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Research paper

Differentiated thyroid cancer in Greece: 1963-2000.

Relation to demographic and environmental factors

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ABSTRACT

Thyroid cancer (TC) is a relatively rare neoplasia, accounting for 0.35%-0.38% of total deaths due to cancer in Greece. Environmental/nutritional factors are considered to play a role in its pathogenesis. The aim of this retrospective review of patients' histories from three of the largest specialized centers in southern Greece, from 1963 to 2000, was to assess associations of differentiated TC (DTC) with demographic and environmental factors. The total number of DTC cases was 610 (119 men or 19.5%, and 491 women or 80.5%), of which 442 cases (72%) were papillary DTCs (pure papillary type: 54.5% and mixed papillary-follicular type: 45.5%), 90 cases (15%) were of the pure follicular type, while 78 cases (13%) were classified as suspicious lesions, requiring follow-up, but not definitively carcinomas. The mean age (±SD) at diagnosis for all groups was 42.3±1.3 years. Fifty percent of the patients were living in Athens at the time of diagnosis. The diagnosis was delayed in patients living in villages compared to those living in cities (mean age ±SD): 43.7±14.1 years and 40.9±13.8 years, respectively; $p<0.05$, t-test). Patients who were born in iodine-sufficient areas (n=162/193, 84%; $X^2=5.09$, P=0.02) had papillary carcinoma more frequently compared to patients who were born in previously iodine-deficient areas (n=159/214, 74%). During the observation period (1963–2000) there appeared to be three different trends in the incidence of newly diagnosed cases: a random variation during the first nine years and a steady increase during the second two decades (starting before the Chernobyl nuclear accident) followed by a significant decline during the last few years. We suggest that the observed variations in the incidence of DTC could be related to the availability of diagnostic tools as well as to increased awareness.

Key words: Thyroid cancer

INTRODUCTION

Thyroid cancer (TC) is a relatively rare neoplasia, accounting for 0.35%-0.38% of total deaths due to cancer in Greece[1]. Environmental/nutritional factors are considered to play a role in the pathogenesis and histology of differentiated TC (DTC). Follicular TC has been associated with iodine deficiency and predominates in areas with endemic goiter, while in iodine-replete areas papillary TC is the predominant form[2]. Various studies have so far compared TC incidence between countries with a greatly differing iodine intake[3,4] or in the same country before and after

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correction of definite iodine deficiency[5]. Overall, the correction of nutritional iodine deficiency has been found to be associated with an increase of papillary to follicular DTC ratio[5].

The aim of the present retrospective analysis was to present data of patients with DTC diagnosed in three of the largest specialized centers in Athens during a roughly forty-year time span, and to assess correlations of DTC with demographic and environmental factors.

MATERIALS AND METHODS

The DTC patients' histories in three of the largest specialized centers for DTC in southern Greece were examined for the years 1963 to 2000. These three centers comprise a university hospital tertiary care unit and two public health system hospitals. From preliminary data it appears that approximately half of DTC patients in the country have been diagnosed and/or treated in these centers. The following parameters were recorded: sex, age at diagnosis, year of diagnosis, histology, prefecture of birthplace, birthplace categorization (village/city), prefecture of residence, residence categorization (village/city) and categorization of birthplace and residence as an iodine-deficient area or not. The characterization of an area as iodine-deficient or not was based on earlier studies conducted in Greece[6-10]. In this study we did not take into account the patients' treatment modalities and disease course due to a paucity of consistently collected data. However, we took care to eliminate duplicate inclusions of patients who had been diagnosed and/or treated at more than one of the participating centers. Some cases of DTC were not included in the analysis because the patients subsequently sought treatment in institutions other than those participating in the study. Statistical analysis implemented the X^2 test, t-test and Pearson correlation.

RESULTS

Six hundred and ten patients were included in this study: 119 men (19.5%) and 491 women (80.5%) (Table 1), of which 442 cases (72%) were papillary DTCs (pure papillary type: 54.5% & mixed papillary-follicular type: 45.5%), 90 cases (15%) were of the pure follicular type, while 78 cases (13%) were classified as suspicious lesions requiring follow-up, but not definitively carcinomas (Table 2).

Table 1. Characteristics of patients with differentiated thyroid cancer (DTC)

Gender	n (%)	Age at diagnosis (yrs) (mean±SD)
Men	119 (19.5)	43.2±13.2
Women	491 (80.5)	41.9±14.3
Total	610 (100)	

Mean age at diagnosis for all categories was in the fifth decade of life. Fifty percent of the patients were living in Athens at the time of diagnosis.

The comparison of different groups of patients with DTC did not yield significant differences, with the exception of patients born in villages (41% of cases) who were diagnosed with DTC later compared to patients born in cities (mean age at diagnosis: 43.7 & 40.9 years, respectively; $P<0.05$, t-test) (Table 3). Moreover, patients who were born in iodine-sufficient areas (n=162/193, 84%; $X^2=5.09$, $P=0.02$, Table 4) had papillary carcinomas more frequently compared to patients who were born in iodine-deficient areas (n=159/214, 74%).

During the first nine years of the observation period, there was the expected random variation in the incidence of new DTC cases without any particular trends. On the other hand, during the second decade there was a steady increase in the incidence of new cases, and a further increase during the third decade (Figure 1). Statistical analysis showed that during these two decades (years 9 – 29) there was a highly significant positive linear correlation between the number of newly diagnosed cases per year both for the total number of DTC as well as for the papillary type ($r=+0.82$, $P<0.001$ and $r=+0.79$, $P<0.001$, respectively); furthermore, there was a trend for a relative increase in the ratio of pure papillary DTC/total DTC

Table 2. Histology of differentiated thyroid cancer (DTC)

Histology	n	Male/Female	Age at diagnosis (yrs) (mean±SD)
Pure papillary	241	46/195	41.7±14.3
Mixed papillary-follicular	201	37/164	42.8±13.7
Follicular	90	17/73	44.4±14.6
Suspicious	78	20/58	39.9±13.7
Total	610		

Table 3. Classification of differentiated thyroid cancer (DTC) by birthplace and residence

	Birthplace		Residence	
	n	Age at diagnosis (yrs) (mean±SD)	n	Age at diagnosis (yrs) (mean±SD)
Village	171	43.7±14.1*	100	42.6±15.1
City	245	40.9±13.8	483	42.4±13.8
Total	416		583	

*P<0.05;t-test for comparison of the means

Table 4. Histology of differentiated thyroid cancer (DTC) by iodine status

	Birthplace (n=407)		Residence (n=569)	
	No ID (n=193)	Mild-severe ID (n=214)	No ID (n=377)	Mild-severe ID (n=192)
Total papillary	162 (84%*)	159 (74%)	285 (75%)	132 (69%)
Pure papillary	79/193 (41%)	72/214 (34%)	141/377 (37%)	77/192 (40%)
Mixed papillary-follicular	83/193 (43%)	87/214 (40%)	144/377 (38%)	55/192 (29%)
Follicular	16 (8%)	30 (14%)	54 (15%)	30 (16%)
TP/F	10.1	5.3	5.3	4.4
PP/F	4.9	2.4	2.6	2.6
Suspicious	15 (8%)	25 (12%)	38 (10%)	30 (16%)

** X^2=5.09; P=0.02, ID: iodine deficiency; TP/F: total papillary DTC/follicular DTC ratio; PP/F: pure papillary DTC/follicular DTC ratio*

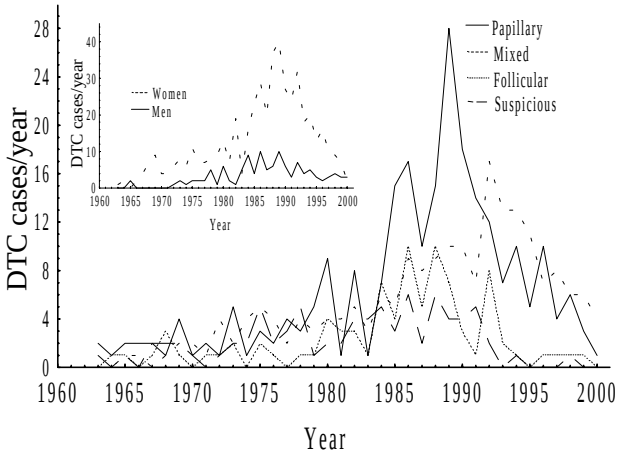

Figure 1. Distribution of differentiated thyroid cancer cases during the study period according to histological diagnosis; *inset: distribution of differentiated thyroid cancer cases diagnosed per year according to gender.*

(r=+0.53, P<0.02). Finally, during the last eight years of the observation period (1993 – 2000) there was a continuous, significant decrease in the number of new cases (r=-0.91, P<0.001).

DISCUSSION

In this report we presented the time course of DTC cases diagnosed in our Units over an approximately 40-year time span. Even at the peak of diagnoses in 1989, the calculated annual incidence was not higher than 5 per 100,000 inhabitants (data not shown) in our catchment area, which is not different from rates of other regions[11]. A preponderance of female patients – for all DTC types– was noted throughout the examined time period, as has been previously reported for DTC as well as for benign thyroid disease[12].

Patients born in iodine-deficient regions were more likely to present with pure follicular DTC as a percentage of the total. It is noteworthy that the iodine nutrition status of the birthplace (iodine deficient or sufficient) was related to DTC histology, while the area of residence was not related to any particular histological type. A link between nutritional iodine deficiency and subsequent diagnosis of DTC has been shown over shorter time periods and/or smaller areas both, in Greece and elsewhere[6,11,13-18].

Dietary iodine sufficiency after nutritional supplementation has been linked to an increase of papillary

to follicular DTC ratio[5,11], while iodine deficiency has been linked to increased follicular and anaplastic carcinoma prevalence[19] or increase of follicular to papillary DTC ratio[11,18,20]. However, in some studies an iodine-rich diet has been associated with follicular DTC[21]. In currently iodine-replete areas, which had also been studied previously, not only did the histological type change in favor of papillary carcinoma but also the absolute number of detected microcarcinomas increased after the correction of iodine deficiency[5]. Such an increase has not however been found in association with an increased dietary iodine intake by Horn-Rosss et al and Bosetti et al[22,23]. Merhy et al found in West Virginia (USA) an increasing aggressive pattern of DTC without an obvious cause[24]. Such a pattern has not been detected in our material.

Low-iodine diet is considered to lead to decreased circulating levels of thyroid hormones and to a subsequent increase in the serum TSH. Hypertrophy and hyperplasia of the thyroid ensue which may then proceed to neoplasia[25]. Moreover, transition from iodine sufficiency to iodine deficiency – after discontinuation of iodine supplementation– was accompanied by a rise in the incidence of papillary carcinoma in Tasmania[26]. Furthermore, thyroid enlargement and goiter are considered by some researchers to be true benign neoplasia[27]. Other factors, such as mutations in the *ras, ret, trk* and *met* proto-oncogenes have been implicated in the pathogenesis of DTC[11] since they are more common in the hyperplastic state.

The specific interest of the present work is that we studied patients born in the same country from both areas with and without nutritional iodine sufficiency and showed, by inference, that patients exposed to a low iodine intake at a young age may be at higher risk for the appearance of follicular rather than papillary DTC during adulthood.

During the observation period (1963 – 2000) there appeared to be three different trends in the incidence of newly diagnosed cases of DTC 1) a random variation during the first nine years with no particular trends, 2) a significant increase during the second decade, followed by a steeper increase in the third decade; 3) a significant decline in the number of cases during the last nine years. The observed increase had already started before the Chernobyl nuclear accident and could be attributed to the increased availability of diagnostic tools. The number of new cases increased further after the Chernobyl accident obviously as a result of more intense TC case-finding. Some radioactive fallout did reach Greece immediately after the disaster[28], however, no significant link between the Chernobyl disaster and neoplastic disease has been observed in the country[29,30]. Furthermore, thus far, an increased incidence of TC has only been definitively shown for children living in the vicinity of the nuclear accident area[31]. Most likeky the elimination of the patients' pool has finally led to a subsequent drop in the DTC diagnosis rate during the fourth decade.

A further observation concerns the relative increase of the papillary subtype during the third decade. This may be due to the increased iodine intake through "silent prophylaxis" (from industrialised food) rather than the salt iodination program, which was undertaken in 1966. One further explanation may be that the carcinomas discovered through increased awareness are usually of the "micropapillary" subtype.

In conclusion, DTC in southern Greece is a rare disease, a finding also consistent with previous studies[32,33]- and is found more frequently in women. The relative frequency of follicular subtype DTC may be higher in patients exposed to a low iodine intake at a young age. The variability in the incidence of DTC during the observation period is probably related to the wider availability of the diagnostic tools as well as to increased awareness after the Chernobyl accident.

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