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Thyroid Cancer Incidence and Trends by Demographic and Tumor Characteristics in Oran, Algeria 1993-2013: A Population based Analysis

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Abstract

Objectives: Incidence rates of thyroid cancer have dramatically increased over recent decades in many countries, particularly papillary histotype tumors and small carcinomas. We carried out an analysis to assess thyroid cancer incidence and trends by demographic and tumor characteristics among 1 443 thyroid cancer patients diagnosed between 1993 and 2013 in Oran district, in North-west Algeria.

Methods: Information on thyroid cancer cases were abstracted through medical records and pathology reports. We used the International Classification for Diseases in Oncology, 3rd edition to characterize morphologies. We calculated age-specific, age-adjusted incidence rates per 100 000 person-years, and annual percent changes (APC) in the incidence.

Results: Age-standardized incidence was 11.7 per 100 000 for females and 2.0 per 100 000 for males. Thyroid cancer incidence increased over time significantly in females compared with males (APC: +5.56%; $p<0.05$ and +3.23%; $p>0.05$), mostly due to an increased incidence of the papillary histotype (APC: +5.48%; $p<0.05$ and +14.38%; $p<0.05$), micro carcinomas in females (APC: +17.34%; $p<0.05$), and carcinomas >40 mm in males (APC: +20.24%;$p<0.05$). During the same period of time the incidence of follicular thyroid carcinoma significantly decreased (APC: -3.74%; $p<0.05$).

Conclusion: The findings of our research are consistent with previous studies carried out in many parts of the world. Although the use of ultrasound and fine needle aspiration cannot be totally ruled out, the role of iodine supplementation implemented in the late 1960s in Algeria may have caused the observed trends. The role of other potential risk factors is also discussed.

Keywords: Thyroid cancer; Incidence; Algeria; Histotype; Annual percent change

Introduction

Among all cancers of the endocrine system, thyroid cancer (TC) is the most frequent. Over the past three decades its incidence increased steadily in many countries, mostly driven by the papillary histotype (PTC) and small carcinomas (≤ 20 mm)[1]. To date, the reasons of such increase are still debated. Some authors have hypothesized that this trend is due to exposure to etiological factors that vary with time, whereas others have stated that the observed increase is apparent due to changes in medical practice. Among all risk factors, exposure to ionizing radiation, especially when it occurs during childhood is the only clearly established risk factor for TC, in particular for PTC. Other risk factors include iodine intake and endemic goiter, heredity hormonal and reproductive factors in females, obesity, and exposure to endocrine disruptors [2]. In Algeria TC is the third most common cancer in females and the eighth in males, with age-standardized incidence rates (ASR) varying from 6.2 per 100 000 to 9.1 per 100 000 in females and 1.4 per 100 000 to 2.1 per 100 000 in males [3].

During the past three decades TC incidence has increased sharply in Algeria; however, no study has reported on incidence trends according to demographics, histology and tumor size. We therefore undertook a detailed analysis of TC incidence and time trends according to sex, histologic type and tumor size over a 21-year period in the Oran district, located North-west Algeria [4].

Methodology

Data source

Oran is a large and populous city in Algeria, with a homogeneous population. The district covers an area of 2 250

km2 and has a population of about 1.5 million (5% of the Algerian population) [5]. The data collection and validation process has been described previously [6,7]. Briefly, we collected TC data using a multisource approach to increase data completeness. Information on confirmed TC cases was abstracted through medical records and pathology reports of patients who have had thyroidectomy between 1 January 1993 and 31 December 2013, in all healthcare services in the district of Oran. Patients included in the cohort were permanent residents of the district of Oran at the time of their TC diagnosis, with histologically confirmed TC. Variables collected included age at TC diagnosis, sex, tumor size, and histologic type [8]. To re-ascertain histological diagnosis, a pathologist conducted a central review of pathology reports for all TC cases included in the study.

Case definition and inclusion criteria

TC (ICD-10 topographic code C73) diagnosis is based on microscopic examination of thyroid specimen. The incidence date was defined according to recommendations of the European Network of Cancer Registries. Patients included in the analysis were those diagnosed with TC between January, 1, 1993 and December 31, 2013, and who were permanent residents of Oran at the time of their TC diagnosis. All TC cases were classified according to the International Classification of Diseases for Oncology, third edition (ICD-O-3), and grouped into 6 major groups: PTC (ICD-O-3 codes: 8050, 8260, 8340-8344, 8350, 8450-8460), Follicular thyroid carcinoma (FTC) (ICD-O-3 codes: 8190, 8290, 8330-8335), Anaplastic thyroid carcinoma (ATC) (ICD-O-3 codes: 8012, 8020-8035, 8300), Medullary carcinoma of the thyroid (MCT)(ICD-O-3 codes: 8345, 8346, 8347, 8510-8513), carcinomas with no other specification (carcinomas NOS) (ICD-O-3: 8000, 8010-8015, 8230, 8337), and other specified carcinomas (ICD-O-3: 8052, 8333, 8337, 8070, 8140, 9591, 8800) **(Table 1)**.

ICD-O-3 codes					
PTC	FTC	ATC	MCT	Carcinomas NOS	Other specified carcinomas
8050	8190	8012	8345	8000	8052
8260	8290	8020-8035	8346	8010-8015	8333
8340-8344	8330-8335	8300	8347	8230	8337
8350			8510-8513	8337	8070
8450-8460					8140
					9591
					8800

Table 1: International Classification of Diseases for Oncology, third edition (ICD-O-3).

Statistical analysis

Variables of interest were age at TC diagnosis in years, analyzed as a continuous variable and categorical (<45 years versus ≤ 45 years), sex, incidence date, period of TC diagnosis grouped in four 5-year groups (1993-1997, 1998-2002, 2003-2007, 2008-2013), histologic types (PTC, FTC, ATC, MCT, other carcinomas specified, and carcinomas NOS), and tumor size in its largest diameter, in millimeters. When multimodality was present the size of the largest tumor was taken into account in the analysis. Tumor size was analyzed as a continuous variable and then sub classified into categories: 4 categories (≤ 10 mm, 11-2 mm, 21-40 mm, and >40 mm), and 2 categories (≤ 20 mm and >20 mm).

Age-specific and age-standardized incidence rates

TC age-specific and age-standardized incidence rates (ASR) were calculated by the direct standardization method using the world standard population as a reference. Incidence rates were expressed per 100000 person-years using SEER*Stat Version 6.4.4. TC incidence rates were reported if there were at least 10 cases. ASRs were computed for the entire cohort, by sex, for the periods 1993-1997, 1998-2002, 2003-2007, 2008-2013,byage group, histotype, and tumor size. The Join point regression program (Join point regression software, Version 4.7.0.0), of the Surveillance Research Program, United States National Cancer Institute, was used to assess the temporal trends in the age-adjusted rates over the 21-year period according to the method proposed by Kim et al. Join point analysis models were based on regression with age-standardized incidence rates as the dependent variables and with year as the independent variable. Join point regression analysis was also used to calculate incidence trends for age-specific rates of 5-year age groups. The analysis included logarithmic transformation of the rates, standard error, maximum number of five join points, and minimum of four years between two join points. This approach helped identify possible join points where a significant change in the trend occurred. The method identifies join points based on regression models with 0-5 join points. The final model selected was the most parsimonious, with the APC based on the trend within each segment. The same approach was used to calculate incidence trends of ASR for all TC patients, for women and men overall, for women and men aged <45 years and ≤ 45 years, for all histotypes, with the assumption that rate of increase or decrease is constant over the period studied. Because log-transformation cannot be performed in cases of ASR=0 (when no cases were observed in a given year, the zero value of the ASR in a given year was replaced by 1 per 1000 000. To describe time trends we used the expressions “significant increase” or “significant decrease” when the slope of the trend was statistically significant ($p<0.05$). For statistically non-significant trends ($p>0.05$), we used the terms “stable” for APC between -0.5%and 0.5%, “statistically non-significant increase” (for APC>0.5%), and “statistically non-significant decrease” (for APC<-0.5%). All statistical tests were two-sided.

Results

Cohort general characteristics

From 1993 to 2013, 7 521 thyroid surgeries were performed in permanent residents of Oran Of these 1443 was TC (19.3%). Women accounted for 1248 (86.5%) (Female-to-male sex-ratio=6.4:1). Mean age at diagnosis (± SD) was 44.3 ± 15.3 years and mean size of TC (± SD) was 26.8 ± 17.5 mm. Among all TC patients, 20.7% hadmicrocarcinomasand14.8% had carcinomas >40 mm. Small carcinomas (≤ 20 mm) accounted for 50.4%. The most common histotypes were PTC (58.3%), FTC (29.7%), ATC (4.1%), and MCT (0.8%).

Thyroid cancer age-adjusted incidence rates by sex and tumor characteristics

The overall sex and age-specific, histology-and size-specific TC ASRs for the period 1993 to 2013. Overall the ASR was 11.7per 100000 for females and 2.0 per 100000 for males. Significantly higher ASRs were observed for TC patients ≥ 45 years (13.6per 100000; 95% CI, 12.6-14.7) compared with their younger counterparts (4.3per 100000; 95% CI, 4.0-4.6). Higher ASRs were observed for PTC (3.9; 95% CI, 3.7-4.2; p<0.05) and FTC (2.0; 95% CI, 1.8-2.2), whereas lower ASRs were observed for ATC (0.2; 95% CI, 0.1-0.3) and MCT (0.1; 95% CI, 0.0-0.1).When taking into account TC size, ASRs for small (≤ 20 mm) vs. larger carcinomas (>20 mm) were similar.

Age-adjusted time trends according to age and histology

ASRs for TC across are 4 time periods, by sex, age, major histologic types and tumor size. For the entire cohort ASRs increased from 2.6 in 1993-1997 to 7.8 in 2008-2013 with a higher and significant APC during the period 1998-2002 (APC: +22.0%; p<0.05). The ASRs were consistently higher for women compared with men across the 4 time periods and increased from 4.5 in 1993-1997 to 13.4 in 2008-2013 in women (APC: +3.72%; p<0.05), with the highest APC observed for the period 1998-2002 (APC: +20.4%; p<0.05). In men ASR has quadrupled from 1993 to 2002, and then stabilized from 2002 onwards. Higher ASRs were observed in patients aged ≤ 45 years across the four time periods, but significantly higher increases over time in ASRs occurred in patients <45 years (APC:+4.30%; p<0.05). A striking observation is the higher and significant APC in the two age categories in 1998-2002 (+16.5% and +25.9%).

The change in TC incidence was mostly due to increased ASRs of PTC, which accounted for 78.4% of the overall increase, from 1.0 (95%CI, 0.7-1.4 in 1993-1997) to 5.3 (95%CI, 4.9-5.9 in 2008-2013) (APC:+7.37% p<0.05). Increases in ASRs were observed for FTC until 1998-2002 (1.1 to 3.1), with a downturn starting in 2003-2007 (2.6to 1.7in 2008-2013) (APC: -3.78%; p<0.05). Higher and significant APCs were observed in 1998-2002 for PTC (+21.4%) and FTC (+19.6%). Based on a few TC cases, ASRs for all other histotypes did not vary with time.

Tumor-size specific time trends

ASRs of all TC size categories increased with time except for carcinomas >40 mm. Microcarcinoma increased 10-fold (APC: +13.10%; p<0.05), carcinomas 11-20 mm increased 5.8-fold (APC: +9.15%; p<0.05), carcinomas 21-40 mm increased 4.8-fold (APC: +4.80%; p<0.05), and carcinomas >40 mm increased 3.0-fold, although not significantly (APC: +4.40%; p>0.05). When taking into account tumor size categories ≤ 20 mm and >20 mm, there was a 7.1-fold increase in carcinomas ≤ 20 mm (APC: +10.34%; p<0.05) and a 4.1-fold increase in carcinomas >20 mm (APC: +4.53%; p<0.05). Increased ASRs over time were observed for carcinomas ≤ 20 mm in women, with the highest increase for micro carcinomas, whereas in men increased ASRs were observed for all tumor size categories except for micro carcinomas (data not shown). ASRs for PTC increased significantly in females for all size groups in particular microPTC (APC: +16.7%; p<0.05), whereas in males APCs were significant for carcinomas >10 mm. In males higher APC was observed for carcinomas >40 mm (+20.24%; p<0.05) compared with APC for PTC >40 mm (+10.78%; p<0.05), which may reflect a trend towards increased ASRs over time of the other TC histologic subtypes.

Age-specific time trends

The age-specific trends overall and for histologic subtypes. For women the overall age-specific ASRs gradually increased until age 50-54 years and remained high until age 70-74 years, whereas for men the age-specific ASRs rose slowly with age to peak at age 70-74 years. These age-specific patterns were also observed in women and men with PTC [9]. The female-to-male rate ratios were higher at 20-34 and 50-54 years. From 1993 to 2013 TC incidence rates tripled in Oran, mostly driven by an increased incidence of PTC, while that of FTC significantly decreased. ASRs were higher in females compared with males and in TC patients ≤ 45 years old across the 4 time periods; however, the increase in ASRs over time was only significant for TC patients aged<45 years. Increased ASRs were observed in all tumor size categories for PTC, except micro PTC in men [10]. The most striking finding was the increased APC during the period 1998-2002, for women, in both age groups, for PTC and FTC.

Discussion

To date, our study is the first in North Africa to use population-based data to describe TC incidence trends according to sex, age, histotypes, and tumor size. In our study the observed ASRs of 11.7 per 100 000 in women and 2.0 per 100 000 in men are in the range of western countries with high ASRs such as France, Italy and the USA, but about 2-fold higher than the ASR observed in the district of Setif in eastern Algeria [11]. Higher ASRs of TC in females compared with males have also been reported in Europe, North America, and in Setif in Algeria. Our findings of ASRs varying with age are also consistent with studies showing higher ASRs at older ages. The APC observed in the residents of Oran is in the range of countries with moderate acceleration of the incidence such as China, Australia, Canada and the United Kingdom [12]. Comparing APCs in females and

men in the district of Setif and that of Oran, similarities were observed in men in both districts, while for females the APC in Setif was virtually higher than that experienced by females in the district of Oran. ASRs of PTC and TC ≤ 20 mm over time is also consistent with previously reported trends. The upward trend in ASRs of PTC >40 mm has also been observed in North America and France.

Exposure to ionizing radiation during childhood has been hypothesized to have caused the observed upward trends for TC incidence over recent decades, in particular for PTC. The link between nuclear tests carried out in the early 1960s in Algeria, the over-use of medical imaging, and their role in the cancer epidemic observed in the country over the last three decades is currently debated. However, no data is available in Algeria to validate such assumptions [13].

The disparity of TC incidence by sex has been attributed to hormonal factors, and the greater use of healthcare services by females compared with males. The disparities in access to healthcare services that have been suggested to influence TC incidence and trends should not influence TC rates in Oran because the general population has free access to healthcare services and benefits from universal insurance coverage since 1974 [14]. The most striking observation is the increased ASRs among females only for PTC and FTC and carcinomas >20 mm during the period 1998-2002. A few factors can explain this trend: the evolution of medical practices with the advent of thyroid ultrasound in the early 1990s and fine needle aspiration in 1998, and the dramatic expansion of the private medical sector since the early 1990s. Furthermore we suspect that the gradual return to greater social stability and security in the early 2000s nationwide may have encouraged the general population to seek actively medical care, in particular females. The increased incidence among females compared with males is consistent with the fact that females in Oran tend to take up medical care more readily than males. In a previous investigation the fortuitous discovery of a mass in the neck was reported by 83.1% of females and 69.8% of males. We hypothesize that a detection effect may have caused, at least in part the observed increase in TC incidence during this time period. In males, however, the higher APC for TC >40 mm cannot be attributed to medical practice and increased detection. Known or still unknown risk factors for TC played a role in these observed trends [15]. Furthermore, the increased APC for all histologies combined was higher than the APC for PTC >40 mm, suggesting that the incidence of TC of histologies other than PTC have also increased.

PTC accounted for 78.4% of the overall observed TC increase, whereas incidence of FTC declined over time. A diagnostic effect alone would have increased all histologic types similarly, such as the increase observed for the period 1998-2002. Other risk factors may have affected the observed trends [16]. In Algeria, apart from iodine intake, obesity, and diabetes information on the prevalence and trends of other risk factors is scarce.

Algeria is known for its history of iodine deficiency and goiter endemicity. Iodine status has been suspected to increase the risk of TC among females compared with males, potentially explaining the observed difference in incidence by sex in Oran [17]. Furthermore, differences in risk according to histotype have been associated with iodine intake. In Africa FTC histotype predominates in regions with iodine deficiency. When iodized table salt is introduced in a population with a previous history of iodine deficiency the PTC-to-FTC ratio increases within 15 to 40 years, with no real increase in the overall TC incidence. In 1967 the program of table iodized-salt was implemented in Algeria. The increased PTC-to-FTC ratio with time observed in Oran might be due to a shift from iodine deficient to iodine sufficient-to-excessive supplementation status. In 2006-2009, a study assessed iodine status in a group of females in the district of Oran and found that the UIC was in the optimal range. Considering the 15 to 40 year latency for the clinical expression of past phases of iodine nutrition, we assume that the low ratio of PTC-to-FTC in the first period of the study (1993-1997) reflects the iodine-deficiency period, whereas the increase in the ratio of PTC-to-FTC in the later period reflects the late effects of iodine supplementation. Among TC patients 90.9% had goiter or thyroid cold nodules at presentation, a characteristic commonly observed in populations with excessive nutritional iodine intake. In this context the increased number of large thyroid surgeries, may have led to the discovery of small carcinomas in the Oran population as shown elsewhere [18].

Obesity increases the risk of PTC especially in women. In our cohort, only 20.7%of patients had anthropometric data documented. Among these, 21.3%were obese and 4% were overweight. The prevalence of obesity has increased in Algerian adults, with rates of 30.1% (95% CI: 27.8%-32.4%) in women and 9.1% (95%CI: 7.1%-11.0%) in men aged 35-70 years in 2010.

About 50% of patients with PTC have diabetes. Between 1998 and 2009 the prevalence of diabetes has increased from 7.1% to 10.5%among adults in Oran [19].

Strengths of this study include a sizable and unselected TC cases diagnosed in a homogeneous population. We have used multiple sources of TC information to achieve a high level of data completeness and validity. Only TC cases microscopically verified and those with validated place of residence were included in the cohort. In the course of data collection, special effort was made to retrieve all information on demographics and anatomopathological features including tumor size. In 1988 the WHO new revision of morphologies classified the papillary thyroid cancer of follicular variant as PTC. However since our cohort included TC cases diagnosed between 1993 and 2013, this revision cannot have affected the observed trends for PTC [20]. Information on histologic types was complete and accurate, with lower frequencies of TC cases poorly specified in the most recent years, which reflects improved classification of poorly specified histology by pathologists over time. Our study had a few data limitations that should be stated. We could not retrieve all pathology reports of TC patients diagnosed in the 1990s, and all information on tumor size. However, we do not expect these limitations to have altered our study because the observed trends are consistent with a context of iodine deficiency and high prevalence of nodular goiter in the cohort. Furthermore, histology-specific and size-specific incidence trends are similar to data published elsewhere.

Conclusion

Within 21 years, the incidence of TC has tripled in Oran. The most important findings were a rise in TC incidence mostly due to increased incidence of PTC, in particular PTC of small size in women and larger ones in men. Changes in medical activity, improvements in education, along with lifestyle and environmental factors may have played a role. The increasing PTC-to-FTC ratio observed during the study period suggests that the introduction of iodized-salt in the late 1960s might have caused the observed trends. The understanding of TC etiology is still limited. Future large-scale studies assessing risk factors and host susceptibility are needed to clarify the effect of iodine supplementation program and other factors on PTC and FTC trends, and mechanisms that promote the development of TC, and lead to the implementation of prevention programs.

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