1

An Epidemiological Analysis of Thyroid Cancer in a Spanish Population: Presentation, Incidence and Survival

A. Rego-Iraeta, L. Pérez-Mendez and R.V. García-Mayor
Department of Endocrinology, Diabetes, Nutrition and Metabolism,
University Hospital of Vigo
Spain

1. Introduction

Accurate statistics on cancer occurrence and outcome are essential both for the purposes of research and for planning and evaluation programmes for cancer control (Parkin, 2006). Although tumours of thyroid account for only 1% of the overall human cancer burden, they represent the most common malignancies of the endocrine system and pose a significant challenge to pathologists, surgeons and endocrinologists. Among epithelial tumors, carcinomas of follicular cell origin far outnumber those of C-cell origin. The vast majority of carcinomas of follicular cell origin are indolent malignancies with 10 year survivals in excess of 90 %.

1.1 Classification

Thyroid follicular epithelial-derived cancers are divided into three categories: papillary cancer, follicular cancer and anaplastic cancer. Papillary and follicular cancers are considered differentiated cancers, and patients with these tumours are often treated similarly despite numerous biologic differences. Most anaplastic (undifferentiated) cancers appear to arise from differentiated cancers. Other malignant diseases of the thyroid include medullary thyroid cancer (which can be familial, either as part of the multiple endocrine neoplasia type 2 syndrome or isolated familial medullary thyroid cancer), primary thyroid lymphoma, or metastases from breast, colon, or renal cancer or melanoma. In countries with adequate iodine intake, differentiated thyroid cancer accounts for more than 85% of all cases, being the most common type papillary (60-80%). Tumor histology is a critical determinant of patient outcomes; differentiated thyroid cancer is associated with the best survival rate and medullary and anaplastic have significantly poorer outcomes (Hundahl et al., 1998). Certain subtypes, such as the tall and columnar cell variants of papillary cancer and the insular variant of follicular cancer are more common in older patients with higher stage disease and have a worse prognosis than usual forms of thyroid cancer. The traditional separation of thyroid cancer into the major groups of papillary, follicular, medullary and undifferentiated (anaplastic) carcinoma, based on morphology and clinical

features, is strongly supported by advances in molecular studies showing the involvement of distinct genes in these four groups, with little overlap (DeLellis & Williams, 2004).

1.2 Staging and prognostic factors

Numerous staging systems have been created in an attempt to accurately prognosticate outcomes for individual patients; two careful studies have compared the efficacy of the various staging systems and found that none is superior (Brierley et al., 1997; Sherman et al., 1998). Consequently, the European Thyroid Association (ETA) (Pacini et al., 2006) and the American Thyroid Association (ATA) (Cooper et al., 2009) have recommended the use of the Tumour, Node, Metastasis (TNM) classification of the American Joint Commission on Cancer (AJCC) and the International Union Against Cancer because it is universally available and widely accepted for other disease sites. An interesting feature of the TNM staging system compared to other classifications is the age factor. While the staging of head and neck cancers relies exclusively in the anatomical extent of disease, it is not possible to follow this pattern for the particular group of malignant tumors that arise in the thyroid gland. The effect of age is such significance in behavior and prognosis, that both the histologic diagnosis and the age of the patient are included in the staging system for these tumors. The AJCC classification is based on the TNM system, which relies on assessing three components: (1) extent of the primary tumour (T), (2) absence or presence of regional lymph node metastases (N), and (3) absence or presence of distant metastases (M). The fifth edition (Fleming et al., 1997), (Table 1) was revised as the sixth edition (Greene et al., 2002), (Table 2). A major alteration was the reclassification of tumour staging (T). For differentiated (papillary and follicular) and medullary tumours confined to the parenchyma of the thyroid gland without extrathyroidal extension, there is no evidence to suggest that using a size cut-off of 1 cm provides better prognostic stratification compared with the 2-cm cut-off used for

	Papillary or Follicular		**Medullary**	**Anaplastic**
Stage	**Age < 45 years**	**Age > 45 years**	**Any age**	
I	Any T Any N M0	T1 N0 M0	T1 N0 M0	
II	Any T Any N M1	T2 N0 M0 T3 N0 M0	T2 N0 M0 T3 N0 M0 T4 N0 M0	
III		T4 N0 M0 Any T N1 M0	Any T N1 M0	
IV		Any T Any N M1	Any T Any N M0	Any T Any N Any M

Table 1. AJCC TNM classification for thyroid cancer (fifth edition). **T1** - Tumor 1 cm or less in greatest dimension limited to the thyroid. **T2** - Tumour more than 1 cm, but not more than 4 cm, in greatest dimension limited to the thyroid. **T3** - Tumour more than 4 cm in greatest dimension limited to the thyroid. **T4** - Tumour of any size extending beyond the thyroid capsule. **T4a** - Excluded. **T4b** - Excluded. Regional lymph nodes are the cervical and upper mediastinal lymph nodes. **N1a** - Metastasis in ipsilateral cervical lymph node(s). **N1b** - Metastasis in bilateral, midline, or contralateral cervical or mediastinal lymph node (s). **M0-** no distance metastases; **M1-** distance metastases.

other head and neck sites. Therefore, fifth edition T1 (≤1 cm) and T2 (between 1 and 4 cm) were redefined as sixth edition T1 (≤2 cm) and T2 (between 2 and 4 cm). In the sixth edition, T3 includes not only large tumours (4 cm or more) but also tumours with minimal extension, and T4 consists of T4a and T4b. The fact that diverse outcomes may be expected in these two groups of patients is now recognized in the sixth edition: tumors that involve the sternothyroid muscle are classified as T3, while extension to larynx, trachea, oesophagus, recurrent laryngeal nerve, or subcutaneous soft tissue, all of which are surgically resectable, is classified as T4a. Tumours that invade the prevertebral fascia or encase the carotid artery or mediastinal great vessels are not resectable for cure, and these patients are staged T4b. Thus, the sixth edition divides fifth edition T4 tumors into T3 (minimal invasion), T4a (extended invasion), and T4b (more extensive unresectable invasion) tumours according to the degree of extrathyroid extension. The degree of extension has been closely related to adverse prognoses. Therefore, the sixth edition is expected to predict more accurately different outcomes in patients with extrathyroid extension compared with the fifth edition.

	Papillary or Follicular		**Medullary**	**Anaplastic**
Stage	**Age < 45 years**	**Age > 45 years**	**Any age**	
I	Any T, Any N, M0	T1 N0 M0	T1 N0 M0	
II	Any T Any N M1	T2 N0 M0	T2 N0 M0	
III		T3 N0 M0 T1 N1a M0 T2 N1a M0 T3 N1a M0	T3 N0 M0 T1 N1a M0 T2 N1a M0 T3 N1a M0	
IVA		T4a N0 M0 T4a N1a M0 T1 N1b M0 T2 N1b M0 T3 N1b M0 T4a N1b M0	T4a N0 M0 T4a N1a M0 T1 N1b M0 T2 N1b M0 T3 N1b M0 T4a N1b M0	T4a Any N M0
IVB		T4b Any N M0	T4b Any N M0	T4b Any N M0
IVC		Any T Any N M1	Any T Any N M1	Any T Any N M1

Table 2. AJCC TNM classification for thyroid cancer (sixth edition). **T1** - Tumor 2 cm or less in greatest dimension limited to the thyroid. **T2** - Tumour more than 2 cm, but not more than 4 cm, in greatest dimension limited to the thyroid. **T3** - Tumour more than 4 cm in greatest dimension limited to the thyroid or any tumour with minimal extrathyroid extension (extension to sternothyroid muscle or perithyroid soft tissues). **T4** - Excluded. **T4a** - Tumour of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, oesophagus, or recurrent laryngeal nerve. **T4b** - Tumour invades prevertebral fascia or encases carotid artery or mediastinal vessels. **T4a** - Intrathyroidal anaplastic carcinoma—surgically resectable. **T4b** - Extrathyroidal anaplastic carcinoma—surgically unresectable. Regional lymph nodes are the central compartment, lateral cervical, and upper mediastinal lymph nodes. **N1a** - Metastasis to Level IV (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes). **N1b** - Metastasis to unilateral, bilateral, or contralateral cervical or superior mediastinal lymph nodes. **M0-** no distance metastases; **M1-** distance metastases.

TNM classification is also used for hospital cancer registries and epidemiologic studies. One of the greatest inadequacies of TNM system is that it is a static representation of the patient's disease at the time of presentation; it does not allow for modification of risk during lifelong follow-up. Most patients with papillary cancer in the TNM system are classified as stage I disease (Hundahl et al., 1998), with an associated mortality rate of 1.7% (Loh et al., 1997). It is important to note, however, that there is a 15% recurrence rate 10 years after initial treatment (Loh et al., 1997). Recurrent or persistent disease, therefore, may necessitate additional therapy and can certainly affect the patient's quality of life. Further limitations of tumour staging include the lack of consideration of tumour histology, extracapsular extension of the tumour or molecular characteristics of the primary tumour. As is well known, these factors can predict poorer outcomes for individual patients. As TNM staging was developed to predict risk of death and not recurrence, the ATA (Cooper et al., 2009) has created a more functional definition of risk stratification for individual patients that is similar to one outlined by the ETA (Pacini et al., 2006). Patients are classified as low-risk if they have the following characteristics: no local or distant metastases, resection of all macroscopic tumour, no tumour invasion into locoregional tissues, tumour that is not an aggressive histological variant, no vascular invasion, and no uptake outside the thyroid bed on the post-treatment whole body scan (if ^{131}I is given). Intermediate-risk patients are those with any of the following criteria: microscopic tumour invasion into the perithyroidal tissues at initial surgery, cervical lymph node metastases or ^{131}I uptake outside the thyroid bed on the initial post-treatment scan, or tumour with aggressive histology or vascular invasion. Finally, high-risk patients have macroscopic tumour invasion, incomplete tumour resection, distant metastases or elevated thyroglobulin out of proportion to what is seen on the post-treatment scan (Cooper et al., 2009). This stratification was designed to help identify patients who are at higher risk for recurrent disease and may benefit from more aggressive postoperative management (Cooper et al., 2009). Such a definition of risk is more intuitive for the management of patients with thyroid cancer and is more in accordance with the clinical behaviour of these tumours.

1.3 Epidemiology

Epidemiology has shown the influence of factors such as age and sex on thyroid cancer incidence. Thyroid cancer is rare in children below 16 years, with an annual incidence between 0.02 and 0.3 cases per 100,000 children and occurs exceptionally before age 10. In adults, the mean age of diagnosis is the mid 40´s to early 50´s for the papillary type, 50´s for the follicular and medullary types and 60´s for the less common undifferentiated types. It is well established that thyroid cancer is 2 to 4 times more common in women than in men, although this will differ among countries. Nevertheless, this sex difference is far less pronounced before puberty and after menopause. Several epidemiological studies have examined several reproductive traits, but the cause of this increased prevalence of thyroid cancer in women is unclear. The annual incidence of thyroid cancer varies considerably in different registries, with the highest incidence rates in the world reported in Hawaii and Iceland (Ferlay et al., 2007; Kolonel et al., 1990). In Europe, the highest incidence occurs in Iceland, followed by Finland, while relatively low incidence characterizes the United Kingdom and Denmark (Ferlay et al., 2007,). These differences have been attributed to ethnic or environmental factors, but different standards of health care may also play a role in the efficiency of cancer detection. Although thyroid cancer incidence is low in general

when compared with other diseases and tumours, over the last few decades, increasing rates have been reported in several countries, including Europe (Akslen et al., 1993; Colonna et al., 2002 ; dos Santos Silva et al., 1993; Gomez-Segovia et al., 2004; Petterson et al., 1991; Reynolds et al., 2005; Szybinski et al., 2003), the United States (Davies & Welch, 2006; Merhy et al., 2001; Zheng et al., 1996), Canada (Liu et al., 2001), and Australia (Burgess, 2002). Curiously, this increase has occurred almost exclusively in papillary thyroid cancer, with an epidemic of micropapillary thyroid carcinoma (MPTC) representing up to 43% of operated cancers in the present series (Leenhart et al., 2004a). The reasons for the rise in thyroid cancer incidence are not completely understood and considerable controversy exists now about whether this increase is real or only apparent due to an increase in diagnostic activity (Leenhart et al., 2004a; Leenhart et al., 2004b; Colonna et al., 2007). Recently, some researchers (Colonna et al., 2007; Davies & Welch, 2006; Kent et al., 2007) have suggested that this increase is predominantly due to the increased detection of small, subclinical tumours through the use of medical imaging. Moreover, thyroid surgery is constantly increasing, with more systematic use of total thyroidectomies even for benign pathologies, which makes it easier to detect MPTC. According to the World Health Organization (WHO), the term MPTC is used for a papillary carcinoma of the thyroid no larger than 1 cm in diameter (Hedinger et al., 1988). With the new classification published in 2004, the previous definition of MPTC now includes the additional criteria of being found incidentally (LiVolsi, 2004). MPTC seems to be present in a significant proportion of the general population with large variations in the prevalence rate between different geographic areas (6–35%) (Sampson et al., 1974), which may also be due to differences in the depth of the pathological examination (Martinez-Tello et al., 1993). Although the mortality risk for an individual patient with thyroid cancer is the greatest concern for patients and clinicians alike, most patients have excellent 10-20-year disease specific survival (Hundahl et al., 1998). EUROCARE (European Cancer Registry-based Study on Survival and Care of Cancer Patients) is a collaborative project between European cancer registries (Capocaccia et al., 2003). A major aim of EUROCARE is to estimate and compare cancer survival in European populations. EUROCARE-2 (Teppo & Hakulinen, 1998) was the first publication on thyroid cancer survival in Europe. This study included all malignant thyroid tumors (excluding lymphomas) in patients 15 or older. Relative survival was analyzed using population-based EUROCARE -2 data from 1985-1989. The overall 5-year relative survival rate, standardized by age (Table 3), was 67% for men and 78% for women across Europe. Substantial variation in this 5-year rate was observed between countries ranging from 56% in Slovenia to 100% in Austria (men), (Teppo & Hakulinen, 1998). Higher than average survival rates were observed in Finland, Iceland, The Netherlands and Sweden. Relative survival was higher in the younger population group. In the age group 15 - 44 years, for men the rate was at least 86% and for women at least 94 %. In contrast, much lower rates were seen in the the group of older population (75 + years). EUROCARE-3 study (Sant et al., 2003) analyzed the survival of adult cancer diagnosed from 1990 to 1994 in 22 European countries and followed them until the end of 1998. Neoplasms in situ were collected but not included in the analysis of survival. The overall relative survival of patients diagnosed with thyroid cancer in this period was 83% at 5 years. Austria, Finland, France, Iceland, Italy, Norway, Malta, Spain, Switzerland and Sweden had rates above the European average. Most of these countries also had high survival for this cancer in EUROCARE-2. Denmark, Germany, The Netherlands,

England, Scotland, Wales and the countries of Eastern Europe had survival below the European average (Table 3). Again, the most favorable outcomes were observed in patients aged 15-44 years; for the oldest patient's survival was five times lower. Part of variation in thyroid cancer survival was attributed to variations in the distribution of histological types. Other likely factors contributing to this are differences in the stage distribution and varying efficacy of treatment (Sant et al., 2003; Teppo & Hakulinen, 1998).

	EUROCARE-2		EUROCARE-3	
	female	**male**	**female**	**male**
Iceland	90	88	85	87,4
Austria	87	100	88	81
Sweden	84	74	85	80
The Netherlands	84	77	79	68,6
Finland	82	77	86	79
France	81	61	85	74
Switzerland	78	-	90	-
Spain	**78**	**70,6**	**85,7**	**82**
Italy	77	66	85	72,6
Germany	77	62	77	69,4
Estonia	76	57	77	58
England	74	64	79	71
Scotland	73	67	76	73
Denmark	72	63	80	76,6
Slovakia	71	63	76	-
Eslovenia	70	56	77	83
Poland	66	64	66	57
EUROPE	**78**	**67**	**81,4**	**71,8**

Table 3. Thyroid cancer 5-year Relative Survival (%) from 1985 to 1989 (EUROCARE-2) and from 1990 to 1994 (EUROCARE-3) in European countries.

In the U.S., the National Cancer Data Base (NCDB) represents a national electronic registry system of incident cancers. Between 1985 and 1995, NCDB captured demographic, patterns-of-care, stage, treatment, and outcome information for a sample of 53,856 thyroid carcinoma cases. The 10-year overall relative survival rates for U. S. patients with papillary, follicular, Hürthle cell, medullary, and undifferentiated/anaplastic carcinoma was 93%, 85%, 76%, 75%, and 14%, respectively (Hundahl et al., 1998). Relative survival, the survival analogue of excess mortality, is commonly used in population-based studies of cancer survival although its utility is not restricted to this area. Relative survival is the ratio of the observed survival in a group of patients to the survival probability estimated over the same period in a group of people in the general population of similar age and sex. It is usual to estimate the expected survival proportion from nationwide population life tables stratified by age, sex, calendar time, and, where applicable, race (Berkson & Gage, 1950). In order to be comparable between different populations, relative survival figures must be either age-specific or age-adjusted. A major advantage of relative survival is that information on cause of death is not required, thereby circumventing problems with the inaccuracy or no

availability of death certificates (Percy et al., 1981). However, our interest is typically in net survival rather than all-cause survival, that is, we are interested in mortality due to cancer. Cause-specific survival is commonly estimated in cancer clinical trials and only those deaths which can be attributed to the cancer in question are considered to be events, while all other deaths are considered censorings. Using cause-specific survival to estimate net survival requires that reliably coded information on cause of death is available. The distinguishing feature of survival analysis is that at the end of the follow-up period the event (such as death due to cancer) will probably not have occurred for all patients. For these patients the survival time is said to be censored, indicating that the observation period was cut off before the event occurred. For example, a person who had the cancer and died 10 years later of car accident would be censored at death, having contributed 10 person-year of survival to the analysis. A person who had the cancer and died 10 years later of the cancer would contribute an event, a death due to the cancer, having also contributed 10 person-years of survival time. A 90 % cancer specific survival at 10 years would mean that 90 % of patients had not died from their cancer, while 10 % had died from their cancer (Kaplan, 1958). Calculation of cause-specific survival is especially important when studying diseases with a favorable prognosis, as is the case at hand, where the patients live long enough to be exposed to other causes of death. The indolent course of thyroid cancer requires very large cohorts of patients followed over several decades to confirm significant differences in prognostic factors and treatment efficacy. Neither randomized clinical trials nor meta-analysis are available and evidence is based on a number of retrospective studies with multivariate for mortality risk factors or data from national cancer registries (Gilliland et al., 1997; Hundahl et al., 1998). Unfortunately, very remarkable differences in patient's selection, staging systems, and clinical management affect the available studies. In particular, radioiodine treatment is not routinely carried out in a standard manner and outcome results of different studies are thus not comparable (Sciuto et al., 2009). Since scarce data exist on the epidemiology of thyroid cancer in Spain, the main aim of this study was to analyze changes in thyroid cancer presentation, incidence, prevalence and survival in South Galicia (north-western Spain) over a 24-year period (1978–2001) and compare these results with those described in the leading international series. The people of this region are homogeneous in terms of ethnicity. This period spans the population's transition from mild iodine deficiency to iodine sufficiency after beginning iodine prophylaxis in 1985 (Garcia-Mayor et al., 1999; Rego-Iraeta et al., 2007). As a high incidence of thyroid cancer owing to improved screening procedures is generally associated with an elevated proportion of small carcinomas, we have specifically considered the impact of MPTC on thyroid cancer incidence and trends in tumour size over time as an indicator of enhanced medical procedures for thyroid cancer. We have also studied the proportion of our population undergoing thyroid surgery over the study period and the percentage of thyroid cancers found per thyroidectomy performed.

2. Materials and methods

2.1 Identification of thyroid cancer cases

Data on thyroid cancer incidence in the period from 1978 to 2001 (inclusive) were obtained from the Pathology Registry of the University Hospital of Vigo which belongs to the Spanish public health system and collects data on about 97% of the cancerous lesions verified by

microscopic examination. This ensures virtually complete ascertainment for all the new cases of thyroid cancer diagnosed in our population during the study period. Over the observation period, a total of 329 cases of thyroid cancer were registered. Seven cases (six lymphomas and one Angiosarcoma) were excluded from the study based on rarity. The remaining 322 cases of primary thyroid cancer were assigned to one of the four major diagnostic categories: papillary thyroid carcinoma; follicular thyroid carcinoma, including Hürthle carcinomas; medullary thyroid carcinoma; and anaplastic thyroid carcinoma, diagnosed according to the WHO classification (Hedinger et al., 1988). Original histology slides for all cases of follicular carcinomas (53 cases) were reviewed by two hystopathologists blinded to the original diagnosis. Nine of them were reclassified as papillary carcinomas and 44 cases were classified as true follicular carcinomas. All tumour stages were classified according to fifth edition of AJCC (Fleming et al., 1997) since most studies reported having used this classification. In the present study all papillary carcinomas of the thyroid <1 cm in diameter were classified as MPTC (Hedinger et al., 1988). All thyroid cancer cases were also characterized by sex, date of birth, and date of diagnosis. We also recorded data on number of thyroidectomies recorded in the registry which were almost exclusively performed by two senior surgeons during the study period. Near-total thyroidectomy has been used as standard treatment protocol for thyroid cancer and comprises neck dissection if confirmed lymph node involvement; one course of ablative radioiodine treatment with 100 mC, further radioiodine therapies with 100 mC if needed, with an interval of 6 months-1 year and thyrotropin-suppressive thyroid hormone therapy with levothyroxine lifetime.

2.2 Follow up the vital status of patients

Active follow-up of patients was carried-out through searches in medical records and phone contacts. A detailed review of the medical record to ascertain the cause of death was made. Mortality data were taken into account only when primary cause of death was directly related to thyroid cancer and all other deaths were considered censorings. Cause-specific 1-, 5-, 10-, 20- and 25 year survival rates were used as measures of survival.

2.3 Study population

The studied population had an average of 500,000 inhabitants. Corresponding population data by size, age, sex, and year were available from official statistics. Data during the period 1978–2001 show that Vigo's population increased by 6.3%. The male to female ratio remained stable at about 0.92. The people of the region are homogeneous in terms of ethnicity. For studies of genetic characteristics, the Spanish Galician region is considered a relatively isolated European population at the westernmost continental edge (Salas et al., 1998).

2.4 Statistical analysis

Trends in age, sex, histological type, and tumour size (differentiated thyroid carcinoma) at diagnosis were analyzed. Data on number of thyroidectomies performed were also recorded. The general descriptive analyses were performed using Microsoft Excel and SPSS

12.0 software (SPSS, Inc., Chicago, IL). Data were analyzed using the chi-square test for nonparametric data. A p value below 0.05 was considered to be statistically significant. Results were expressed as mean± standard deviation of the mean (mean±SD) for quantitative variables. Data were analyzed using the Student t test for normally distributed variables and the chi-square test for nonparametric data. Crude incidence rates, expressed per 100,000 inhabitants each year were calculated. In order to compare incidence rates between populations that differ with respect to age (since age has such a powerful influence on the risk of cancer), age standardized incidence rates were also calculated; standardization was performed using the World Standard Population (direct method) (Bray, 2002). For the whole group of thyroid cancer, the overall incidence by sex for each year from 1978 to 2001 was calculated. Due to the small sample size, which produces unstable rates for individual years, rates were calculated for several years combined (1978 to 1985, 1986 to 1993, and 1994 to 2001). Incidence trends for each of the distinct histological categories, including MPTC incidence, were also examined. The prevalence of thyroid cancer was defined as the number of persons in our defined population whom have been diagnosed of thyroid cancer, and who were still alive in three cross-sectional surveys performed in December 1985, December 1993, and December 2001. The prevalence rates have been reported per 100,000 inhabitants. A 95% confidence interval (CI) for the rates was determined to compare incidence and prevalence rates. Survival from the data of initial surgery to each endpoint, i.e. cancer specific survival, was estimated by the Kaplan–Meier product-limit method at 1, 5, 10, and 20 and, in some cases, at 25 years of diagnosis. The log-rank test was used to assess difference between subgroups. Age at diagnosis was grouped into the same five categories used by previous EUROCARE studies: 15-44, 45-54, 55-64, 65-74 and 75-99 years. We used multivariate Cox analysis to calculate those independent variables related to the survival of differentiated thyroid cancer.

3. Results

A total of 322 cases of primary differentiated thyroid cancer were diagnosed in our area between 1978 and 2001. The mean age at diagnosis was 46.6 years (range, 8–91 years). Eight patients were younger than 18 years at diagnosis. The female to male ratio was 3.6/1.

3.1 General characteristics on thyroid cancer

3.1.1 Histological distribution

Out of 322 cases of primary thyroid cancer, papillary was the predominant tumour type with 245 cases (76%), followed by follicular with 44 cases (13.7%), medullary with 23 cases (7.1%), and anaplastic with 10 cases (3.1%), (Table 1). The papillary to follicular ratio in the entire period was as high as 5.8; when MPTC cases were excluded, this ratio was 2.

3.1.2 Age and sex distribution

The youngest age at presentation corresponded to medullary and papillary cancers of the thyroid. Anaplastic cancer and Hürthle cells occurred at older ages. Of the total of thyroid cancers, 78.3% of the cases were females and 21.7% outstanding men. This female predominance is maintained in all histologic types (Table 4).

3.1.3 Pathologic Tumor-Node-Metastases (pTNM) distribution

Altogether, 73% of the primary tumours presented with T1 to T3 tumor size; 15 % were locally invasive to extrathyroidal soft tissues (T4), 22% had metastatic involvement of cervical lymph nodes and 4.7% had distant metastases. Of 11.8% of cases the tumor size was unknown. Among all tumors, medullary and papillary carcinomas were the most commonly presented with cervical lymphadenopathy while follicular carcinoma the most often presented distant metastasis (Table 4). In our series, we identified 95 MPTC out of a total of 245 papillary thyroid cancers (38.7%). Of these, 87 cases (91%) were incidentally diagnosed in thyroidectomies performed for thyroid pathologies other than thyroid cancer.

	Papillary	Follicular	Hürthle	Medullary	Anaplastic	Total
Nº cases (%)	245 (76%)	32 (10%)	12 (3.7%)	23 (7.1%)	10 (3.1 %)	322
Mean age (range)	44 (8-91)	50 (23-78)	61 (33-91)	43.8 (19-78)	71 (52-89)	46.6 (8-91)
Female/Male	4	3.5	5	2.28	1.5	3.6
T_1-T_3	80 %	56 %	78 %	52 %	0 %	73 %
T_4	10.6 %	22 %	8 %	17.4 %	100 %	15 %
N_1	23 %	12.5 %	8 %	39 %	20 %	22 %
M_1	2.4 %	19 %	0 %	13 %	0 %	4.7 %

Table 4. Thyroid cancer characteristics at diagnosis (1978-2001).

3.1.4 Distribution of pTNM stages of thyroid cancer at diagnosis (1978-2001)

Most of thyroid cancer patients (75 %) presented low pathological tumor-node,-metastases (stages I and II). Most papillary cancers presented with either stage I (63 %) or stage II (18 %). Stage III accounted for fewer than 12 % of cases. Few (1.2 %) patients presented with distant metastases and had stage IV disease. For follicular and Hürthle cancers these figures were 37, 28, 15, 6% and 25, 58, 8 and 0 % respectively. Most patients with medullary thyroid cancer (43.5 %) had stage II; patients with stage I accounted for only 4 %; and stages III and IV, 26 % and 13 % respectively. Figure 1, illustrates the distribution of pTNM stage and histologic subgroup of thyroid cancer patients.

3.1.5 Trends in thyroid cancer presentation: Tumour size

Table 1 shows no significant change over time for sex distribution and age between the three time periods (1978–1985, 1986–1993, and 1994–2001). The proportion of MPTC among total papillary thyroid cancers cases increased significantly over time: 16.7% (1978 to 1985), 23% (1986 to 1993), and 43% (1994 to 2001). The papillary to follicular ratio significantly increased over time from 2.3 to 3.6 and 11.5. When MPTC was excluded, the papillary to follicular ratios were 1.9, 2.7, and 6.6, respectively. Besides MPTC cases, no significant variations were observed with respect to tumour size (pT) at presentation, in papillary and follicular over time. For some patients there was no precise pathological description about tumour size (pTx), (Table 5).

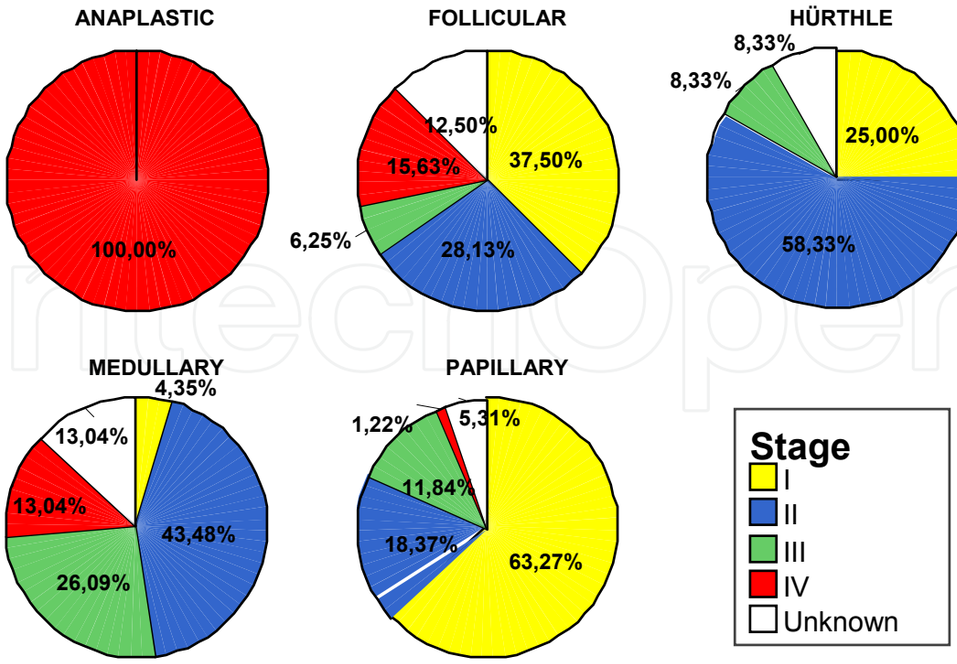


Fig. 1. Thyroid cancer pTNM stages and histologic distribution at diagnosis (1978-2001).

		1º Period 1978-1985	2ºPeriod 1986-1993	3ºPeriod 1994-2001	p
Female/Male		4.3	3.6	3.4	0.854
Mean age ± DT (years)		42.2±16.5	46.8±17.2	47.6±16.7	0.601(1º vs 3º)
Papillary/Follicular		2.3	3.6	11.5	0.000*
Papillary (no-MPTC)/Follicular		1.9	2.7	6.6	0.013*
(%) MPTC/ Total Papillary		16.7 %	23 %	43 %	0.010*
Papillary (no- MPTC)	$T_{2\ (n=81)}$	47.8 %	45.8 %	60 %	0.360
	$T_{3(n=20)}$	8.7 %	20.8 %	10 %	
	$T_{4(n=27)}$	17.4 %	18.8 %	17.5 %	
	$T_{x\ (n=22)}$	26.1 %	14.6 %	12.5 %	
Follicular	$T_{1\ (n=4)}$	7.7 %	16.7 %	0 %	0.213
	$T_{2\ (n=20)}$	38.5%	38.9%	61.5 %	
	$T_{3\ (n=4)}$	0 %	11.1 %	15.4 %	
	$T_{4\ (n=8)}$	15.4 %	16.7 %	23.1 %	
	$T_{x\ (n=8)}$	38.5 %	16.7 %	0 %	

Table 5. Time trend of thyroid cancer presentation (1978-2001).

3.2 Trends in thyroid surgery

A total of 2345 thyroidectomies were performed during the studied period. During this period the percentage of the population undergoing a thyroid surgery significantly increased from 13.76 per 100,000 each year (95% CI 12.35–14.56) to 23.83 (95% CI 22.17–

24.73) and 45.01 (95% CI 42.45–46.39) in 1978–1985, 1986–1993, and 1994–2001, respectively. The proportion of thyroid carcinomas among operated patients rose from 9.92% in 1978–1985 to 12.31% in 1986–1993 and to 15.35% in 1994–2001, respectively ($p < 0.015$). Total thyroidectomy accounted for 48% of initial surgical procedures (1978–1985) and 74% during 1994–2001.

3.3 Trends in thyroid cancer incidence

As shown in Fig. 2 and Table 6, incidence rates were considerably lower for males than for females. Overall crude incidence of thyroid cancer in women increased significantly from 1.61 per 100,000 each year (1978 to 1985) to 4.43 (1986 to 1993) and 10.29 (1994 to 2001). These figures in men were 0.35, 1.31, and 3.24, respectively. Age-standardized incidence rates (ASR) over this period show the same tendency, with a significant increase in females: 1.56 per 100,000 each year (1978 to 1985) to 3.83 (1986 to 1993) and 8.23 (1994 to 2001); and males: 0.33, 1.19, and 2.65, respectively (Table 6).

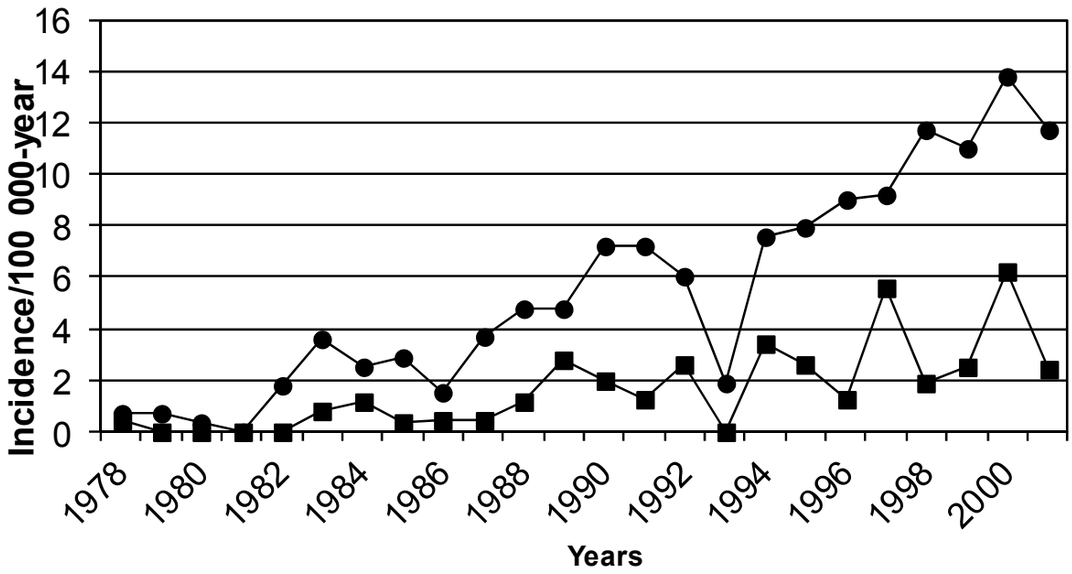


Fig. 2. Annual crude incidence of thyroid cancer, by sex (1978-2001); females (circles) and males (squares).

	Females			Males		
Period (years)	Crude Incidence	ASR *	IC (95 %)	Crude Incidence	ASR *	IC (95 %)
1978-1985	1.61	1.56	1.03-2.08	0.35	0.33	0.08-0.58
1986-1993	4.43	3.83	2.93-4.71	1.31	1.19	0.67-1.70
1994-2001	10.29	8.23	6.82-9.63	3.24	.65	1.82-3.46

Table 6. Time trend of crude and age-standardized incidence rates of thyroid cancer, by sex. (*) Age-standardized incidence rate (ASR).

3.3.1 Trends in thyroid cancer incidence by histopathology: Incidence of MPTC

Figure 3 displays the overall (males and females) crude incidence rates of thyroid cancer in relation to the histological types; the increase in the incidence of thyroid cancer over the three periods of time was primarily due to an increase in papillary cancer incidence. After the second period, the incidence of follicular cancer decreased and there was no significant change in the incidence of MTC and anaplastic cancer. Table 7 shows that the increase in the incidence of PTC was the result of an increased incidence of both MPTC and papillary measuring more than 1 cm (Papillary non-MPTC). This occurred both in males and females.

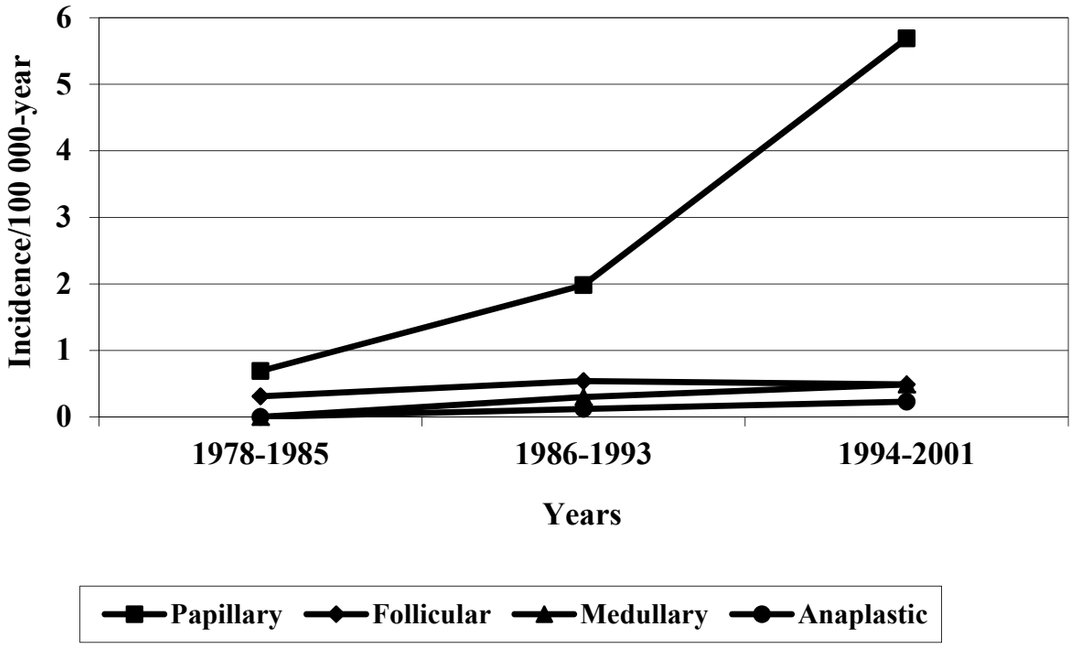


Fig. 3. Time trend of crude incidence rates of thyroid cancer, by histology.

	Females				Males			
Period	Papillary No-MPTC Incidence	CI (95%)	MPTC Incidence	CI (95%)	Papillary No-MPTC Incidence	CI (95%)	MPTC Incidence	CI (95%)
1978-1985	0.97	0.55-1.38	0.14	-0.02-0.29	0.15	-0.02-0.32	0.10	-0.04-0.24
1986-1993	2.19	1.49-2.88	0.81	0.38-1.23	0.75	0.32-1.17	0.12	-0.05-0.30
1994-2001	4.82	3.65-5.98	3.94	2.89-4.99	1.58	0.89-2.27	0.79	0.30-1.28

Table 7. Time trend of papillary thyroid cancer crude incidence rates, by sex
(CI: Confidence Interval)

3.4 Trends in thyroid cancer prevalence

Table 8 shows that prevalence of thyroid cancer increased substantially between 1985 and 2001 in both sexes. Thyroid cancer was significantly more prevalent in female than in male subjects.

Year	Sex	Prevalence	CI (95%)
1985	Female	**12.53**	8.38-16.68
1993	Female	**65.89**	53.23-78.56
2001	Female	**128.34**	111.75-144.92
1985	Male	**2.72**	0.70-4.73
1993	Male	**17.85**	10.99-24.71
2001	Male	**35.66**	26.56-44.77

Table 8. Time trend of thyroid cancer prevalence, by sex.

3.5 Thyroid cancer survival

We followed a total of 321 cases of thyroid cancer. The median follow-up was 7.7 years, ranging between 4 and 27.8 years. We recorded a total of 43 deaths, of which 30 (70%) were directly related to thyroid cancer, yielding a cancer- specific mortality rate of 9. 3 % for the whole cohort. Over 4 %(4.3) of cancer -specific deaths was represented by patients with differentiated thyroid carcinomas. Among the remaining 13 deaths not attributable to thyroid cancer, 9 (69%) were due to second malignancies (three breast cancer case, 1 prostate cancer case, 1 case of sigmoid colon cancer, 1 case of liver cancer, 1 case of glioblastoma multiform, 1 case of pancreatic cancer , 1 case of multiple myeloma) and 4 (31%) were attributed to other causes. Overall survival of patients diagnosed with thyroid cancer in the period 1978-2001 was 88 % at 25 years, being 90 % for women and 80% for men; although survival was higher in women, there were no significant differences between both genders (p = 0, 097), (Table 9). When excluding MPTC, we observed a decrease in thyroid cancer survival. Thus, the overall survival of thyroid cancer was 84% at 25 years, being 87% in women and 76% in men, again without significant differences between genders (p = 0.15), (Table 10).

Gender	Patients	Survival				
		1 year	5 years	10 years	20 years	25 years
Female	251	97%	93%	91%	90%	90%
Male	75	95%	91%	84%	80%	80%
Total	321	96%	93%	89%	88%	88%

Table 9. Overall cause-specific survival of thyroid cancer (1978-2001).

Gender	Patients	Survival				
		1 year	5 years	10 years	20 years	25 years
Female	180	96%	91%	89%	87%	87%
Male	56	94%	89%	81%	76%	76%
Total	236	95%	90%	86%	84%	84%

Table 10. Overall cause-specific survival of thyroid cancer (1978-2001), excluding MPTC.

3.5.1 Cause –specific survival according to age

Table 11 and Figure 4, reflect the cause-specific survival by age group (excluding MPTC) and emphasizes the influence of age on the prognosis of patients with thyroid carcinoma. As can be seen there is one more striking decline in survival after 55 years of age.

Age	Patients	Survival				
		1 year	5 years	10 years	20 years	25 years
ago-44	117	100%	98%	96%	94%	94%
45-54	45	97%	95%	95%	95%	95%
55-64	34	90%	84%	74%	63%	-
65-74	22	86%	77%	69%	57%,18 years	-
75-91	18	83%	59%	47%	47%,18 years	-

Table 11. Cause-specific survival of thyroid cancer by age group, excluding MPTC (1978-2001).

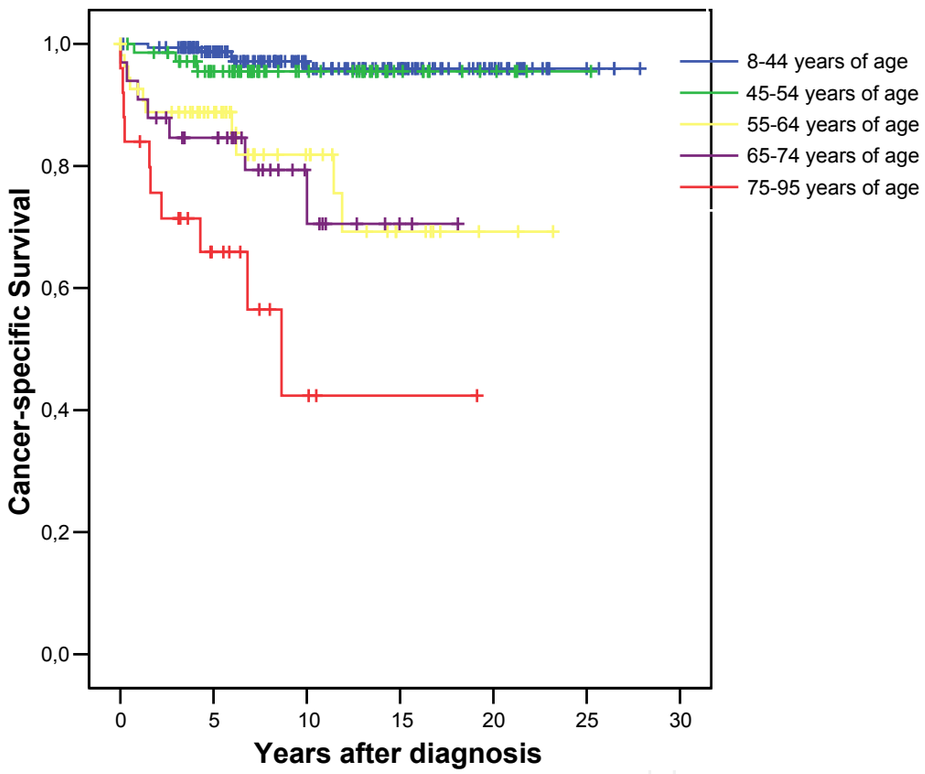


Fig. 4. Cause-specific survival of thyroid cancer by age group, excluding MPTC (1978-2001).

3.5.2 Cause -specific survival according to histological type

As known, histologic type is a strong determinant of thyroid cancer survival. In our series, papillary thyroid cancer patients had 25-year specific-survival greater than 93 %, even when excluding MPTC. The survival of MPTC was 100% at 25 years in the present study. Follicular and medullary carcinoma patients had lower survivals (83% at 25 years and %at 20 years, respectively). However, the prognosis was is ominous for anaplastic thyroid carcinoma (Table 12 and Figure 5).

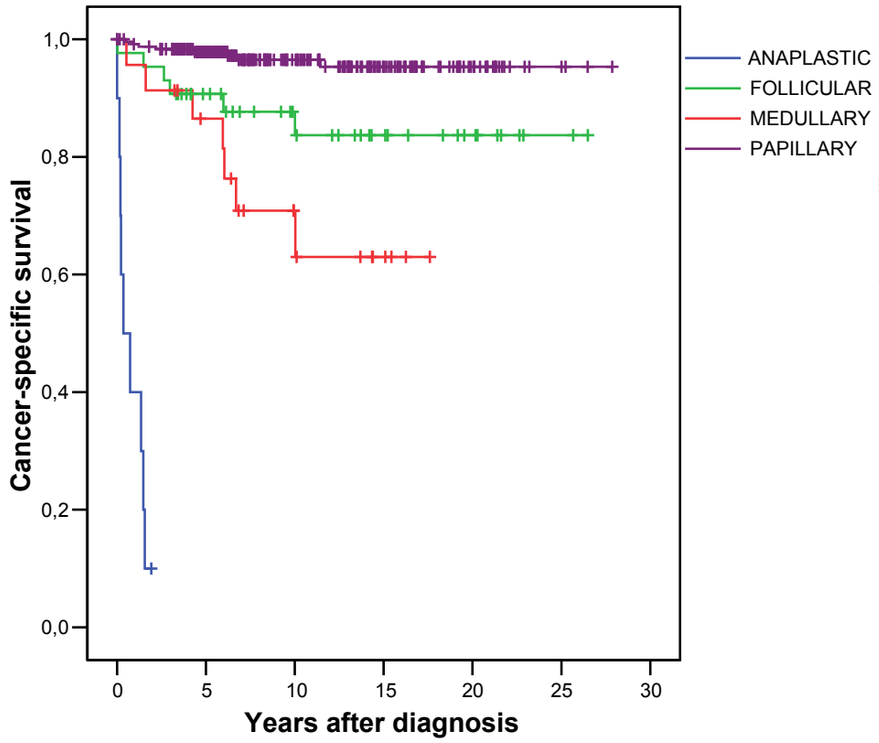


Fig. 5. Cause–specific survival of thyroid cancer according to histological type (1978-2001).

Histologic type	Patients	Survival				
		1 year	5 years	10 years	20 years	25 years
Papillary (total)	245	99%	97%	96%	95%	95%
Papilar (no MPTC)	160	98%	96%	95%	93%	93%
Follicular (including Hürthle)	43	97%	90%	87%	83%	83%
Medullary	23	95%	86%	70%	63%	-
Anaplastic	10	40%	10%	-	-	-

Table 12. Cause-specific survival of thyroid cancer according to histological type (1978-2001).

3.5.3 Cause –specific survival according to p TNM stage distribution

Stage at diagnosis is a strong prognostic factor for thyroid cancer survival. Thus, cause specific-survival vas 100% at 25 years of follow- up in stage I. At more advanced stages survival decreases progressively (Table 13).

Stage	Patients	Survival				
		1 year	5 years	10 years	20 years	25 years
I	171	100%	100%	100%	100%	100%
II	71	100%	100%	97%	94%	-
III	38	97%	88%	69%	69%	69%
IV	21	37%	15%	15%	0%	-
Unknown	20	100%	100%	94%	94%	94%

Table 13. Cause-specific survival of thyroid cancer by pTNM stage (1978-2001).

3.5.4 Prognostic analysis in differentiated thyroid carcinoma

Risk factors associated with differentiated thyroid cancer mortality were identified by Cox regression analysis. Univariate and multivariate analysis results for thyroid cancer mortality are illustrated in Table 14. In the univariate analysis, the following factors were significantly associated with mortality for differentiated thyroid cancer: age, follicular histology, local tumor extension and distant metastases at presentation. Neither sex nor the presence of lymph node metastases contributed to mortality risk. Multivariate analysis confirmed as independent predictor variables of increased risk of cancer mortality-only age and presence of distant metastases.

Variables	**Variables**	**Univariate Analysis** RR (CI 95 %)	**Multivariate Analysis.** RR (CI 95 %)
Sex	Female	1	
	Male	1,5 (0,48-4,95)	
	8 – 44	1	
	45 – 54	2,3 (0,14-36,7)	3,17 (0,2-51,6)
Age (years)	55 – 64	20,7 (2,42-178)	17,8 (2,12-150)
	65 – 74	30,5 (3,4-274)	15,6 (1,6-147)
	> 75	38,5 (3,90-377)	38,5 (3,30-338)
Histology	Papillary	1	
	Follicular	4,07 (1,41-11,76)	
	T1	1	
Tumoral size	T2	2,75 (0,26-24,5)	
	T3	3,33 (0,20-53,5)	
	T4	24,80 (3,1-198)	
Regional extension	N0	1	
	N1	2,5 (0,78-8,40)	
Distance extension.	M0	1	
	M1	29,9 (10,4-85)	17,68 (6,11-51,1)

Table 14. Univariate and Multivariate survival analysis of prognostic factors of differentiated thyroid cancer (1978-2001).

4. Discussion

The main objective of epidemiological studies is to measure the frequency of disease. Prevalence measures are particularly useful in the healthcare planning. Furthermore, incidence reflects the "flow" from health to illness in populations and therefore constitutes the basis of causative research. On the other hand, survival measures are an indicator of the global efficiency of healthcare services. These questions are also fundamentally important in thyroid cancer, since an understanding of the basic causes and related risk factors may lead to novel interventions and preventive measures. The reason why we carried out this work was the paucity of data on the major epidemiological features of thyroid cancer in our country (Spain) and particularly in our region (Galicia). In this study we conducted an epidemiologic survey in our community, to evaluate time trends in presentation, incidence, prevalence and survival of thyroid cancer between January 1978 and December 2001; a period that spans our community transition from mild iodine deficiency to iodine sufficiency after beginning iodine prophylaxis (iodized salt) in 1985. Several factors could have an impact on the epidemiology of thyroid cancer in our area. On the one hand, the eradication of iodine deficiency in our population in the last decades (Garcia-Mayor et al., 1999; Rego-Iraeta et al., 2007; Rodriguez I et al., 2002), on the other hand, the progressive increase in the use of diagnostic techniques and the preference for carrying out near-total thyroidectomy since the nineties, (compared to the "lumpectomy" or hemithyroidectomy) which is known to increase the likelihood of detecting microscopic carcinomas incidentally, mainly papillary lineage. In Galicia, like in the rest of Spain, 97% of the population receives health care through the public health system, with other kinds of medical care being negligible (Etxabe & Vazquez, 1994). This ensures virtually complete case ascertainment for diagnosed thyroid cancer in the population. Given that practically the whole population of Galicia is registered with the social security system, our study is representative of the Galician population (North-western Spain).

The general characteristics of our patients with thyroid cancer such as the mean age at diagnosis (46.6 years old) and the predominance of females to males (3.6/1) were similar to those reported in other studies around the world (Blanco Carrera et al., 2005; Gilliland et al., 1997; Sant et al. 2003; Scheiden et al., 2006**;** Sciuto et al., 2009). Agree with this, the youngest age at presentation corresponded to medullary and papillary thyroid carcinomas, followed by follicular carcinoma, Hürthle cell cancer and finally by the anaplastic carcinoma. The histological distribution of thyroid cancer in the present series was similar to that reported in iodine-sufficient areas, with a higher proportion of papillary thyroid cancer (76% over overall thyroid carcinomas). It represents the same pattern that was reported in the USA (Hundahl et al., 1998; Scheiden et al., 2006; Schlumberger et al., 2008) and some European countries **(**Blanco Carrera et al., 2005; Farahati et al., 2004; Sant et al. 2003; Scheiden et al., 2006**)**. Likewise, in our series the ratio papillary/follicular was high, which is the predominant pattern reported in the Western world (Sant et al., 2003; Teppo & Hakulinen, 1998). This happened even in the first period of our study when there was a mild iodine deficiency in our population (median iodine of 60µg/l) (Garcia-Mayor et al., 1999). This ratio increased over time, even when MPTC were excluded from the calculation. We speculate that the amelioration of iodine nutrition, which happened in our population over the last decades (Garcia-Mayor et al., 1999; Rego-Iraeta et al., 2007), may explain this finding to some degree. However, an increase in the incidence of papillary thyroid cancer has also

been reported in Luxemburg, considered an iodine deficient area (Sant et al., 2003), and in Tasmania (Australia), in spite of the recurrence of mild iodine deficiency (Burgess et al., 2000). This phenomenon may be related with a dose-threshold effect for iodine nutrition and modulation of tumour genesis (Burgess et al., 2000), or alternatively, environmental factors other than iodine nutrition may be contributing.

In our study, most of patients (75 %) had low pathological p-TNM stages (stages I and II) at presentation. These results are similar to those described in a cohort of more than 2700 patients with thyroid cancer at the Mayo Clinic of Rochester who underwent thyroidectomy from 1940 to 1997 (Schlumberger et al., 2008). Among papillary carcinoma cases, this series reported extrathyroidal invasion in 15 % (range 5 to 34%), and clinically evident lymphadenopathy at presentation in about one third of cases. Only 1 to 7% of papillary carcinomas had metastases at diagnosis. However, it is noteworthy that about 35 to 50 % of removed neck nodes have histologic evidence of involvement (Schlumberger et al., 2008), so that our low rate of lymph node involvement may reflect the fact that node dissection is not performed routinely in our environment. Regional lymph node metastases from follicular carcinomas are uncommon (4 to 6% of patients). Indeed, wherever they are observed, other alternative diagnoses, should be considered. Around 5 to 20% of these tumors have distant metastases at presentation (Schlumberger et al., 2008). In our series, 12.5% of follicular carcinomas and 8% of Hürthle cell carcinomas had lymph nodes at diagnosis. In accordance with previous observations, we found distant metastases in 19% of follicular carcinomas, although we found no distant metastases in the group of the Hürthle cell carcinomas. In relation to staging at presentation, we compared our results with the case material of the Mayo Clinic, between 1940 and 1997.

The distribution of pathological stages I, II, III and IV for papillary carcinoma at the Mayo Clinic was respectively 60, 22, 17 and 1%, very similar to the corresponding in our study, which was 63, 18, 12 and 1.2% for the same stages. With regard to follicular carcinomas, the Mayo Clinic study found that the distribution of stages I, II, III and IV was 22, 53, 4 and 17% for follicular carcinoma and 17, 69, 9 and 5% for the Hürthle cell carcinoma. Curiously, stage I was more frequent among our follicular carcinomas (the distribution of stages I, II, III and IV for follicular carcinoma was 37, 28, 6.2 and 15.6% and for Hürthle carcinoma 25, 58, 8 and 0%; respectively). With reference to medullary carcinoma, the Mayo Clinic cohort data revealed a predominance of stage I (stage I, II, III and IV; 57, 19, 22 and 2% respectively), while in our study only 4.3 % of patients presented with stage I. This is probably due to earlier introduction of RET proto-oncogene testing at the Mayo Clinic.

Thyroid cancer has increased dramatically in most countries in the last 30 years (Kilfoy et al., 2009), excluding countries such as Iceland, Sweden and Norway (Engholm et al., 2009). In the present study, the incidence of thyroid cancer is increasing over time. When comparing incidence rates among different populations there are two points to bear in mind; first, since a rapid increase in thyroid cancer incidence is seen, it is important to consider the period of time the rate refers to, and secondly due to the differences in the age distribution among different populations, it is necessary to display an age-standardized rate of incidence (ASR). Most of the series, report ASR referred to world population. In the present investigation, both crude incidences and ASR show an increasing trend over time. In comparison with other European countries, our ASR in the final period of time, 1994-2001, (8.2 per 100,000-year in women and 2.65 in men) is similar to the reports from our

neighbouring countries such as Portugal, France and Italy and is higher than that reported by the IARC for Spain (period 1997- 1999) (Ferlay et al., 2004). A previous study in our community (Garcia-Mayor et al., 1997), reported a decrease in the number of patients requiring surgical treatment with an increase in the frequency of malignancy in the surgical specimens after the introduction of FNAB in the management of nodular thyroid disease in 1991. However, when we studied the total number of thyroid surgeries performed in our population, we found that the rate of population undergoing thyroid surgery significatively increased over time with an increase in the ratio of total thyroidectomy for other kind of thyroidectomy. Undeniable, this trend makes it easier to detect MPTC. In fact, 43 % of our operated cancers were MPTCs in the latter period studied versus a 16.7 % in the first period. A similar trend has been reported in France where there was an increase in thyroid cancer incidence, mainly due to the papillary type, with an epidemic of microcarcinomas (43% of operated cancers, for the period 1998–2001) (Leenhardt et al., 2004a). This trend has been reported in many other studies (Chow et al., 2003; Colonna et al., 2007; Scheiden et al., 2006; Verkooijen et al., 2003). The improvement in diagnostic tools (image procedures and fine-needle aspiration biopsy) (Colonna et al., 2007; Scheiden et al., 2006) and greater extensiveness and number of thyroidectomies performed, which makes it easier to detect MPTCs (Leenhardt et al., 2004a), has been suspected to be of etiological importance in the observed increase of papillary thyroid cancer. One study (Kovacs et al., 2005) estimated the prevalence of thyroid microcarcinomas found at autopsies is 100–1000 times higher than in clinical cancer; they were not related to iodine intake and were exclusively of the papillary type (MPTC). It suggests that a large proportion of the population probably lives with undetected thyroid cancer and fits with the hypothesis of an apparent increase in thyroid cancer incidence. Any interpretation of reports of the incidence of papillary thyroid carcinoma must take into account the remarkably high prevalence of MPTC in thyroids removed for reasons other than thyroid cancer and in autopsy series (Hedinger & Sobin 1988). In this sense, it is noteworthy, that many cancer registries do not specify the contribution of MPTC to the incidence of thyroid cancer, so differences in the inclusion criteria can cause mistakes in the comparison of the incidences (Teppo & Hakulinen 1998). For these reasons we have separately analyzed the incidence of MPTC and the incidence of papillary cancer not including MPTC (Papillary non MPTC). In the present investigation, we found 245 cases of papillary cancer, of which 95 cases (38.7 %) were MPTC carcinomas (pT1). Remarkably, most of these tumours (91%) were detected incidentally after thyroid surgery performed for reasons other than thyroid cancer. Although the incidence of MPTC is increasing in our population, also an increase in the incidence of tumours greater than 1 cm (Papillary non MPTC) was evident in both sexes. Similar findings have been reported in studies performed by Burgess in Australia (Burgess, 2002; Burgess & Tucker 2006). We also observed an increase in the ratio of total thyroidectomy for other kind of thyroidectomy over time. A recent study performed by Mitchell et al. in USA (Mitchell et al., 2007), examined trends in surgical therapy for thyroid cancer. They hypothesized that if a true increase occurs in the incidence of thyroid cancer, then thyroidectomy, as the primary treatment for thyroid cancer, should also increase during the same period. This study reported a regional difference in the incidence of thyroid cancer with an increase in North-eastern and Southern and an actual decrease in the Midwest United States. Newly papillary thyroid cancer accounted for most of this increase. Furthermore, thyroidectomy, in these

areas seemed to mirror their respective regional changes in incidence. Supporting the hypotheses of recent changes in medical practice as the cause of the increase in thyroid cancer incidence, some authors (Davies & Welch, 2006; Kent et al., 2007) found a shift in the tumour size distribution of thyroid cancer toward smaller papillary cancers in recent years, suggesting an apparent (not real) increase in thyroid cancer incidence due to increased detection of subclinical tumours. However, besides MPTC, we did not observe a significant change in tumour size over time in differentiated thyroid carcinomas at presentation with a percentage of pT_2, pT_3 and pT_4 lesions which remain stable over time. Moreover, there are three questions to be in mind; firstly, the increase in thyroid cancer incidence in our area has happened equally in the incidence of MPTC and in the incidence of PTC greater than 1 cm.; secondly, there has not been a shift over time in thyroid cancer tumour size, besides MPTC, and thirdly, there is no similar increase in the incidence of other histological types of thyroid cancer (Rego-Iraeta et al., 2009). Interestingly, Kent and colleagues (Kent et al., 2007) found that the incidence of medium-sized tumours (2-4 cm) remained stable over time, but were surprised to discover a slight increase in large tumours (larger than 4 cm). Several others papers from U.S. support the notion that the increase in incidence is not entirely due to increased screening and detection. Thus, Enewold and colleagues found, among white women, the rate of increase for cancers larger than 5 cm. almost equaled that for the smallest papillary cancers. Chen et al. similarly reported an increase in differentiated thyroid cancer of all sizes with the most rapid increase occurring in females. Cramer et al. showed an increase in the incidence of papillary thyroid cancers with a significant increase in all size categories. A report by Morris & Myssiorek drew similar conclusions based on data demonstrating significant rises in the incidence of large (>4 cm), and well-differentiated cancers with clinically significant pathological adverse features (Chen et al., 2009; Cramer et al., 2010; Enewold et al., 2009; Hodgson et al., 2004; Morris & Myssiorek, 2004). Improved detection has undoubtedly occurred and may explain much of the increase in small well-differentiated cancers. However, the most important evidence that increased diagnostic activity is not the sole cause for this increase is that large and more advanced cancers are increasing as well as small tumours. This trend suggest than some environmental factor, besides increased diagnostic activity, may be contributing to the increase in thyroid cancer incidence. Thyroid cancer can be induced in experimental animals directly by mutagenic carcinogens and indirectly through hormone imbalance.

The only well established risk factor for thyroid cancer in humans is ionizing radiation. Sex hormones, iodine deficiency and other factors (nutritional, volcanoes) have been proposed as risk factors for thyroid cancer, but the findings are inconsistent (Nagataki & Nystrom, 2002). The increase in thyroid cancer risk could be attributed to ionizing radiation exposure. Studies of individuals living in the Chernobyl areas have shown an increased risk among those exposed as children (Cardis et al., 2006). In our study, only 8 cases of thyroid cancer in people of 18 years of age or less could be identified, so ionizing radiation exposure cannot explain the recent increase in incidence of thyroid cancer in our community. However, a longer latency period for low doses of radiation could not be ruled out (Yamashita, 2006). Some authors have suggested that iatrogenic exposure to radiation during imaging by computed tomography, especially in children when radiation sensitivity of the thyroid gland is greater, could contribute to the increase in thyroid cancer (Baker & Bhatti, 2006); however this link remains unproven at the moment. Nutritional factors such as a low fruit

and vegetable and selenium consumption have been linked to thyroid cancer and cancer in general (Clark et al., 1996; Franceschi et al, 1990; Rayman, 2000). The role of Brassica vegetable in cancer protection (Keck & Finley, 2004; Verhoeven et al., 1996) has also been reported. Remarkably, our soils are acidic with low selenium content and the consumption of these Brassica vegetables (cabbage), traditional in our community of the North-West of Spain, has decreased over the last decades due to the globalization of our diet and loss of the popularity of these foods because of their goitrogenous potential.

Contrary to what happened with reports on the incidence of thyroid cancer, reports on prevalence are scarce. In the USA, the prevalence estimate for thyroid cancer was 310,000 in 2001 (Sherman & Fagin 2005), averaging about 105 cases per 100,000 population. In our study, we observed an increase in the prevalence of thyroid cancer from 8 cases per 100,000 population in 1985 to 83 cases in 2001. The prevalence varied for both sexes, with the figure being greater in women (128 cases per 100,000 in 2001). The increase in thyroid cancer incidence seen in our area together with the good prognosis of this neoplasia can explain the increase in the prevalence of thyroid cancer. These data should be taken into account when planning health resources for the management of these patients.

In the present study, we also performed an analysis of cause–specific survival in our patients diagnosed of thyroid cancer between 1978-2001. In the case of deceased patients, we investigated the exact cause of death by reviewing the medical records to carry out the calculation of cause-specific survival. Throughout the follow-up period, we recorded in our series a total of 43 deaths, of which 70% were directly related to thyroid cancer. Among the remaining deaths not attributable to thyroid cancer, 69% were due to second malignancies. A high percentage of secondary neoplasms as the cause of death in thyroid cancer patients is also reflected in other series, for example, a Norwegian and a Dutch study found a 38% and 58% of deaths, respectively, attributable to other malignancies (Akslen et al., 1991; Eustatia-Rutten et al., 2006). In Europe we have data on thyroid cancer survival from the EUROCARE database. As the first publication on cancer survival in Europe, EUROCARE-1 (1978-1985) (Berrino et al., 1995) did not involved thyroid cancer, EUROCARE-2 (1985-1989) (Teppo et al., 1998) was the first publication on thyroid cancer survival. We also have more recent data from the EUROCARE-3 (1990-1994) (Sant et al., 2003). Both studies were population-based and used relative survival, i.e. an estimate of excess mortality. Five-year relative survival collected for Spain in the EUROCARE-3 (85.7% women and 82% in men) places it slightly above the European average (81.4% females and 71.8% in men). In our study, we observed an overall thyroid cancer cause-specific survival after excluding MPTC (91% in women, 89% in men) that is better than those previously reported over European countries as was reflected in the EUROCARE 2 and 3. As expected, we observed that survival decreases gradually with age in our study. We found a 5-year survival of 65% in the group older than 75 years (59% when excluding the MPTC). With regard to the histologic distribution, cause-specific survival at 25 years in our series is 95% for papillary thyroid carcinoma (93% if we exclude MPTC) and 83% for follicular carcinoma (including Hürthle cell). In the case of medullary carcinoma, the 20-year survival rate was 63%. As expected, anaplastic carcinoma was an ominous prognosis with a 5-year survival rate of 10%. We can compare these results with those of the cohort of patients with thyroid cancer at the Mayo Clinic (Schlumberger et al., 2008), where the cause-specific survival at 25 years for papillary thyroid carcinoma was 95%, wich was significantly higher than the rates found

for medullary, Hürthle and follicular thyroid carcinoma, wich were 79, 71 and 66%, respectively. Curiously, patients with medullary thyroid carcinoma at the Mayo Clinic have similar or better outcomes than those patients with non papillary follicular thyroid carcinoma; as more patients have been diagnosed by genetic testing, most of them have curable disease and better survival. With regard to survival by histologic type, we found very similar results to those published in the U.S. series (Hundahl et al., 1998) where 10-year overall relative survival rates for patients with papillary, follicular, Hürthle cell, medullary, and undifferentiated/anaplastic carcinoma were 93, 85, 76, 75 and 14%, respectively (Hundahl et al., 1998). In our series, 10-year cause-specific survival for papillary thyroid carcinoma was 96% (95% if we exclude the MPTC, 87% for follicular carcinoma (including Hürthle cell), 70 % for medullary carcinoma and 0% for anaplastic carcinoma. A similar distribution of histologic types and pTNM stages may be one explanation for these similar results. With regard to staging, as expected, we found a survival of 100% at 25 years for tumors which were presented in stage I. Accordingly; we did not record any deaths due to thyroid cancer in our 95 cases of MPTC. Survival gradually worsened with more advanced staging at presentation, being only 15% at 10 years for stage IV tumors. In our study, the stage of tumors at presentation was generally favorable, which may have contributed positively to overall survival. Despite being a relatively benign disease, a continual decline in cancer-specific survival is noted in all tumor stages at successive follow-up intervals. This underscores the need of life-long surveillance for thyroid cancer patients.

Another objective of this study was to describe the prognostic factors associated with thyroid cancer survival. Because these variables are often strongly interrelated, we have identified risk factors associated with mortality from differentiated thyroid cancer using the Cox regression analysis. This was determined only in the group of differentiated thyroid carcinomas, as the rest of the tumors represent a little large in total thyroid cancers and they have a different clinical behavior. Age, follicular histotype, local tumor extension as well as distant metastases were found to have a significant negative influence on survival in the univariate analysis. However, in the multivariate analysis, only age and distant metastases were found to retain their independent prognostic values. Multiple studies have identified several prognostic factors, but overall the findings have been inconsistent, possibly due to bias introduced by the use of different institutional series with different distributions of histologic types and differences in follow-up and histologic classification of disease. Therefore, we do not know the relative importance of each of these features as prognostic factors and whether the findings in one population can be generalized to other populations (Gilliland et al., 1997). Although the majority of studies reported the effect of age on the prognosis of patients with differentiated thyroid carcinoma, data from some studies (Elisei et al. 2010; Gilliland et al., 1997**;** Hundahl et al., 1998; Sciuto et al. 2009) also suggest an effect on other thyroid histologies as well. The association between age and survival is not explained by differences in stage at diagnosis, differentiation, socio-demographic variables, or treatment. It has been speculated that other age-dependent factors such as nutritional or immune status, or differences in the spectrum of genetic alterations in tumors in the elderly, may play a role in survival (Gilliland et al., 1997**).** In this sense, several studies have found that survival does not differ for patients of similar ages and stages diagnosed with papillary or follicular carcinoma (Thoresen et al. 1989; Torres et al., 1985). Children and people younger than 20 years tend to present with higher stage disease and greater likelihood of

locoregional and distant metastases, despite it, children generally have excellent survival rates, the exception to this rule is the disease in children aged < 10 years (Sipos & Mazzaferri, 2010). In the same line as most of the studies (Beenken et al., 2000; Eichhorn et al., 2003; Gilliland et al., 1997; Lerch et al., 1997; Mazzaferri, 1999; Shah et al., 1992), we found that the presence of distant metastases at presentation is an independent risk factor in the prognosis of differentiated thyroid carcinoma. The main cause of death from differentiated thyroid cancer is distant metastases (Mazzaferri, 1993). Mortality is high with distant disease, with 50 % survival at 3.5 years according to one recent study (Sampson et al., 2007). However, survival is improved in younger patients (Sampson et al., 2007), patients with microscopic rather than macroscopic disease (Durante et al. 2006), and patients with iodine-avid tumours (Durante et al. 2006; Sampson et al., 2007). Furthermore, the ability to achieve a negative post-treatment scan after multiple doses of radioiodine was associated with 92% overall 10-year survival, compared with 19% survival for patients who did not achieve a negative post-treatment scan (Durante et al. 2006). Numerous factors affect outcome of patients with thyroid cancer; in spite of these various factors, only a few are considered in the currently recommended TNM staging system. The clinician must therefore have a complete understanding of the various prognostic factors and how they contribute to the outcome, so that the patient can be counselled accordingly about treatment and long-term surveillance decisions (Sipos & Mazzaferri, 2010).

5. Conclusions

In conclusion, we have analyzed for the first time, the descriptive epidemiology of thyroid cancer in Vigo, Galicia (Spain), between 1985 and 2001. Long term follow-up ascertainment was practically complete, providing valid information on thyroid cancer prognosis. The results of this study can be summarized as follows: the first point to note is the histologic distribution of thyroid cancer in our population; wich is similar to that found in areas with high iodine intake, with a clear predominance of differentiated thyroid carcinoma and a high ratio of papillary to follicular carcinomas. As in many other regions and countries, the incidence of thyroid cancer is increasing and this trend is primarily caused by an increase in the incidence of papillary type. Our data showing an increase in papillary cancers larger than 1 cm suggest that some environmental factor may be contributing to this trend. There is a significant increase in the prevalence of thyroid cancer over time, especially among women. These data should be taken into account when planning health resources for management of this disease. Cause-specific survival of thyroid cancer in our study is higher than the European average, similar to that found in the U.S. series of thyroid cancer. Possible explanations for these results are: a high proportion of differentiated carcinoma, particularly papillary thyroid carcinoma, and a favorable stage (I and II) of the tumors at presentation. This study has some limitations: the relatively limited number of cases, particularly for selected histologic type; the study is merely descriptive, so it is not possible to give a definitive explanation for the observed increase in the incidence of thyroid cancer. His strength is also limited because we could not continue the study beyond 2001 in order to see if this trend continues or instead, the incidence of thyroid cancer reaches a plateau. Furthermore, information on a number of variables, such as vascular invasion, tumour recurrence and treatment (dose and frequency of I-131) were not controlled and may have influenced on survival. Further studies in these areas seem prudent.

6. References

Akslen, L., Haldorsen, T., Thoresen, SO., Glattre, E. (1993). Incidence pattern of thyroid cancer in Norway: influence of birth cohort and time period. *International Journal of Cancer,* Vol.53, pp. 183-187, ISNN 0020-7136

Baker, S. & Bhatti, WA. (2006). The thyroid cancer epidemic: is it the dark side of the CT revolution? *European Journal of Radiology,* Vol.60, No.1, pp. 67-69, ISNN 0720-048X

Beenken, S., Roye, D., Weiss, H., Sellers, M., Urist, M., Diethelm, A., Goepfert, H. (2000). Extent of surgery for intermediate-risk well-differentiated thyroid cancer. *American Journal of Surgery,* Vol.179, pp. 51- 56, ISNN 0002-9610.

Berkson, J. & Gage, RP. (1950). Calculation of survival rates for cancer. *Proceedings of the Staff Meeting.* Vol.25 No.11, pp. 270-286, ISNN 0092-699X

Berrino, F., Sant, M., Capocaccia, R., Hakulinen, T., Esteve, J. (Eds). (1995). *Survival of cancer patients in Europe: the EUROCARE study,* International Agency for Research on Cancer, ISBN 92 832 2132 X, Lyon.

Blanco Carrera, C., Pelaez Torres, N., Garcia-Diaz, JD., Maqueda Villaizan, E., Sanz JM., Alvarez Hernandez, J. (2005). Epidemiological and clinicopathological study of thyroid cancer in east Madrid. *Revista Clínica Española,* Vol.205, pp. 307-310, ISNN 0014-2565

Bray F. (2002). Age-standardization, In: *Cancer Incidence in Five Continents,* Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB (Eds), pp. 87-91, International Agency for Research on Cancer (IARC) Scientific Publications, ISBN 92 832 2155 9, Lyon.

Brierley, J., Panzarella, T., Tsang, RW., Gopodarowicz, MK., O'Sullivan, B. (1997). A comparison of different staging systems predictability of patient outcome. Thyroid carcinoma as an example. *Cancer,* Vol.79, pp. 2414-2423, ISNN 0008-543X

Burgess, J., Dwyer, T., McArdle, K., Tucker, P., Shugg, D. (2000). The changing incidence and spectrum of thyroid carcinoma in Tasmania (1978-1998) during a transition from iodine sufficiency to iodine deficiency. *The Journal of Clinical Endocrinology and Metabolism,* Vol.85, pp. 1513-1517, ISNN 0021-972X

Burgess, J. (2002). Temporal trends for thyroid carcinoma in Australia: an increasing incidence of papillary thyroid carcinoma (1982-1997). *Thyroid,* Vol.12, pp. 141-149, ISNN 1050-7256

Burgess, J. & Tucker, P. (2006). Incidence trends for papillary thyroid carcinoma and their correlation with thyroid surgery and thyroid fine-needle aspirate cytology. *Thyroid,* Vol.16, pp. 47-53, ISNN 1050-7256

Capocaccia, R., Gatta, G., Roáis, P., Carrani, E., Santaquilani, M., De Angelis, R., Tavilla, A. and the Eurocare Working Group. (2003). The EUROCARE-3 methodology of data collection, standardisation, quality control and statistical analysis. *Annals of Oncology,* Vol.14, pp. 14-27, ISNN 0923-7534

Cardis, E., Howe, G., Ron, E., Bebeshko, V., Bogdanova, T., Bouville., A, Carr, Z., Chumak, V., Davis, S., Demidchik, Y., Drozdovitch, V., Gentner, N., Gudzenko, N., Hatch, M., Ivanov, V., Jacob, P., Kapitonova, E., Kenigsberg, Y., Kesminiene, A., Kopecky, KJ., Kryuchkov, V., Loos, A., Pinchera, A., Reiners, C., Repacholi, M., Shibata, Y., Shore, RE., Thomas, G., Tirmarche, M., Yamashita, S., Zvonova, I. (2006). Cancer

consequences of the Chernobyl accident: 20 years on. *Journal of Radiological Protection,* Vol.26, pp. 127-140, ISNN 0952-4746

Chen, A., Jemal, A., Ward, EM. (2009). Increasing incidence of differentiated thyroid cancer in the United States, 1988-2005. *Cancer,* Vol.115, No.16, pp. 3801-3807, ISNN 0008-543X

Chow, S., Law, SC., Au, SK., Mang, O., Yau, S., Yuen, KT., Lau, WH. (2003). Changes in clinical presentation, management and outcome in 1348 patients with differentiated thyroid carcinoma: experience in a single institute in Hong Kong, 1960-2000. *Clinical Oncology (Royal College of Radiologists (Great Britain)),* Vol.15, pp. 329-336, ISNN 0936-6555

Clark, L., Combs, GF Jr., Turnbull, BW., Slate, EH., Chalker, DK., Chow, J., Davis, LS., Glover, RA., Graham, GF., Gross, EG., Krongrad, A., Lesher, JL Jr., Park, HK., Sanders, BB Jr., Smith, CL., Taylor, JR . (1996). Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group. *Journal of the American Medical Association,* Vol.276, pp. 1957-1963, ISNN 0098-7484

Colonna, M., Grosclaude, P., Remontet, L., Schvartz, C., Mace-Lesech, J., Velten, M., Guizard, A., Tretarre, B., Buemi, AV., Arveux, P., Esteve, J. (2002). Incidence of thyroid cancer in adults recorded by French cancer registries (1978-1997). *European Journal of Cancer,* Vol.38, pp. 1762-1768, ISNN 0959-8049

Colonna, M., Guizard, AV., Schvartz, C., Velten, M., Raverdy, N., Molinie, F., Delafosse, P., Franc, B., Grosclaude, P. (2007). A time trend analysis of papillary and follicular cancers as a function of tumour size: a study of data from six cancer registries in France (1983-2000). *European Journal of Cancer* Vol.43, pp. 891-900, ISNN 0959-8049

Cooper, D., Doherty, GM., Haugen, BR., Kloos, RT., Lee, SL., Mandel, SJ., Mazzaferri, EL., McIver, B., Sherman, SI., Tuttle, RM. (2006). American Thyroid Association Guidelines Taskforce. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid,* Vol.16, No.2, pp. 109-142, ISNN 1050-7256

Cramer, J., Fu, P., Harth, KC., Margevicius, S., Wilhelm, SM. (2010). Analysis of the rising incidence of thyroid cancer using the Surveillance, Epidemiology and End Results national cancer data registry. *Surgery,* Vol.148, No.6, pp. 1147-1152, discussion: pp. 1152-1143, ISNN 0263-9319

Davies, L. & Welch, HG. (2006). Increasing incidence of thyroid cancer in the United States, 1973-2002. *Journal of the American Medical Association,* Vol. 295, pp. 2164-2167, ISNN 0098-7484

DeLellis RA. & Willliams ED. (2004). Thyroid and parathyroid tumours, In *World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Endocrine Organs.* DeLillis RA, Lloyd RV, Heitz PU, Eng C. (Eds), pp. 49-133, IARC Press, ISBN 92 832 2416 7, Lyon

dos Santos Silva, I., Swerdlow, AJ. (1993). Thyroid cancer epidemiology in England and Wales: time trends and geographical distribution. *British Journal of Cancer,* Vol. 67, pp. 330-340, ISNN 0007-0920

Durante, C., Haddy, N., Baudin, E. et al. (2006). Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. *The Journal of Clinical Endocrinology and Metabolism,* Vol.91, pp. 2892-2899, ISNN 0021-972X

Eichhorn, W., Tabler, H., Lippold, R., Lochmann, M., Schreckenberger, M., Bartenstein, P. (2003). Prognostic factors determining long-term survival in well-differentiated thyroid cancer: an analysis of four hundred eighty-four patients undergoing therapy and aftercare at the same institution. *Thyroid,* Vol.13, No.10, pp. 949-958, ISNN 1050-7256

Elisei, R., Molinaro, E., Agate, L., Bottici, V., Masserini, L., Ceccarell,i C., Lippi, F., Grasso, L., Basolo, F., Bevilacqua, G., Miccoli, P, Di Coscio, G., Vitti P, Pacini, F., Pinchera, A. (2010). Are the clinical and pathological features of differentiated thyroid carcinoma really changed over the last 35 years? Study on 4187 patients from a single Italian institution to answer this question. *The Journal of Clinical Endocrinology and Metabolism,* Vol.95, No.4, pp. 1516-1527, ISNN 0021-972X

Enewold, L., Zhu, K., Ron, E., Marrogi, AJ., Stojadinovic, A., Peoples, GE., Devesa, SS. (2009). Rising thyroid cancer incidence in the United States by demographic and tumor characteristics, 1980-2005. *Cancer Epidemiology and Biomarkers Prevention,* Vol.18, No.3, pp. 784-791, ISNN 055-9965

Engholm, G., Ferlay, J., Christensen, N., Bray, F., Gjerstorff, M., Klint, A., Køtlum, J., Ólafsdóttir, E., Pukkala, E.,Storm, H. (2009). NORDCAN: Cancer Incidence, Mortality, Prevalence and Prediction in the Nordic Countries, Version 3.5. Association of the Nordic Cancer Registries. Danish Cancer Society. Available from: http://www.ancr.nu.

Etxabe, J., Vazquez, JA. (1994). Morbidity and mortality in Cushing's disease: an epidemiological approach. *Clinical Endocrinology (Oxford),* Vol.40, pp. 479-484, ISNN 0300-0664

Eustatia-Rutten, C., Corssmit, EPM, Biermasz, NR., Pereira, AM-, Romjin, JA., Smit, JW. (2006). Survival and death causes in differentiated thyroid carcinoma. *The Journal of Clinical Endocrinology and Metabolism,* Vol. 91, pp. 313-319, ISNN 0021-972X

Farahati, J., Geling, M., Mader, U., Mortl, M., Luster, M., Muller, JG., Flentje, M., Reiners, C. (2004). Changing trends of incidence and prognosis of thyroid carcinoma in lower Franconia, Germany, from 1981-1995. *Thyroid,* Vol.14, pp. 141-147, ISNN 1050-7256

Ferlay, J., Bray, F., Pisani, P., Parkin, DM. (2004). GLOBOCAN 2002: Cancer Incidence, Mortality and Prevalence Worldwide. IARC CancerBase Nº5, version 2.0 Lyon: IARC Press. Available from: http://www-dep.iarc.fr/

Ferlay, J., Autier, P., Boniol, M., Heanue, M., Colombet, M., Boyle, P. (2007). Estimates of the cancer incidence and mortality in Europe in 2006. *Annals of Oncology,* Vol.18, pp. 581-592, ISNN 0923-7534

Fleming, ID., Cooper, JS., Henson, DE., Hutter, RVP., Kennedy, BJ., Murphy, GP., O´Sullivan, B., Sobin, LH., Yarbro, JW. (Eds). (1997). *AJCC Cancer Staging Manual,* Lippincott-Raven Publishers, ISBN 0-397-584114-8. Philadelphia.

Franceschi, S., Talamini, R., Fassina, A., Bidoli, E. (1990). Diet and epithelial cancer of the thyroid gland. *Tumori,* Vol. 76, pp. 331-338, ISNN 0300-8916

Garcia-Mayor, R., Perez Mendez, LF., Paramo, C., Luna Cano, R., Rego-Iraeta, A., Regal, M., Sierra, JM., Fluiters, E. (1997). Fine needle aspiration biopsy of thyroid nodules: impact on clinical practice. *Journal of Endocrinological Investigation,* Vol.20, pp. 482-487, ISNN 0391-4097

Garcia-Mayor, R., Rios, M., Fluiters, E., Perez Mendez, LF., Garcia- Mayor, EG., Andrade, A. (1999). Effect of iodine supplementation on a pediatric population with mild iodine deficiency. *Thyroid,* Vol.9, pp. 1089-1093, ISNN 1050-7256

Gilliland, F., Hunt, WC., Morris, DM, Key CR (1997). Prognostic factors for thyroid carcinoma. A population-based study of 15,698 cases from the Surveillance, Epidemiology and End Results (SEER) program 1973-1991. *Cancer,* Vol.79, pp. 564-573, ISNN 0008-543X

Gomez Segovia I., GH, Kresnik E, Kumnig G, Igerc I, Matschnig S, Stronegger WJ, Lind P. (2004). Descriptive epidemiology of thyroid carcinoma in Carinthia, Austria: 1984-2001. Histopathologic features and tumor classification of 734 cases under elevated general iodination of table salt since 1990: population-based age-stratified analysis on thyroid carcinoma incidence. *Thyroid,* Vol.14, 277-286, ISNN 1050-7256

Greene, FL., Page, DL., Fleming, ID., Fritz, A., Balch, CM., Haller, DG., Morrow, M. (Eds). (2002). *American Joint Committte on Cancer: AJCC Staging Manual*. Springer-Verlag, ISBN 978-0387952710, New York.

Hedinger, CE., Williams, ED., Sobin, LH. (1988). Histological typing of thyroid tumours, In: *International Histological Classification of Tumours,* World Health Organization (Ed), pp. 1–20 Springer-Verlag, ISBN 0387192441, New York.

Hodgson, N., Button J., Solorzano CC. (2004). Thyroid cancer: is the incidence still increasing?. *Annals of Surgical Oncology* Vol.11, No.12, pp. 1093-1097, ISNN 1068-9265

Hundahl, S., Fleming, ID., Fremgen, AM., Menck, HR. (1998). A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S.1985-1995. *Cancer,* Vol.83, pp. 2638-2648, ISNN 0008-543X

Kaplan, E. (1958). Nonparametric estimation from incomplete observations. *Journal of the American Statistical Association,* Vol.53, pp. 457-481, ISNN 0162-1459

Keck, A. & Finley, JW. (2004). Cruciferous vegetables: cancer protective mechanisms of glucosinolate hydrolysis products and selenium. *Integrative Cancer Therapies,* Vol.3, pp. 5-12, ISNN 1534-7354

Kent, W., Hall, S., Isotalo, PA., Houlden, RL., George, RL., Groome, PA. (2007). Increased incidence of differentiated thyroid carcinoma and detection of subclinical disease. *Canadian Medical Association Journal,* Vol.177, No.11, pp. 1357-1361, ISNN 0820-3946

Kilfoy, B., Zheng, T., Holford, TR. et al. (2009). International patterns and trends in thyroid cancer incidence, 1973-2002. *Cancer Causes Control* Vol.20, No.5, pp. 525-531, ISNN 0957-5243

Kolonel, L., Hankin, JH., Wilkens, LR., Fukunaga, FH., Hinds, MW. (1990). An epidemiologic study of thyroid cancer in Hawaii. *Cancer Causes Control,* Vol.1, No.3, pp. 223-234, ISNN 0957-5243

Kovacs, G., Gonda, G., Vadasz, G., Ludmany, E., Uhrin, K., Gorombey, Z., Kovacs, L., Hubina, E., Bodo, M., Goth, MI., Szabolcs, I. (2005). Epidemiology of thyroid

microcarcinoma found in autopsy series conducted in areas of different iodine intake. *Thyroid,* Vol.15, pp. 152-157, ISNN 1050-7256

Leenhardt, L., Grosclaude, P., Cherie-Challine, L. (2004). Increased incidence of thyroid carcinoma in France: a true epidemic or thyroid nodule management effects? Report from the French Thyroid Cancer Committee. *Thyroid,* Vol.14, pp. 1056-1060 (a), ISNN 1050-7256

Leenhardt, L., Bernier, MO., Boin-Pineau, MH., Conte Devolx, B., Marechaud, R., Niccoli-Sire, P., Nocaudie, M., Orgiazzi, J., Schlumberger, M., Wemeau, JL., Cherie-Challine, L., De Vathaire, F. (2004). Advances in diagnostic practices affect thyroid cancer incidence in France. *European Journal of Endocrinology,* Vol.150, pp. 133-139. (b), ISNN 0804-4643

Lerch, H., Schober, O., Kuwert, T., Saur, HB. (1997). Survival of differentiated thyroid carcinoma studied in 500 patients. *Journal of Clinical Oncology,* Vol.15, pp. 2067-2075, ISNN 0732-183X

Liu, S., Semenciw, R., Ugnat, AM., Mao, Y. (2001). Increasing thyroid cancer incidence in Canada, 1970-1996: time trends and age-period-cohort effects. *British Journal of Cancer,* Vol. 85, pp. 1335-1339, ISNN 0007-0920

LiVolsi, VA. (2004). Papillary carcinoma, In *World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Endocrine Organs.* DeLillis RA, Lloyd RV, Heitz PU, Eng C. (Eds), pp. 57-66, IARC Press, ISBN 92 832 2416 7, Lyon.

Loh, K., Greenspan, FS., Gee, L., Miller, TR., Yeo, PP. (1997). Pathological tumor-node-metastasis (pTNM) staging for papillary and follicular thyroid carcinomas: a retrospective analysis of 700 patients. *The Journal of Clinical Endocrinology and Metabolism,* Vol.82, pp. 3553-3562, ISNN 0021-972X

Martinez-Tello, F., Martinez-Cabruja, R., Fernandez-Martin, J., Lasso-Oria, C., Ballestin-Carcavilla, C. (1993). Occult carcinoma of the thyroid. A systematic autopsy study from Spain of two series performed with two different methods. *Cancer,* Vol.71, pp. 4022-4029, ISNN 0008-543X

Mazzaferri, EL. (1993). Thyroid carcinoma: papillary and follicular, In: *Endocrine tumors*. Mazzaferri EL, Samaan N. (Eds), pp. 278-333, Blackwell Scientific Publications, ISBN 0865422672, Cambridge, MA.

Mazzaferri, EL. (1999). An overview of the management of papillary and follicular thyroid carcinoma. *Thyroid* Vol. 9, pp. 421-427, ISNN 1050-7256

Merhy, J., Driscoll, HK., Leidy, JW., Chertow, BS. (2001). Increasing incidence and characteristics of differentiated thyroid cancer in Huntington, West Virginia. *Thyroid,* Vol.11, pp. 1063-1069, ISNN 1050-7256

Mitchell, I., Livingston, EH., Chang, AY., Holt, S., Snyder, WH. 3rd., Lingvay, I., Nwariaku, FE. (2007). Trends in thyroid cancer demographics and surgical therapy in the United States. *Surgery,* Vol.142, pp. 823-828; discussion 828-821, ISNN 0263-9319

Morris, L. & Myssiorek, D. (2010). Improved detection does not fully explain the rising incidence of well-differentiated thyroid cancer: a population-based analysis. *American Journal of Surgery,* Vol.200, No.4, pp. 454-461, ISNN 0002-9610

Nagataki, S. & Nystrom. E. (2002). Epidemiology and primary prevention of thyroid cancer. *Thyroid,* Vol.12, pp. 889-896, ISNN 1050-7256

Pacini, F., Schlumberger, M., Dralle, H., Elisei, R., Smit, JW., Wiersinga, W. (2006). European Thyroid Cancer Taskforce. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. *European Journal of Endocrinology,* Vol.154, No.6, pp. 787-803. Erratum in: Eur J Endocrinol. 2006 Aug; 2155 (2002):2385, ISNN 0804-4643

Parkin, DM. (2006). The evolution of the population-based cancer registry. *Nature Reviews. Cancer,* Vol.6, pp. 603-612, ISNN 1474-175X

Percy, C., Stanek, E 3rd., Gloeckler L. (1981). Accuracy of cancer death certificates and its effect on cancer mortality statistics. *American Journal of Public Health,* Vol.71, No.3, *pp.* 242-250, ISNN 0090-0036

Pettersson, B., Adami, HO., Wilander, E., Coleman, MP. (1991). Trends in thyroid cancer incidence in Sweden, 1958-1981, by histopathologic type. *International Journal of Oncology,* Vol.48, pp. 28-33, ISNN 1019-6439

Rayman, M. (2000). The importance of selenium to human health. *The Lancet,* Vol. 356, pp. 233-241, ISNN 0099-5355

Rego-Iraeta, A., Perez-Fdez, R., Cadarso-Suarez, C., Tome, M., Fdez-Marino, A., Mato, JA., Botana, M., Solache, I. (2007). Iodine nutrition in the adult population of Galicia (Spain). *Thyroid,* Vol.17, pp. 161-167, ISNN 1050-7256

Rego-Iraeta, A., Perez-Mendez, LF., Mantinan, B., Garcia-Mayor, RV. (2009). Time trends for thyroid cancer in northwestern Spain: true rise in the incidence of micro and larger forms of papillary thyroid carcinoma. *Thyroid,* Vol.19, pp. 333-340, ISNN 1050-7256

Reynolds, R., Weir, J., Stockton D., Brewster, DH., Sandeep, TC., Strachan, MW. (2005). Changing trends in incidence and mortality of thyroid cancer in Scotland. *Clinical Endocrinology (Oxford),* Vol. 62, pp. 156-162, ISNN 0300-0664

Rodríguez, I., Luna, R., Ríos, M., Fluiters, E., Páramo, C., García-Mayor, RV. (2002). Iodine deficiency in pregnant and fertile women in an area of normal iodine intake. *Medicina Clínica,* Vol.18, pp. 217-218, ISNN 0025-7753

Salas, A., Comas, D., Lareu, MV., Bertranpetit, J., Carracedo, A. (1998). mtDNA analysis of the Galician population: a genetic edge of European variation. *European Journal of Human Genetics,* Vol. 6, pp. 365-375, ISNN 1018-4813

Sampson, E., Brierley, JD., Le, LW., Rotstein, L., Tsang, RW. (2007). Clinical management and outcome of papillary and follicular (differentiated) thyroid cancer presenting with distant metastasis at diagnosis. *Cancer,* Vol.110, pp. 1451-1456, ISNN 0008-543X

Sampson, R., Woolner, LB., Bahn, RC., Kurland, LT. (1974). Occult thyroid carcinoma in Olmsted County, Minnesota: prevalence at autopsy compared with that in Hiroshima and Nagasaki, Japan. *Cancer,* Vol.34, pp. 2072-2076, ISNN 0008-543X

Sant, M., Aareleid, T., Berrino, F., Bielska Lasota, M., Carli, PM., Faivre, J., Grosclaude, P., Hedelin, G., Matsuda, T., Moller, H., Moller, T., Verdecchia, A., Capocaccia, R., Gatta, G., Micheli, A., Santaquilani, M., Roazzi, P., Lisi, D. (2003). EUROCARE-3: survival of cancer patients diagnosed 1990-94-results and commentary. *Annals of Oncology,* Vol.14, No.Suppl 5, pp.61-118, ISNN 0923-7534

Scheiden, R., Keipes, M., Bock, C., Dippel, W., Kieffer, N., Capesius, C. (2006). Thyroid cancer in Luxembourg: a national population-based data report (1983-1999). *British Medical Cancer,* Vol.6, pp.102, ISNN 1471-2407

Schlumberger, M., Filetti, S., Hay, ID. (2008). Nontoxic diffuse and nodular goiter and thyroid neoplasia, In: *Williams Textbook of Endocrinology*. Kronenberg HM, Melmed S, L Polonsky KS, Larsen PR (Eds), pp. 411–442, Saunders, ISBN 978-1-4160-2911-3, Philadelphia.

Sciuto, R., Romano, L., Rea, S., Marandino, F., Sperduti, I., Maini, CL. (2009). Natural history and clinical outcome of differentiated thyroid carcinoma: a retrospective analysis of 1503 patients treated at a single institution. *Annals of Oncology,* No.10, pp. 1728-1735, ISNN 0923-7534

Shah, J., Loree, TR., Dharker, D., Strong, EW., Begg, C., Vlamis, V. (1992). Prognostic factors in differentiated carcinoma of the thyroid gland. *American Journal of Surgery,* Vol.164, pp. 658- 661, ISNN 0002-9610

Sherman, S., Brierley, JD., Sperling, M., et al. (1998). Prospective multicenter study of thyroid carcinoma treatment: initial analysis of staging and outcome. National Thyroid Cancer Treatment Cooperative Study Registry Group. *Cancer,* Vol.83, pp. 1012-1021, ISNN 0008-543X

Sherman, S. & Fagin, J. (2005). Why thyroid cancer? *Thyroid,* Vol.15, pp. 303-304, ISNN 1050-7256

Sipos, J., Mazzaferri, EL. (2010). Thyroid cancer epidemiology and prognostic variable. *Clinical Oncology (Royal College of Radiologists (Great Britain)),* Vol.22, No.6, pp. 395-404, ISNN 0936-6555

Szybinski, Z., Huszno, B., Zemla, B., Bandurska-Stankiewicz, E., Przybylik-Mazurek, E., Nowak, W., Cichon, S., Buziak-Bereza, M., Trofimiuk, M., Szybinski, P. (2003). Incidence of thyroid cancer in the selected areas of iodine deficiency in Poland. *Journal of Endocrinological Investigation,* Vol.26, pp. 63-70, ISNN 0391-4097

Teppo, L. & Hakulinen, T. (1998). Variation in survival of adult patients with thyroid cancer in Europe. *European Journal of Cancer,* Vol. 34, pp. 2248-2252, ISNN 0959-8049

Thoresen, S., Akslen, LA., Glattre, E., Haldorsen, T., Lund, EV., Schoultz, M. (1989). Survival and prognostic factors in differentiated thyroid cancer-a multivariate analysis of 1,055 cases. *British Journal of Cancer,* Vol.59, No.2, pp. 231-235, ISNN 0007-0920

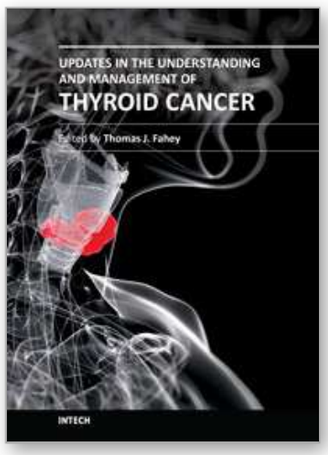
Torres, J., Volpato, RD., Power, EG., Lopez, EC., Dominguez, ME., Maira, JL., Ugarte, JA., Martinez, VC. (1985). Thyroid cancer. Survival in 148 cases followed for 10 years or more. *Cancer,* Vol.56, No.9, pp. 2298-2304, ISNN 0008-543X

Verhoeven, D., Goldbohm, RA., van Poppel, G., Verhagen, H., van den Brandt, PA. (1996). Epidemiological studies on brassica vegetables and cancer risk. Cancer Epidemiology, Biomarkers & Prevention, Vol.5, pp. 733-748, ISNN 1055-9965

Verkooijen, H., Fioretta, G., Pache, JC., Franceschi, S., Raymond, L., Schubert, H., Bouchardy, C. (2003). Diagnostic changes as a reason for the increase in papillary thyroid cancer incidence in Geneva, Switzerland. *Cancer Causes Control,* Vol.14, pp. 13-17, ISNN 0957-5243

Yamashita, S. (2006). Radiation-induced thyroid cancer. *Nippon Rinsho,* Vol.Suppl 1, pp. 493-496, ISNN 0047-1852

Zheng, T., Holford, TR., Chen, Y., Ma, JZ., Flannery, J., Liu, W., Russi, M., Boyle, P. (1996). Time trend and age-period-cohort effect on incidence of thyroid cancer in Connecticut, 1935-1992. *International Journal of Oncology,* Vol. 67, pp. 504-509, ISNN 1019-6439



Updates in the Understanding and Management of Thyroid Cancer
Edited by Dr. Thomas J. Fahey

ISBN 978-953-51-0299-1
Hard cover, 306 pages
Publisher InTech
Published online 21, March, 2012
Published in print edition March, 2012

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

A. Rego-Iraeta, L. Pérez-Mendez and R.V. García-Mayor (2012). An Epidemiological Analysis of Thyroid Cancer in a Spanish Population: Presentation, Incidence and Survival, Updates in the Understanding and Management of Thyroid Cancer, Dr. Thomas J. Fahey (Ed.), ISBN: 978-953-51-0299-1, InTech, Available from: http://www.intechopen.com/books/updates-in-the-understanding-and-management-of-thyroid-cancer/an-epidemiological-analisis-of-thyroid-cancer-in-a-spanish-population-presentation-incidence-and-sur

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen