Rising incidence of thyroid cancer in Singapore not solely due to micropapillary subtype

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ABSTRACT

INTRODUCTION The annual incidence of thyroid cancer is known to vary with geographic area, age and gender. The increasing incidence of thyroid cancer has been attributed to increase in detection of micropapillary subtype, among other factors. The aim of the study was to investigate time trends in the incidence of thyroid cancer in Singapore, an iodine-sufficient area.

MATERIALS AND METHODS Data retrieved from the Singapore National Cancer Registry on all thyroid cancers that were diagnosed from 1974 to 2013 were reviewed. We studied the time trends of thyroid cancer based on gender, race, pathology and treatment modalities where available.

RESULTS The age-standardised incidence rate of thyroid cancer increased to 5.6/100,000 in 2013 from 2.5/100,000 in 1974. Thyroid cancer appeared to be more common in women, with a higher incidence in Chinese and Malays compared with Indians. Papillary carcinoma is the most common subtype. The percentage of papillary microcarcinoma has remained relatively stable at around 38% of all papillary cancers between 2007 and 2013. Although the incidence of thyroid cancer has increased since 1974, the mortality rate has remained stable.

CONCLUSION This trend of increase in incidence of thyroid cancer in Singapore compares with other published series; however, the rise seen was not solely due to micropapillary type. Thyroid cancer was also more common in Chinese and Malays compared with Indians for reasons that needs to be studied further.

KEYWORDS

Thyroid – Cancer – Epidemiology

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Introduction

Thyroid cancer is the most common endocrine malignancy and accounts for less than 1% of all malignancies. The annual incidence is estimated to be 0.5–10/100,000 population in the United States. In Singapore, thyroid cancer is the eighth most common cancer in women, with an annual incidence of 1100 cases/year.¹ Thyroid cancer can be differentiated into papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), medullary thyroid carcinoma (MTC) arising from the parafollicular cells and anaplastic thyroid carcinoma (ATC).

The incidence of thyroid cancer is increasing globally and is the fastest rising cancer in women.^{2–5} The exact cause of the increase in the incidence of thyroid cancer remains a subject of debate. Factors implicated in the rising incidence include increased screening,⁶ increased diagnostic imaging and pathological detection of small cancers.^{2,7} Population screening with ultrasound of the thyroid is not recommended in Singapore, unlike in South Korea. In Korea, screening led to an increase from 12.2 cases/100,000 population in 1993–1997 to 59.9 cases/100,000 in 2003–2007 among

people aged 15–79 years.^{8,9} It may be the case, however, that incidence is truly rising,^{10,11} which may be due to an increase in unrecognised carcinogens.¹²

The first reported study from Singapore on the incidence of thyroid cancer between the years 1968 and 1977 was in 1982.¹⁵ The aim of our study was to investigate the time trends in the incidence of thyroid cancer in Singapore from 1974 to 2013 using the National Cancer Registry. We also looked at the trends in pathology, treatments, mortality and racial differences, as Singapore has a population made up of various ethnicities.

Materials and methods

This was a retrospective analysis of 5496 thyroid cancers treated in Singapore between the years 1974 and 2013. The anonymised data were obtained from the Singapore Cancer Registry and included the patients treated in all hospitals in Singapore. The Singapore Cancer Registry was started in 1968 to provide information on cancer patterns and trends in Singapore. However, thyroid cancer data were only available from 1974.

Demographic data and data on tumour subtype, size and mortality were available for the period while additional data on tumour size and treatment were only available from 2003. The histological type of all cases was coded according to the International Classification of Disease for Oncology (ICD-O), 3rd edition, as follows: papillary (8260/3), follicular (8330/3), medullary (8345–8346/3), and anaplastic (8012, 8020–8021/3). As papillary thyroid cancer accounted for majority of the cases, a sub-analysis was performed in relation to size and this information was available only from 2007 for 1334 patients. The size of PTC was categorised as less than or equal to 1 cm (microPTC), 1.1–2 cm, 2.1–5 cm and greater than 5 cm. Data on staging were not available for the cohort and hence were not included in the analysis.

Treatment modalities were thyroidectomy (data not specified as total or partial), adjuvant radiotherapy, adjuvant chemotherapy, palliative chemoradiotherapy or no treatment. The data pertaining to treatment for thyroid cancer were only available from 2003 and the timeframe of the adjuvant treatment following surgery was also not available. For all included cases, the overall incidence and mortality for each year were calculated and age-adjusted to the world standard population.

The incidence rates were age adjusted and expressed per 100,000 individuals and the rates were calculated over time for the various histological categories of thyroid cancer. The association between two factor variables was estimated using Chi square analysis. Statistical analysis was performed using SPSS version 21. All tests were two-sided and a *P* value less than .05 was considered statistically significant.

The project was approved by the Institutional Research Board (DSRB:2014/00466).

Results

The age-standardised incidence rate (ASR) of thyroid cancer increased by 224% (2.5/100,000 in 1974 to 5.6/100,000 in 2013). The ASR of men was 1.5/100,000 in 1974 compared with 2.7/100,000 in 2013 (increased by 180%) while that for women was 3.7/100,000 in 1974 compared with 8.4/100,000 in 2013, increased by 227% (Fig 1). Thyroid cancer affected women more than men by ratio of three to one. The median age at diagnosis was 64.5 years for men and 46 years for women in 1974 compared with 52 years and 51years, respectively, in 2013. The increased incidence was predominantly seen in Malays, in whom the incidence increased by 290% (2.1/100,000 in 1974 to 6.0/100,000 in 2013) as compared with Chinese and Indians (Fig 2).

The distribution of histological categories was 75% papillary, 17% follicular, 2% medullary, 1% anaplastic and 5% others (lymphoma and metastasis). The follicular, medullary and anaplastic cancer showed no change in incidence over time. The increase in incidence of thyroid cancer is primarily due to increase in incidence of papillary subtype and this increase was mainly due to the increase in diagnosis of smaller cancers (defined as those less than 5 cm; Fig 3).

The data pertaining to tumours size in PTC were only available from 2007 and when this subgroup was analysed, microPTCs accounted for about 38% of the total cancers, tumours of 1.1–5 cm accounted for 58% and those more than 5 cm comprised 4%. Both micropapillary cancers and intermediate size cancers (up to 5 cm) showed an increase in ASR from 1 to 1.76 for microPTCs and 0.68 to 1.57 for tumours of 1.1–5 cm. The ASR of the larger cancers decreased from 0.19 to 0.12 over the study period. However,

Figure 1 Age-standardised incidence rate of thyroid cancer by sex of patient

Figure 2 Age-standardised incidence rate of thyroid cancer per ethnicity over the study period

Figure 3 Incidence of papillary thyroid cancer per size of tumour

the percentage of patients diagnosed with micropapillary carcinoma remained the same (36.3% in 1974 vs 38.6% in 2013, $P = 0.21$; Table. 1).

In relation to treatment data available from 2005 onwards, 1293 (95%) patients underwent surgery, 52 patients (4%) underwent adjuvant radiotherapy following surgery for local recurrent and persistent disease and 11 patients (0.9 %) received palliative chemotherapy following surgery for

advanced metastatic disease. Details pertaining to adjuvant radioiodine ablation were not available and hence were not analysed. Similarly, the data on the exact type of surgery and nodal dissection details were not captured in the registry; 13 patients (1%) only underwent radiotherapy without any form of surgery with locally advanced disease and 59 (4%) patients chose not to have any form of treatment. Although the incidence of thyroid cancer increased from 1974, the

Table 1 The percentage of micropapillary in the cohort of thyroid cancers is highlighted with no significant increase over the study period.

Year	Total papillary thyroid carcinoma (n)	Micropapillary thyroid carcinoma (%)
2007	178	36.3
2008	168	39.5
2009	162	32.3
2010	209	44.0
2011	234	32.7
2012	259	41.5
2013	278	38.7

mortality rate remained stable (Fig 4). The overall cause specific mortality for the whole cohort was 2% (114 deaths) over the period.

Discussion

The first study that investigated the incidence of thyroid cancer in Singapore was in 1982 by Lee.¹⁵ The crude incidence rates were reported to be 1/100,000 population for men and 3/100,000 for women. The author also showed a decline in the incidence among women over the period 1968–1977 and no difference in the incidence between the various ethnic groups. Our study of the incidence of thyroid cancer over the period 1974 to 2013 showed a rising incidence of thyroid cancer, mainly from papillary cancer with a two- to threefold increase in ASR; the rise being the highest for tumours up to 5 cm. Racial disparity showed that Malays had the highest rise, followed by Chinese and Indians. The findings reported here are similar to other published series.^{14–17}

In this study, micropapillary cancers showed an increase of 80%; however, the percentage of micropapillary cancers diagnosed to the ratio of total cancers remained nearly the same (around 36–38%) over the time studied. Cramer et al. showed a consistent rate of increase for micropapillary cancers at 19% per year and larger cancers between 10–12% per year.¹⁶ Our study showed an increase at an average of about 10% per year. Some of the reasons attributed to the increase of smaller cancers are widespread adoption of ultrasonography and fine-needle aspiration of thyroid nodules and changes in pathological reporting criteria.^{2,5} The subsidised healthcare system in Singapore does not have a thyroid screening programme, unlike other countries in South East Asia, and most patients undergo investigation for thyroid-related symptoms. Data pertaining to the use of thyroid ultrasound in Singapore are not available. However, it is still possible that the smaller tumours may have been picked up on incidentally in employment health screens or via imaging investigations for other medical conditions.

Our study also showed that it was not only the micropapillary cancers that had increased over time but also the intermediate size cancers up to 5 cm, like the surveillance, epidemiology and end results data study on the rising incidence of thyroid cancer (16, 18). There is no doubt that screening detects small cancers with a prevalence of about 14 percent as shown by Han et al (19) in South Korea. Most of the cancers that were diagnosed were subclinical and rarely lethal and microcarcinomas type (20). As a result, patients undergoing surgery for micropapillary cancers increased from 14% to 56% from 1995 to 2015. The overprescribed surgery did have an impact on patients outcomes in the form of permanent hypoparathyroidism in 10% of patients and recurrent laryngeal nerve palsy in 2% (6). Other potential harmful effects of US screening of small thyroid cancers and related surgery includes life-long thyroid hormone replacement (21), unnecessary lymph node

Figure 4 Incidence and mortality of thyroid cancer for the population studied

dissection and radioiodine ablation, psychological morbidity (22) and higher health costs for little benefit (23).

Morris and Myssiorek showed that, using surveillance, epidemiology and end results data, during 1973–2006, the incidence of small thyroid cancers quadrupled, those with a size more than 2 cm doubled.¹⁸ Even the larger cancers (defined as more than 5 cm) more than doubled in incidence. The incidence of thyroid cancers with extrathyroidal extension more than doubled, 0.8/100,000 to 1.7/100,000 and cervical nodal metastasis in patients aged more than 45 years tripled from 1.0/100,000 to 2.9/100,000. Similar reports of increasing incidence of thyroid cancers of all sizes in recent years, using a Joinpoint model, was published by Chen *et al.* from the United States.²⁴ The exact reasons for the increase in larger cancers remains to be investigated.

Factors that been associated with increased risk of thyroid cancer include that of exposure to radiation especially in childhood,^{25,26} higher body mass index,²⁷ reproductive factors,^{28,29} environmental and dietary factors.³⁰ A higher incidence of thyroid cancer was observed in areas where a high amount of fish was consumed in iodine-sufficient areas.³⁰ Singapore is an area where a high amount of seafood is consumed and it is an iodine-sufficient area, so there may be an implicating factor in the rising incidence but this needs clarification with further studies.

A few published series have shown sociodemographic differences in outcomes of thyroid cancer,^{31–33} which has been attributed to variations in access to care,³⁴ differences in tumour biology among various races³⁵ and effect of environmental factors or lifestyle patterns.³⁶ We noticed a disproportionate increase in incidence of thyroid cancer, with incidence rising to almost threefold in Malays compared with 2.5 times in Chinese and about twofold in Indians. In Singapore, subsidised healthcare is available to all and socio-economic status is no more prevalent in any specific ethnic group. The other important fact is that Malays are the second largest race in the population of Singapore after the Chinese. The difference in the disparities appear to be greater in women, so the reasons behind such an increase in one ethnic group requires further investigation.

We did not study the outcomes in terms of presentation with localised or distant disease, regional and distant metastasis, as these data were not available. Despite the increasing incidence over the years, mortality has largely remained stable. This similar trend is seen in various studies around the world. The study has a few limitations. First, changes in the registration data quality may affect time trends. In this study, time trends for cancers were available from 1974 but complete pathological and treatment data were available only in the latter half of the study. Second, staging details were not available. Finally, treatment outcomes especially recurrences and response to treatment modalities were not available apart from mortality.

Conclusions

In conclusion, the incidence of thyroid cancer has risen significantly over the past three decades, which is attributable to mainly to small thyroid cancers. The reason for the increased incidence is unclear but may be multifactorial and is partly accounted for by early detection. Additional studies are necessary to determine whether the increased incidence is due to environmental, biological or occupational exposure.

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