age-standardized rate per 100 000 person-years.

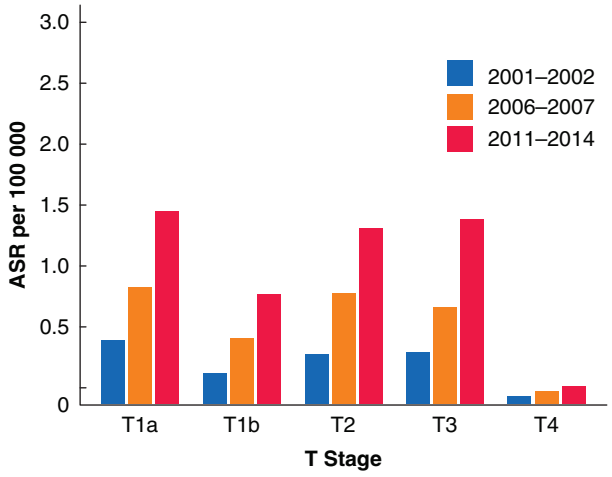

Fig. 5 Tumour staging (T) of patients with differentiated thyroid cancer in Västra Götaland County

ASR, age-standardized rate per 100 000 person-years.

cent) and three patients (4 per cent) alive with persistent or recurrent disease. In the second cohort (2006–2007, 138 patients) with a mean observation time of 9 years, 10 patients (7.2 per cent) had died from DTC and 11 (8.0 per cent) were alive with persistent or recurrent disease. In the last cohort with mean observation time of 3 years (2011–2014; 473 patients), seven patients (1.5 per cent) had died from DTC and 26 (5.5 per cent) were alive with persistent or recurrent disease. All 25 patients who died of DTC belonged to the palpation group and their tumours were advanced at the time of diagnosis: mean primary tumour size was 64 (range 21–120) mm and mean age was 73.4 (range 41–86) years. Fourteen of these patients had stage T4 tumours of which four were PDTC, and 10 patients with fatal outcome were stage T3. One deceased patient with multifocal DTC was classified as T2 but was primarily diagnosed due to a vertebral metastasis. Five patients had recurrent laryngeal nerve paralysis at diagnosis.

Of 40 patients with persistent or recurrent disease, comprising 5.8 per cent of the total number with DTC in the three cohorts altogether, the majority (36 patients) belonged to the palpation group, two belonged to incidental group and two were diagnosed by imaging. Two patients in this group were subclassified as PDTC.

Discussion

This registry-based study supported by examination of clinical patient records has shown that between 2001 and 2014 there was a three-fold increased incidence of DTC. Increased incidence was identified for both PTC and FTC. The majority of patients (64 per cent) were primarily diagnosed due to clinical findings, usually by a palpable nodule that eventually led to TC diagnosis. Significant increases were noted for DTC tumours of all size categories (less than 1, 1–2, 2–4 and larger than 4 cm) and T stages up to and including T3. Incidental tumours diagnosed after surgery for benign thyroid conditions also increased significantly, representing 30 per cent of all cases. The observed rise in incidentally detected tumours could be explained by a five-fold increase in the number of thyroidectomies carried out in VG County between 2001 and 2014 (estimated to have increased five-fold according to register data obtained from National Board of Health and Welfare: https://sdb.socialstyrelsen.se/if_ope/val.aspx). Only 5 per cent of the tumours were detected by imaging, confirming the notion that ultrasonography had only a minor role in diagnosing thyroid malignancies in Western Sweden. No changes in age and sex distribution were observed indicating data selection was unbiased.

The findings are consistent with a real increase in the incidence of DTC that required surgery on the basis of clinical signs, where management was in accordance with national and international guidelines. This contradicts previous observations[15,16] arguing that the increased TC incidence in recent years is due to imaging regardless of tumour size or stage. Many previous reports infer detection of PTC microcarcinomas as the major cause of the increased TC incidence[2,3,5,26,27]. 'Over-diagnosis' of TC on the basis of the striking increase of microcarcinomas[28,29], has led to significant divisions of opinion. Some experts have raised concerns of overtreatment of small and indolent cancers that are unlikely to harm the patient if left untreated[26,30,31]. Frequent findings of previously undiagnosed thyroid microcarcinomas at post-mortem examinations[32–34], are consistent with a probable accumulation of small tumours over time. These may be increasingly detected when neck ultrasonography and other sensitive diagnostic procedures are more widely used. In accordance with these observations, almost two thirds of incidentally detected tumours in the present study consisted of microcarcinomas. The present findings that imaging contributed only to a minor extent to TC detection in Western Sweden is in line with previous evidence that the Nordic countries did not belong to those with the highest reported TC incidence[28,29]. Differences in TC incidence between the Western Region of Sweden and the country as a whole, and the other the Nordic countries suggest that factors other than increased diagnostic activities account for this finding.

With the exception of ionizing radiation[36–38], the underlying risks of developing DTC are largely unknown, although several environmental and individual factors have been considered[39–46]. Increasing exposure to medical and other forms of ionizing radiation, especially in young individuals, is inferred as possible causal explanation to a rising incidence of PTC[47]. This includes repeated pulmonary X-ray screening for tuberculosis, an increasing use of CT scans, dental X-ray and breast cancer screening in the last decades, which probably contribute to an accumulated risk of thyroid exposure to

ionizing radiation[48,49]. Since radiation-induced PTC generally develops after a long delay, 30 years or more[50], a causal relationship is difficult to evaluate.

Iodine deficiency has been proposed as a risk factor. Theoretically the Swedish population should have adequate iodine levels since the iodization of salt was introduced in Sweden in 1938[54]. However, recent studies suggest that risk groups may suffer from iodine insufficiency[55,56]. Long-term demographic changes of the Swedish society due to immigration probably also contribute to an altered pattern of thyroid disorders related to iodine imbalance and the risk of developing TC. A family-cancer database survey revealed an increased risk for DTC among first-generation immigrant populations in Sweden before 2010[57]. A nationwide SCR-based study found no regional differences in TC incidence except for iodine-sufficient *versus* -deficient areas in Sweden before 1981[58].

As DTC is usually cured with surgery and radioactive iodine treatment[59,60] mortality rates cannot be evaluated without long follow-up times. Follow-up of disease-specific death performed 10–15 years after diagnosis (excluding the third cohort) indicated that approximately 10 per cent of DTC patients had advanced tumours with poor prognosis. According to the NORDCAN registry (https://nordcan.iarc.fr/en) the incidence-based mortality rates of all types of TC are similar comparing the Western Region of Sweden with the entire country and the other Nordic countries. This indicates that despite differences in registered TC rates, the number of patients with fatal disease did not change, at least not before 2007.

Interestingly, all DTC deaths in the present study occurred in patients with tumour-related symptoms and thus included in the palpation group. The vast majority of DTC patients with persistent and recurrent disease also belonged to this group. Although the present series of patients with DTC comprised a limited number of cases of PDTC, all showed signs of progression from PTC or FTC, justifying the primary DTC diagnosis. The validity of the mortality rates is strengthened by data from a stable population and all Swedish citizens are identifiable by an individual personal number. Complete follow-up data reduce selection bias. If mortality rate is calculated merely on the basis of palpable primary tumours, the cumulative risk of dying of DTC is estimated to 15.6 per cent.

The present study contradicts previous assumptions that the increased incidence of TC observed in most countries would be solely explained by detection of small and clinically unnoticed tumours as a consequence of more frequent diagnostic investigations. The majority of tumours were detected by palpation suggesting a real increase in the incidence of clinically significant thyroid malignancies.

Disclosure. No competing financial interests exist.

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