Trends in thyroid carcinoma among thyroidectomy patients: a 12-year multicenter study

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BACKGROUND: Thyroid malignancy, the most diagnosed cancer of the endocrine system, represents 2% of all malignancies worldwide. The increasing incidence of thyroid cancer has been linked to the increasing sensitivity of modern diagnostic methods which overdiagnosis small thyroid tumors.

OBJECTIVES: Assess the distribution and trends in thyroid cancer among thyroidectomy patients.

DESIGN: Descriptive, based on medical record review.

SETTINGS: Two tertiary care centers in Riyadh.

PATIENTS AND METHODS: We included patients who underwent thyroid surgery from January 1, 2004 to December 31, 2016 who ranged in age from 9–90 years regardless of initial diagnosis.

MAIN OUTCOME MEASURES: Distribution of thyroid carcinomas by type, age and sex and trends over the time period.

SAMPLE SIZE: 979 patients.

RESULTS: Of 979 patients, 84.5% were <55 years old, with the majority being female. Thyroid malignancy ranked second to benign tumors, and the most common type of thyroid cancer was papillary thyroid carcinoma (91% of malignant tumors), followed by follicular thyroid cancer (4.7% of malignant tumors). After thyroid microcarcinomas were isolated from the sample and studied separately, we found the overall trend for thyroid cancer to be stable, and that the annual increases in rates were due to increased diagnosis of thyroid microcarcinoma in the period from 2010 to 2016.

CONCLUSION: Our study shows that increases in thyroid cancers may be attributed to a rise in the rates of diagnosis of thyroid microcarcinomas.

LIMITATIONS: The main limitation is the retrospective nature of this design. Also, a multicenter collaboration would prove beneficial in evaluating the trends of thyroid cancer in Saudi Arabia on a much larger scale.

CONFLICT OF INTEREST: None.
TRENDS IN THYROID CANCER

Thyroid malignancy, the most diagnosed cancer of the endocrine system, represents 2% of all malignancies worldwide. Incidence rates vary according to age, sex, geographic populations, and ethnic groups. The worldwide incidence rate for thyroid cancer falls within a wide range, according to the International Agency for Research on Cancer (IARC). Regions with the highest thyroid cancer rate include the Pacific Islands (Hawaii), Central America, Japan, East Asia (Korea, Hong Kong), Kuwait, and Iceland.

In Saudi Arabia, an increase in the incidence of thyroid cancer has been observed in all the Saudi Cancer Registry reports published since 2008. Thyroid cancer comprised 6.8% of all newly diagnosed cases in 2008, 7% in 2010, and 7.6% in 2013. This rise in incidence rates has been linked to an increased overall diagnosis of thyroid microcarcinomas. This descriptive study aimed to estimate the frequency of thyroid cancer among patients undergoing thyroid surgery and determine whether the increase in thyroid carcinomas was due to an increase in cancer cases or due to an increased detection of microcarcinomas.

PATIENTS AND METHODS
We performed a retrospective chart review that included patients who underwent thyroid surgery for different etiologies. Patients data were obtained from two tertiary care hospitals in Riyadh, Saudi Arabia. We reviewed all data in databases from both institutions, and in paper and electronic medical records. All patients who underwent a total or hemi-thyroidectomy between 1 January 2004 and 31 December 2016 were included regardless of initial diagnosis, age, or sex. Patients lost to follow-up or those missing a detailed pathology report were excluded. The primary sources of diagnostic information were obtained from initial fine-needle aspiration (FNA) results and final pathology reports post-surgery. To ensure consistency, FNA and histology results were coded and staged using the Bethesda System for Reporting Thyroid Cytopathology (BSRTC) and the World Health Organization international classification of cancer, respectively. We treated microcarcinomas as a separate entity in our analysis since we wanted to observe its trend independently. The study was approved by the Institutional Review Boards from both centers. Descriptive statistics and frequencies were performed using SAS version 9.3 (SAS Institute Inc., Cary, North Carolina).

RESULTS
We examined the records of 979 patients who met the inclusion criteria. Most patients (85%) were <55 years old, and the majority were females (69%) (Table 1). The most common diagnosis was benign thyroid disease, and most subjects were identified as euthyroid, regardless of the pathology. Of the 509 benign thyroid diseases, multinodular goiter (MNG) followed by autoimmune thyroiditis were the most common benign pathology. The most common type of thyroid cancer was papillary thyroid carcinoma followed by follicular thyroid cancer. Other cancer types are described in Table 2. Microcarcinoma was identified in 170 (17.3%) of our study patients, with papillary thyroid microcarcinoma being the most prevalent subtype. Stratification of the pathological diagnoses according to sex indicated that females showed the highest frequency across all pathology levels. Moreover, female patients who were <55 years old had the highest frequency of thyroid disease, whether benign or malignant (Table 3). Most FNA results were classified as category II (n = 412, 42.1%) of the BSRTC system, followed by categories III (n = 238, 24.3%), VI (n = 148, 15.1%), and IV (n = 73, 7.5%).

Our initial analysis revealed that the overall trend of thyroid cancer was increasing. We looked closely at the sample of patients included from the years 2010 to 2016, since data prior to 2010 was too small to observe a temporal trend per year. We then divided those 938 patients into three categories as follows: benign disease, thyroid cancer, or thyroid microcarcinoma. After sub-classifying thyroid microcarcinoma into a separate category, we found the disease trend for new cases of thyroid cancer to be stable over the period from 2010 to 2016 (32%) (Figure 1). However, the trend in the number of cases of thyroid microcarcinoma increased, causing an overall increase in the incidence of thyroid cancer.

DISCUSSION
An increasing incidence in thyroid cancer has been reported in Saudi Arabia over recent decades. In a report concerning the incidence of thyroid cancer in King Faisal Specialist Hospital and Research Center from 2000 to 2010, thyroid cancer was identified as the second most common malignancy among females, comprising approximately 9% of all malignancies and accounting for approximately 11% of all newly diagnosed cancers among females in Saudi Arabia in 2008. Moreover, the 2008 Saudi Cancer Registry report showed that thyroid cancer accounted for 6.8% of all newly diagnosed cancers that year, making it the second most common cancer among females and the thirteenth most common among males, with a male to female ratio of 28:100. In 2010, a further report by the Saudi Cancer Registry revealed that thyroid cancer accounts for 6.8% of all newly diagnosed cancers that year, making it the second most common cancer among females and the thirteenth most common among males, with a male to female ratio of 28:100. In 2010, a further report by the Saudi Cancer Registry revealed that thyroid cancer accounts for 6.8% of all newly diagnosed cancers that year, making it the second most common cancer among females and the thirteenth most common among males, with a male to female ratio of 28:100.
### Table 1. Patient clinical characteristics, 2004–2016 (n=979).

| Characteristic                  | Female | Male |
|--------------------------------|--------|------|
| Female sex                     | 788 (80.5%) |
| Age (years) Overall            | 41.1 (13.2) |
| <55                            | 827 (84.5%) |
| ≥55                            | 152 (15.5%) |
| Body mass index (kg/m²)        | 30.85 (7.05) |
| Thyroid pathology              |         |
| Benign                         | 509 (52%) |
| Malignant                      | 300 (30.6%) |
| Microcarcinoma                 | 170 (17.4%) |
| Thyroid function               |         |
| Euthyroid                      | 773 (79%) |
| Hyperthyroid                   | 50 (5.1%) |
| Hypothyroid                    | 151 (15.4%) |
| Missing                        | 5 (0.5%) |
| Thyroiditis in pathology       |         |
| Yes                            | 328 (33.5%) |
| No                             | 635 (64.9%) |
| Not mentioned by pathologist   | 16 (1.6%) |
| Multifocality                  |         |
| Single focus of carcinoma      | 233 (23.8%) |
| Multiple foci of carcinoma     | 201 (20.5%) |
| Not mentioned by pathologist   | 39 (13%) |

Data are mean (standard deviation) or number (percentage). Female:male ratio 4.13

### Table 2. Distribution of thyroid diseases, from 2004 to 2016, based on pathological diagnosis (n=979).

| Category                              | n (%)       |
|---------------------------------------|-------------|
| **Benign**                            |             |
| Multinodular goiter                   | 509 (51.9)  |
| Autoimmune thyroiditis                | 397 (40.5)  |
| Follicular adenoma                     | 48 (4.9)    |
| Grave’s disease                       | 31 (3.1)    |
| Follicular neoplasm of undetermined malignant potential | 10 (1.02) |
| Hürthle cell adenoma/nodule           | 7 (0.7)     |
| Atypical Hürthle cell nodule          | 1 (0.1)     |
| Fibromatosis                          | 1 (0.1)     |
| Follicular neoplasm with florid Hashimoto | 1 (0.1) |
| Non-invasive follicular thyroid neoplasm with papillary like features | 1 (0.1) |
| Non-necrotizing granuloma             | 1 (0.1)     |
| Plasma infiltrate                     | 1 (0.1)     |
| **Malignant**                         |             |
| Papillary thyroid cancer              | 273 (27.8)  |
| Follicular thyroid cancer             | 14 (1.4)    |
| Hürthle cell cancer                   | 4 (0.4)     |
| Medullary thyroid cancer              | 4 (0.4)     |
| Anaplastic thyroid cancer             | 2 (0.2)     |
| Poorly differentiated cancer          | 2 (0.2)     |
| B-cell lymphoma                       | 1 (0.1)     |
| **Microcarcinoma**                    |             |
| Papillary thyroid microcarcinoma      | 164 (16.7)  |
| Follicular thyroid microcarcinoma     | 6 (0.6)     |

Data are number (percentage).

### Table 3. Distribution of thyroid diseases by age and sex (n=979).

| Thyroid diseases categories | Thyroid diseases categories | Male | Female |
|-----------------------------|-----------------------------|------|--------|
|                            | <55 years                   | ≥55 years | <55 years | ≥55 years |
| Benign                      | 66 (6.7)                    | 18 (1.8) | 363 (46.1) | 62 (37) |
| Malignant                   | 56 (5.7)                    | 16 (1.6) | 201 (20.5) | 27 (2.8) |
| Micro-carcinoma             | 29 (3)                      | 6 (0.6)  | 112 (11.4) | 23 (2.3) |
| Total                       | 151 (15.4)                  | 40 (4.1) | 676 (69.1) | 112 (11.4) |

Data are number (percentage).
cases accounted for 7.0% of all newly diagnosed cases and was the second most common cancer among females and the twelfth most common cancer among males.²

Our study was conducted on a sample pooled from two tertiary care center registries in Riyadh, Saudi Arabia. These hospitals accept patient referrals from across the country; therefore, the data collected does not represent only one city, but gives an estimated prevalence in Saudi Arabia. The data collected from 2004 to 2016 revealed that more patients who had undergone thyroid surgery had benign thyroid disease. In comparison to international studies that report that thyroid cancer comprises between 7% and 15% of all thyroid nodules,¹¹ the records in our study showed a higher proportion of thyroid cancer (30.8%). This finding can be attributed to selection bias due to the eligibility and referral acceptance systems at such medical centers, where accepting new referrals for patients with thyroid disease is limited to those in a higher risk group. Patients <55 years showed a higher prevalence of thyroid cancer in both sexes, with males having a higher proportion of thyroid cancer and females having a higher proportion of benign disease. Whether this study is representative of an increasing incidence of thyroid cancer in the whole country is difficult to establish. An extended collaboration between hospitals throughout the country is needed to determine the actual incidence of thyroid cancer and obtain a better understanding concerning the extent of the disease over time.

As noted previously, the worldwide incidence rate of thyroid cancer varies widely. In the United States, thyroid cancer incidence rates have increased dramatically over the past three decades, becoming the fifth most common cancer diagnosed among women.⁸ In Canada, thyroid cancer is the seventh most common cancer, with an estimated 5650 new thyroid cancer cases diagnosed in 2012. The incidence for this cancer is increasing more rapidly than any other cancer.¹²

Since 2011, there was an increase in ultrasound examination of the thyroid in Korea, which led to an increased diagnosis of thyroid cancer, the majority of which were found to be papillary microcarcinomas (PMC), leading to an increase in the number of thyroidectomies. However, mortality due to thyroid cancer remained unchanged,¹³,¹⁴ suggesting thyroid cancer overtreatment. Despite being considered true cancers with cancerous characteristics, PMCs were considered to have a limited proliferation ability, and it has been suggested that they are self-limiting.¹⁴ Thyroid microcarcinoma is a low risk tumor with benign behavior. Data from multiple studies confirm that active surveillance is safe and did not alter the outcome of small thyroid carcinoma, and only a small number will progress to a clinically significant disease.¹⁵ Also, the estimated lifetime disease progression probabilities of papillary microcarcinoma during active surveillance vary greatly according to the age at presentation and older patients have lower disease progression rates than younger patients.¹⁶

An observational trial by Ito et al further confirmed the above findings. They observed patients with PMCs over several decades and found that only 8% showed significant growth within 10 years with no mortality from these thyroid cancers in their entire sample comprised of 1235 patients.¹⁷ From these data, there was no observed reduction in thyroid cancer-related mortality achieved with surgical resection of the PMCs and the American Thyroid Association does not recommend FNA for any thyroid that is smaller than 1 cm.¹⁸ Therefore, there was no justification for the early detection of and surgery for small cancers, because the majority of these are believed to be of a self-limiting nature.¹⁴

It has been proposed that overdiagnosis or the detection of tumors that are not clinically relevant has been responsible, in part, for the increase in incidence in thyroid cancer. Increased usage of highly sensitive imaging modalities involving technologies that are capable of detecting micropapillary thyroid cancer (<1 cm), such as computed topography scan imaging and ultrasonography, can plausibly be considered to have led to an overdiagnosis of thyroid cancer. It has been estimated that, due to over-diagnosis, as much as 50%
of the increase in papillary thyroid cancer incidence has been observed since the 1980s. This is important to evaluate as it could lead to overtreatment of clinically irrelevant tumors, subjecting patients to all possible complications of thyroid surgery. The results in this study confirm these suggestions in that we find the overall increase in the diagnosis of thyroid cancer to be directly linked to the increase in diagnosing microcarcinomas.

In conclusion, the increasing rate of thyroid cancer could be attributed to the increasing efficiency of diagnosing small thyroid tumors, which was observed in our study. Our analysis revealed an increasing trend of thyroid microcarcinomas within the past 7 years as compared to a stable incidence of thyroid cancer. This finding is important since over-diagnosing thyroid microcarcinomas may add to the overall morbidity of thyroid disease by aggressively treating low-risk tumors.

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