RESEARCH ARTICLE

# Thyroid Cancer Epidemiology in Iran: a Time Trend Study

**Ali Safavi[1], Fereidoun Azizi[2], Rozita Jafari[1]*, Samira Chaibakhsh[3], Amir Ali Safavi[4]**

## Abstract

**Background: Considering the rising incidence of thyroid cancer worldwide, the aim of our study was to investigate the temporal trends in the incidence of this cancer in a large population of Iranian patients. Materials and Methods: We used the Iran Cancer Data System (ICDS) Registry to assess the thyroid cancer trend from 2004 to 2010 with regard to different genders, age groups, and morphologies. To do this we analyzed the data of 10,913 new cases of thyroid cancer that occurred during these years. Results: The incidence rate (per one year) of thyroid cancer was 2.20 per 100,000 persons between 2004 and 2010 in Iran. Papillary thyroid cancer was the most common histology type, with an annual rate of 0.29 in Iran. The highest rate of prevalence in thyroid cancer was observed at the age of 45 years at the time of diagnosis. We found a female-to-male ratio of 2 in Iran. A significant decrease was detected in the trend of thyroid cancer in children <19y, which was not correlated to the trend of older patients. Conclusions: As expected, the trend of thyroid cancer increased over the 7 years, primarily contributed by papillary thyroid cancer. A rising pattern of incidence was seen in all the age groups except patients aged under 19 years.**

**Keywords:** Thyroid cancer - epidemiology - trend - papillary cancer - follicular cancer - cancer registry

*Asian Pac J Cancer Prev,* **17 (1)**, 407-412

## Introduction

Thyroid cancer, a relatively rare neoplasm, accounts for 213,000 new cases worldwide annually. Approximately, 1–5% of the cases of this cancer occur in females and <2% in males (Sriplung et al., 2005; El-Basmy et al., 2012; Cossu et al., 2013; Du et al., 2013). Although relatively rare, it is the most common endocrine malignancy in the world (Kilfoy et al., 2009). In the United States and many other places, this incidence increased over two fold from 1984 to 2004 (Grodski et al., 2008; Sprague et al., 2008). The estimated worldwide incidence of the disease has been reported to be 1.7% (Cossu et al., 2013). According to the data recently released by the American National Cancer Institute (NCI), thyroid cancer increased at a rate of 6.5 percent per year from 1997 to 2006, emerging as the fastest increasing cancer among men and women (Kilfoy et al., 2009). From 1995 to 2004, next to only peritoneum, omentum, mesentery cancers and other digestive cancers, thyroid cancer ranked third among the fastest growing cancers (Sprague et al., 2008; Kutikhin et al., 2012).

In agreement with several studies (Guay et al., 2014; Reitzel et al., 2014; Udelsman and Zhang, 2014) findings of Dr. Davies and Dr. Welch (2006) showed that the identification of more "subclinical diseases" has increased the rate of thyroid cancer. As they put it, the growing rate is "not an increase in the true occurrence of thyroid cancer"; rather, better detection methods used by doctors have enabled them to diagnose cancers that could not be detected previously (Davies and Welch, 2010). An estimated incidence of 163968 per 100000 women (2.7%) and 49211 per 100000 in men (0.7%) has been reported worldwide (Ferlay et al., 2013).

Thyroid cancer occurs very rarely in children under the age of 15, comprising 1.5-3% of all childhood cancers; however, the initial presentation may be as early as the age of 5. The annual incidence rate in children is one case per million (Wartofsky, 2010). One of the major risk factors of childhood thyroid cancer is nuclear incidents, which can be avoided if iodine is steadily administered, particularly in young children, as prophylaxis within just a few hours immediately after the incident occurs.

In terms of their morphology and clinical features, thyroid cancers are traditionally classified into two major groups, differentiated (including papillary, follicular, and medullary) and undifferentiated (anaplastic) carcinoma, a classification strongly supported by advances in molecular studies (Dal et al., 2009). Differentiated thyroid carcinoma accounts for about 90% of all cases and is, hence, the most common form of thyroid cancer (Kent et al., 2007). Hence, in this study, we have used the Iran Cancer Data System (ICDS) Registry to investigate the current trend, variation in incidence, epidemiology, and histological characteristics of thyroid cancer in Iran from 2004 to

*[1]Department of Otolaryngology, Head and Neck Surgery, [2]Endocrine Research Center, Research Institute for Endocrine Sciences, [3]Masih Daneshvari Hospital, [4]School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran *For correspondence: dr.rozitajafari57@yahoo.com*

2010. Study initiation date of 2004 was chosen because it coincided with the adoption of national cancer registering for new thyroid cancer cases. The present study covers an extended age ranges (7-90), to include the majority of thyroid cancer cases.

We hypothesized: *(i)* The presence of a recent temporal increase in the incidence of thyroid cancer in female; *(ii)* The presence of a lower age range in the incidence of thyroid cancer.

## Materials and Methods

The Iranian Cancer Data System Registry is a population-based registry of all new cases of cancer occurring across the country. Data available provided by the registry include the year of diagnosis, gender, age group (<9 to 80+ years, and 10-year categories in between) province of diagnosis, and histology type for each case.

Histopathologic diagnoses in the ICDS were coded according to the International Classification of Diseases for Oncology. On the basis of some previous studies (Albores-Saavedra et al., 2007; Chen et al., 2009) we created four histological categories: Papillary cancer (with morphology codes of 8050, 8260, 8340, 8341, 8343, 8344, 8350), follicular cancer (8290, 8330, 8331, 8332, 8335), medullary cancer (8510, 8345, 8510-8513), and anaplastic cancer (8012, 8020, 8021, 8022, 8030, 8031, 8032) (Fritz, 2000).

The correlation between the incidence rate and median urinary iodine concentration were measured for different provinces.

Annual incidence rates per 100,000 persons were calculated for the period of 2004 to 2010, and the subgroups were defined by gender, age group, and cancer histology. Incidence rates were also calculated for different provinces during the 2004-2010 periods to be used in ecology analyses. The ethical approval for the study was granted by the Research Ethics Committee of Tracheal Research Center of Masih Daneshvari Hospital.

*Statistical analysis*

Continuous variables are reported as mean and standard deviation, and categorical variables by frequency and percentage. The trend of incidence was analyzed using Chi-square test for trend. For comparing the incidence rates in the binary variables, a binomial test was performed; statistical significance was considered for p-values<0.05. All analyses were performed by SPSS versions 16 and R.

## Results

A total of 10913 cases of thyroid cancer with an extended age range of 7-90 years were reported to the Iran Cancer Data System Registry during 2004 to 2010. The total incidence rate (per one year) in these 7 years was 2.20 per 100000. Most of the cases were women (74%). Of the thyroid cancers, the most frequent was papillary carcinoma (81%). Table 1 shows the percentage of other pathologies.

*Total trend*

Using Chi-square test for trend, the incidence of thyroid cancer was found to be increasing significantly between 2004 and 2010 (p-value<0.0001).

*Trend in males and females*

Calculating the relative risk of incidence (in males and females) in different years (2004-2010), the highest IRR was observed in 2010 (RR=3.1), while the lowest belonged to 2004 (RR=2.6). Throughout this duration, the incidence was higher in females than in males. Because the data pertained to a population rather than a sample, there was no need to perform a statistical analysis to compare the incidence in females to that in males. Figure 1 illustrates a significant increase (p-value<0.0001 in both). It shows the trend in males and females, which although increasing in both, incurred a sharper trend in females than in males.

*Trend in pathology*

Papillary carcinoma and anaplastic carcinoma were the most and the least frequent pathology respectively observed between 2004 and 2010. Chi-square test for trend was used to assess the trend of papillary cancer, follicular cancer, medullary cancer, and anaplastic cancer; incidence trends for these disorders are illustrated in Figure 2. As seen in Figure 2, the incidence of papillary cancer was much higher than others. The trend of papillary carcinoma appeared to be increasing significantly (p-value<0.0001) except in 2007 when it decreased and the remained close to constant after 2009; the increase in the trend of follicular carcinoma was also significant (p-value=0.002). From 2004 to 2010, follicular carcinoma had an increasing trend except in 2007, 2008 and 2010 when it declined. The incidence of medullary cancer was increased significantly (p-value<0.0001), with a sharp rise in 2005. Unlike the other types of cancer, anaplastic carcinoma had a no significant trend.

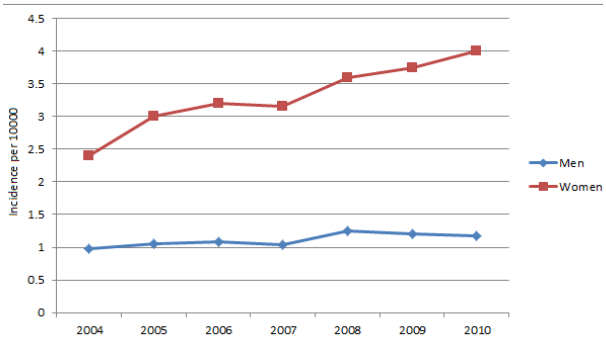


**Figure 1. Trend of Thyroid Cancer during 2004-2010 in Iran**

**Table 1. Percentage of different Thyroid Cancer Pathologies**

| | Frequency | Percent |
|---|---|---|
| Papillary Carcinoma | 8842 | 81 |
| Anaplastic Carcinoma | 273 | 2.5 |
| Follicular Carcinoma | 809 | 7.4 |
| Medullary | 559 | 5.1 |
| Other tumors | 430 | 3.9 |

*Data are presented as Frequency (Percentage)

**Table 2. Mean Age and Frequencies of Patients by Gender for Different Pathologies of Thyroid Lesions**

| | Age | Female | Male | Female / Male Ratio |
|---|---|---|---|---|
| Papillary Carcinoma | 42±16.4 | 6717 (83.1) | 1783 (75.3) | 3.16 |
| Anaplastic Carcinoma | 66.3±11.57 | 166 (2.1) | 92 (3.8) | 1.55 |
| Follicular Carcinoma | 49.19±16.87 | 627 (7.7) | 165 (6.9) | 3.2 |
| Medullary | 44.15±16.91 | 315 (3.9) | 209 (8.6) | 1.29 |
| Other tumors | 53.14±18.44 | 257 (3.2) | 109 (5.4) | 1.69 |

*Data are presented as Frequency (Percentage) and Mean±SD

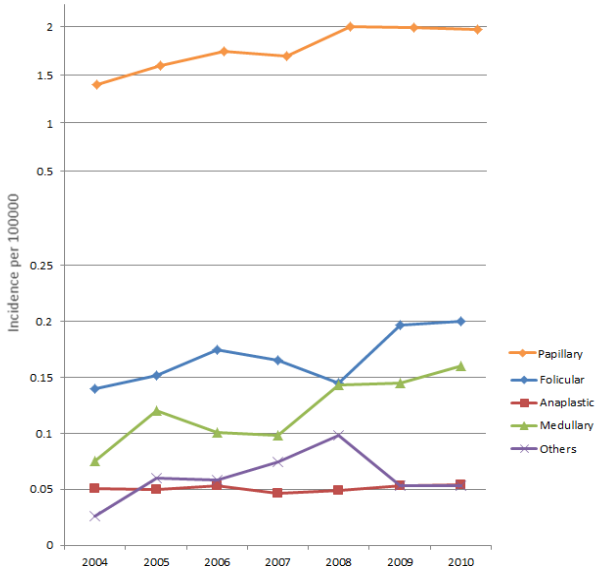


**Figure 2. Trend of Different Pathologies in Thyroid Cancer during 2004-2010 in Iran**

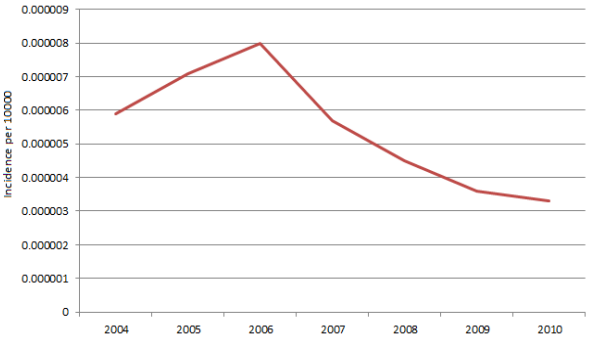


**Figure 3. Trend in the Incidence of Pediatric Thyroid Cancer (<20 y) during 2004-2010 in Iran**

*Pathologies separated by gender*

Pathologies separated by gender are shown in Table 2. Although the percentages of different pathologies in males and females were highly similar, the incidence of papillary cancer was higher in females, and the incidence of anaplastic and medullary cancer was higher in men.

*Trend of age in different pathologies*

Table 2 shows the mean age of the patients in different pathologies. In the case of anaplastic carcinoma and papillary carcinoma, the mean age was higher and lower than in the other groups respectively (i.e. 42 y, and 66.3 y).

*Trend in different age groups*

Incidence trends in the 0-9 and 10-19 age groups decreased significantly, but the incidence in the 20-29, 30-39, 40-49, and >59 age groups showed a significant increase (all p-values<0.0001). The trend in the 50-59 age group was not significant.

*Trend of pediatrics (<20 y)*

The incidence of thyroid cancer in pediatrics was found to be increasing significantly between 2004 and 2010 (p-value<0.0001). The trend is illustrated in Figure 3.

*Correlation between incidence rate and median urinary iodine concentration*

The Spearman correlation between the incidence rates in provinces and the median urinary iodine concentration was calculated and found to be 0.44, which was statistically significant (p-value=0.025).

## Discussion

This study was conducted on the basis of the largest documented data set on thyroid cancer in Iran, during 2004-2010. It allowed making quantifications more precisely than before by using recent trend analysis for different histological types of thyroid cancer and up-to-date analysis of geographical, age, and gender distribution.

The total incidence rate (per one year) was 2.20 per 100000 during 2004-2010 in Iran. A five-year worldwide prevalence of 667377 per 100000 (4.4%) has been reported (Ferlay, Shin, Bray, Forman, Mathers, & Parkin,2013). We observed a marked increase in the thyroid carcinoma incidence in Iran, which is in agreement with findings of several reports from Canada, Australia, Western Europe, Brazil, and the U.S. (Chen et al., 2009; McLeod, 2010; McNally et al., 2012; Pathak et al., 2013; Veiga et al., 2013). These results are in agreement with a report by the World Health Organization that warned against an elevated rate of thyroid cancer in the world (Pathak et al., 2013); this rise, largely limited to the papillary subtype, was reported after a similar pattern was observed in many countries such as the United States, Israel, Brazil, and some areas in the north and west of Europe (Albores-Saavedra et al., 2007; McLeod, 2010; Veiga et al., 2013). It has been reported that the increase in the incidence of PTC in the Netherlands is less noticeable than those of other countries, specifically in the US. It seems that the virtually stable and sufficient iodine taken by the Dutch population during the past decades, the low level of radiation exposure, and probably the more conservative approach toward asymptomatic and incidentally detected thyroid nodules are factors that account for these findings (Netea-Maier et al., 2008).

Different national cancer registries report different time trends for the incidence of thyroid cancer (Kilfoy et al., 2009). From 1998 through 2001, 429 cases of primary thyroid cancer were registered in the Tehran

Metropolitan Area Cancer Registry Office. The incidence of thyroid cancer was 1.0 and 3.5 in 100,000 for males and females respectively. While the incidence of thyroid cancer was slightly high, the descriptive epidemiology of the disease in Iran did not manifest a unique feature. Iranian patients experienced a high rate of survival, which was not significantly different between males and females (Mohagheghi et al., 2009). Unfortunately, as stated in WHO (World Health Organization) reports, in recent years, no study has compared the trend of thyroid cancer incidence in Iran to that of other countries.

In recent years, there seems to have been an increase in the number of endocrinologist and radiologists who are skilled in diagnosing thyroid cancer. In Iran, at least, this increase is accounted for by the increase in the recording of thyroid cancer cases.

A recent report indicates that no plateau has occurred in thyroid cancer incidence rates. As expected, a temporary increase has occurred in the rates because new and more sensitive diagnostic techniques are being widely used (Eser et al., 2010; Roche et al., 2011). However, if the rising incidence was due to the improved disease detection, a more rapid increase would be expected in small early-stage tumors than in large late-stage ones (Aschebrook-Kilfoy et al., 2011). Another study has shown that, while most tumors discovered by imaging were small and early-stage, almost half of advanced (Stage III and IV) WDTCs were initially discovered by imaging studies; this finding is consistent with the hypothesis that the frequent use of imaging studies (thyroid sonogram, computed tomography, magnetic resonance imaging, carotid duplex scan and positron-emission tomography or other imaging studies) may explain the increasing incidence of not only early WDTC but also more advanced thyroid cancers (Malone et al., 2014).

The risk factors known for papillary and follicular thyroid cancers differ; exposure to radiation almost always leads to papillary, but not follicular thyroid cancer (Aschebrook-Kilfoy et al., 2013; Sungwalee et al., 2013). Chronic iodine deficiency is firmly established as a risk factor for goiter and follicular thyroid cancer, while some ecological studies suggest that iodine excess as a result of iodine supplementation can increase the incidence of papillary thyroid cancer (Aceves et al., 2013).

A recent report from Italy has points to space-time differences in thyroid cancer mortality in that country, demonstrating a connection between mortality and living in mountainous regions, which is considered as an indication of iodine deficiency. Socioeconomic differences cannot account for the observed temporal north-south shift, while the efficient prophylaxis program practiced in some northern areas of Italy in the 1980s can explain the disappearance of clusters in those areas between 1995 and 2009 (Minelli et al., 2013). Papillary thyroid cancer was the most common histology, accounting for 81.8% of all thyroid cancers in Iran. Our findings suggest that the annual papillary cancer rate in Iran was 0.29; the mean age of patients with papillary carcinoma was slightly skewed downward toward lower ages between 2004 and 2009. It is also shown the patients aged 45 years at the time of diagnosis accounted for the largest proportion of cases of thyroid cancer in Iran. Papillary thyroid cancer is the predominant cancer type in children (LiVolsi, 2011).

The female-to-male ratios and age distribution in papillary cancer were similar to America (Dinets et al., 2012). Also, there was no significant difference between the percent of papillary cancer in Iran (81%) and the rate worldwide (80%) (Veiga et al., 2013).

Also, the trend in follicular carcinoma was significant (p-value=0.02). Between 2004 and 2010, follicular carcinoma was increasing except in 2007 and 2008 when it declined; the peak age of onset was 30-55 years.

It was reported that this pathology was seen in 10-20 percent of American patients, whereas in Iran it is below this range (7.5%). The ratios for medullary and anaplastic cancer were similar to other worldwide reports (Patel and Shaha, 2006).

Thyroid cancer is the only cancer in which the patient's age is a very important factor that determines how aggressive the disease is and how long the patient will survive (Bilimoria et al., 2007).

Patient's age is an important factor in the prognosis of clinical papillary thyroid carcinoma (PTC). PTMC may be more progressive in young patients than in older ones (Ito et al., 2014).

The rates of prevalence in 20-29, 30-39, 40-49 and >59 decades of life were increasing significantly (all p-values<0.0001); however the trend in the 50-59 decade was not significant.

The F/M (female/male) RR (relative risk) was consistently significant (p-value<0.0001) in all the years in Iran, and a female preponderance was observed for all the histologic types. This finding was not in agreement with the ratio in America (Sprague et al., 2008). Another result showed female-to-male ratio in Southeast England to be 2.7:1, which indicates an increased rate of TC incidence in Southeast England during a 20-year study (Olaleye et al., 2011).

The increase in the incidence rate of thyroid cancer may be partially explained by changes in various reproductive and hormonal factors (Roche et al., 2011). Research findings suggest that female gender and high age are considered as the two factors that are involved in predicting the increased use of diagnostic medical imaging by women aged 45 years< (Kent et al., 2007). According to the Canadian Cancer Society (CCS) in 2011, only two cancers had significantly increased incidence in women, i.e. liver cancer at a rate of 3.3, and thyroid cancer at a rate of 8.8 (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2013).

We found a significant decrease in the trend of prevalence in the 0-9 and 10-19 decades of life. However, this finding is not in agreement with reports from USA (Sprague, Warren, & Trentham-Dietz, 2008). Papillary thyroid cancer is the predominant cancer type in children (Dinets et al., 2012).

There was no significant difference between the ratio in subjects aged 45< years in Iran and America (American Cancer Society, 2009). The gender distribution of thyroid cancer varies from adults to children. A difference not found in individuals below the age of 15 with the girl-boy ratio as low as 1.5:1. In individuals aged 15-20 years,

however, the female-to-male ratio is 3:1 (Patel and Shaha, 2006).

Despite a study conducted in Canada suggesting that thyroid cancers were more frequently diagnosed in Canadian patients of higher socioeconomic status, Canadian patients of lower socioeconomic status suffered from thyroid cancers of more advanced stages when presented to doctors (Siu et al., 2014).

With regard to lack of data about diet, BMI environmental factor, and lifestyle, we were not able to analyze thyroid incidence in association with these factors in Iran.

In our study, we just assessed the effect of median urinary iodine concentration (based on its pattern in Iran) on the thyroid cancer trend and found a positive correlation between them (p-value=0.025).

This study has several limitations. First, changes in the registration data quality may affect time trends. This is especially important when using cancer registry data in the early years of registration. Second, tumor size and diagnostic technique (Fine needle Aspiration, Sonograghy) are not collected in the data released by the Iranian Health Department. There is no report of the recent cases of thyroid cancer in the form of integrated online database in the Iranian Health Department (Cancer section), it is highly recommended that the Iranian Department of Health and the Forensic Medical Council should work together to report cancer-caused deaths by organizing and implementing of an effective uniform database system about the survival rate of thyroid cancer in Iran.

In conclusion, increase in the incidence of thyroid cancer, is largely seen in patients aged over 20 years. The ratios for all histologic types of thyroid cancer papillary, medullary and anaplastic cancer in Iran were similar to other worldwide reports, but except for follicular cancer.

It seems that increase in the number of endocrinologist and radiologists who are skilled in diagnosing thyroid cancer is accounted for by the increase in the recording of thyroid cancer cases.

Future studies are needed to address the role of tumor size and diagnostic technique in rising incidence of thyroid cancer in Iran, to evaluate the survival of thyroid cancer and social determinants in Iran.

## Acknowledgements

We thank the Research Committee of Tracheal Research Center of Masih daneshvari hospital; we also thank Dr Asma Puorhoseingholi, PhD in biostatistics, for her collaboration during the data analysis. The authors wish to acknowledge Miss Niloofar Shiva for critical editing of English grammar and syntax of the manuscript.

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