Singapore Med J 2012; 53(3) : 159

Thyroid malignancy among goitrous thyroid lesions: a review of hospital-based studies in Malaysia and Myanmar

Htwe TT[1], MBBS, MSc

ABSTRACT Endemic goitre is a major concern in many parts of the world, including Southeast Asia. Goitrous thyroid lesion is postulated as a precursor lesion to thyroid cancer (TC). This paper reviews the prevalence rates and characteristics of TC among cases of goitrous thyroid swelling in different parts of Malaysia and Myanmar. Recorded data from hospital-based retrospective studies of thyroid cases, whose study periods ranged from three to 11 years, were analysed. These included research findings from the author's publications as well as other published review articles of retrospective analyses. The incidence of TC varies among gender, age, race/ethnicity and histological type. There appears to be a higher rate of occurrence among females aged 21–60 years. Papillary thyroid carcinoma is the more common histological type compared to follicular cancer. This review also presents a descriptive analysis and discussion on studies conducted in other countries. Further exploration is warranted in order to uncover the possible risk factors for the rising incidence of TC.

Keywords: goiter, thyroid cancer
Singapore Med J 2012; 53(3): 159–163

INTRODUCTION

Thyroid cancer (TC), a malignancy with a rising incidence and a wide spectrum of clinical behaviour and therapeutic responsiveness, is the most common endocrine malignancy. Goitrous thyroid is believed to be a precursor to the development of TC. It has been estimated that the worldwide prevalence of goitre among the general population is about 4%–7%, and the incidence of malignancy in goitrous thyroid is approximately 10%[(1)] Papillary thyroid carcinoma (PTC) is the most common malignant tumour of the thyroid gland, accounting for 85% of all TCs.[(2)] Follicular thyroid carcinoma (FCA) and anaplastic thyroid carcinoma (ANA) have been reported to occur more frequently in endemic goitre regions than in goitre-free areas. This suggests that highly aggressive TCs are more prevalent in countries with endemic goitre.[(3,4)] This is a review of the incidence of TC among cases of goitrous thyroid swellings based on studies done in different parts of Malaysia and Myanmar.

WORLDWIDE SITUATION OF THYROID MALIGNANCY AMONG GOITROUS THYROID LESIONS

There were approximately 20,000 new cases of TC and 1,460 TC deaths in the United States in the year 2004.[(5)] This increased incidence of thyroid carcinoma has been noted in endemic goitre regions such as Columbia and Austria, as well as in non-endemic goitre regions such as Iceland and Germany. The World Health Organization estimated that at least 1.6 billion people are at risk of iodine deficiency disorders. Among these, 655 million are affected by goitre, 27% of whom are in Southeast Asia, followed by the Western Pacific countries.[(6)]

Fig. 1 Seven states in Malaysia identified to have high incidence of goitre by the Ministry of Health Malaysia.

Table I. Description of the five studies reviewed.

Study	City/state/country	Year; duration
Htwe et al[(11)]	Sarawak/Malaysia	2000–2004; 5 yrs
Othman et al[(12)]	Kelantan/Malaysia	1994–2004; 11 yrs
Abdullah[(13)]	Kuala Lumpur/Malaysia	1995–2000; 5 yrs
Author's research*	Perak/Malaysia	2004–2007; 4 yrs
Htwe et al[(14)]	Yangon/Myanmar	1996–1998; 3 yrs

*Unpublished data

THYROID MALIGNANCY IN MALAYSIA AND MYANMAR

Endemic goitre is a major concern in many countries, including Malaysia and Myanmar. The Malaysian Ministry of Health bi-annual report identified seven states with a high incidence of goitre: Sabah, Sarawak, Kelantan, Terengganu, Pahang, Perlis and Kedah[(7-10)] (Fig. 1). Utilising research findings from the author's

[1]Universiti Kuala Lumpur, Royal College of Medicine Perak, Malaysia
Correspondence: Dr Than Than Htwe, Associate Professor and Head (Pathology), Medical Degree Programme, Universiti Kuala Lumpur – Royal College of Medicine Perak, 3 Jalan Greentown, Ipoh 30450, Perak, Malaysia. ththan@rcmp.unikl.edu.my

Table II. Incidence of thyroid cancer cases by year in the five studies.

Study; no. of years	Total no./cancer cases (%)						
	Total	Yr 1	Yr 2	Yr 3	Yr 4	Yr 5	> 5 yrs
Sarawak; 5 yrs	820/55 (6.7)	148/7 (4.7)	165/16 (9.7)	175/10 (5.7)	153/11 (7.2)	124/11 (8.9)	-
Kelantan; 11 yrs	1,486/111 (7.5)	160/12 (7.5)	148/12 (8.1)*	188/4 (2.1)	180/5 (2.8)	191/6 (3.1)	194/2 (1)¶
Kuala Lumpur; 5 yrs	107†	-	-	-	-	-	-
Perak; 4 yrs**	427/47 (11)	78/8 (10.3)	78/9 (11.5)	137/17 (12.4)	134/13 (9.7)	-	-
Myanmar; 3 yrs	1,690/445 (26.3)	502/95 (18.9)	563/137 (24.3)	625/213 (34.1)	-	-	††

*Highest no; ¶Lowest no. in Yr 6; †Study was done only on histopathological types of cancer cases; **Unpublished data; ††Increasing incidence (p > 0.134)

Table III. Demographic distribution of thyroid cancer cases in the five studies.

Demographic	No. of patients				
	Sarawak 2000–2004	Kelantan 1994–2004	Kuala Lumpur 1995–2000	Perak 2004–2007	Myanmar 1996–1998
Gender (M:F)	1:2*	1:5.2	1:5.7	1:4.9	Not studied
Age (yrs)		Peak 30–49	Median 34–40		
< 21	31			3	31
21–40	352			15	240
41–60	371			17	135
> 60	66			12	39
Ethnicity (%)		Not studied			Not studied
Malay	23.9		36.5	72.3	
Iban	33.5		-	-	
Bidayuh	21.0		-	-	
Chinese	14.2		36.5	6.4	
Indians	1.3		22.5	17.0	
Others	6.1		4.5	4.3	
Total/Ca cases	820/55	1,486/111	-/107	427/47	1,690/445

*p-value = 0.01
M: male; F: female; Ca: cancer

publications as well as review articles of published, retrospective analyses, a review was performed on five different studies from Sarawak, Kelantan, Kuala Lumpur, the state of Perak in Malaysia and Myanmar. There was a balanced focus from the four states in Malaysia, of which two states (Sarawak and Kelantan) were classified as having a high incidence of goitre, while Perak and Kuala Lumpur were not goitre-endemic regions. All reports were from hospital-based retrospective studies (conducted over time periods of three to 11 years) of the archived collection of surgically removed thyroid specimens (Table I).[11,12,17]

Among the studies conducted in Malaysia, the most thorough and extensive one was conducted in Kelantan State. The highest number of TC cases was detected in Year 2 of the study (12 out of 148 admitted cancer cases, 8.1%) and the lowest in Year 6 of the study (2 out of 194, 1%). The overall hospital-based incidence of TC out of all cases of thyroid disease admitted in the 11-year study was 3.5%.[12] For the state of Sarawak, a known endemic goitre area, the number of TC cases was 55 out of 820 (6.7%) cases of goitrous thyroid swelling, and the highest number was reported in Year 5 of the study (11 out of 124, 8.9%).[11] The study conducted in Kuala Lumpur recorded only the histological types of TC in its five-year study and did not mention the incidence of TC in the studied population.[16] The four-year Perak study reported an 11% (47 out of 427) incidence of TC among its cases of admitted goitrous thyroid swelling; this was higher than the findings of the Sarawak study. Out of the five studies, the highest percentage of TC detected among cases of goitrous thyroid swelling was from Myanmar (445 out of 1,690, 26.3%),[17] even though the study period was the shortest among all the studies.

An increasing incidence of TC by year has been observed in the Myanmar study,[17] although it was not statistically significant. Overall, these studies revealed that there was a higher incidence of TC among goitrous thyroid swelling cases in Myanmar compared to Malaysia. Further research to exam the reasons for the considerably higher incidence of TC in Myanmar would be interesting. Of note, although not known to be an area endemic for goitrous thyroid, the Perak State yielded a higher percentage of TC cases compared to Sarawak and Kelantan, the two known endemic goitre regions (Table II).

All five studies reported the highest percentage of occurrence in the 21–60 years age group, with a higher percentage among female subjects. Interestingly, there was a significantly higher incidence of TC (p = 0.01) among male subjects in the Sarawak study.[11] This could be due to the lower prevalence of goitrous

Table IV. Percentage of thyroid cancer cases by histopathological diagnosis in the five different studies.

Study; year	Total/Ca (%)	No. (%)						
		PTC	PTCFV	FCA	HCA	Ins	Ana	Med
Sarawak; 2000–2004	820/55 (6.7)	33 (60.0)	6 (10.9)	14 (25.4)	-	-	2 (3.6)	-
Kelantan; 1994–2004	1,486/111 (7.5) 3.5*	(76.6) 2.6*	-	(18.9) 0.6*	(1.8) 0.1*	-	(2.7) < 0.1*	(0.9) < 0.1*
Kuala Lumpur; 1995–2000	– /107**	74 (69)	-	23 (21)	1 (1)	-	2 (2)	7 (7)
Perak; 2004–2007	427/47 (11.0)	27 (57.5)	6 (12.8)	10 (21.3)	1 (2.1)	1 (2.1)	1 (2.1)	1 (2.1)
Myanmar; 1996–1998	1,690/445 (26.3)	221 (49.7)	-	214 (48.0)	-	-	8 (1.8)	2 (0.5)

*Hospital-based incidence of thyroid cancer per 100,000 admitted patients for all thyroid diseases.
**Study was done on cancer cases only.
PTC: papillary thyroid carcinoma; PTCFV: papillary thyroid carcinoma follicular variant; FCA: follicular carcinoma; HCA: Hurthle cell carcinoma; Ins: insular carcinoma; Ana: anaplastic carcinoma; Med: medullary carcinoma

lesion in male subjects, and thus the predisposition toward malignancy among males was significantly higher. Machens et al studied the disparity between male and female patients with TC in 2006,[18] and opined that early diagnosis and treatment of TC in male patients is important, as the disease may behave more aggressively in men, as seen in the marked variations in the risk of hormone-dependent cancers found between males and females.[18,19]

The racial prevalence of TC in Malaysia varies depending on the location of the study. In general, the prevalence rate among Malays was the highest in all the Malaysian studies, as they make up the largest ethnic group. For the state of Sarawak, the ethnic Ibans and Bidayuhs had the next highest prevalence rates, while in Kuala Lumpur, it was the Chinese. In Perak state, where the Indian population was high, the percentage of Indians with TC was highest after the Malays. No ethnic variation study was performed in the Myanmar study (Table III).

Histopathological classification of TC included PTC, papillary thyroid carcinoma follicular variant, FCA, Hurthle cell carcinoma, insular carcinoma, medullary carcinoma (MC) and ANA. In all five studies, PTC was the most common classification followed by FCA, whereas MC and ANA were the least common. The most precise study was from the state of Kelantan, where the hospital-based incidence of TC was expressed from all admitted patients with various thyroid diseases, including non-cancer cases. The Kuala Lumpur study expressed the TC cases only, without mentioning the total patients admitted with thyroid diseases (Table IV).

Othman et al[12] noted that published studies on TC in Malaysia are few, with early hospital-based reports of Malaysian TC incidence reported by Marsden in 1958 and by Lim in 1962.[13,14] The incidence of TC was 2.1% in the Marsden series, based on a total of 4,650 cancer cases seen at the Institute of Medical Research[13] and that of Lim's series was 3.6%, based on 1,047 cancer cases seen at Hospital Kuala Lumpur.[14] Armstrong reported an incidence of 2.4% (out of 368 total cancer cases) from the same hospital in 1979.[15] However, all these figures may be biased, as they were derived from centres that managed cancer patients only and may not reflect the actual incidence of the disease in the population.[12] A recent study by Abdullah in 2002 was likewise conducted in Kuala Lumpur.[16] Unlike these studies, Othman et al's[12] study in 2009 was conducted in the state of Kelantan, which has been known to have a high rate of iodine deficiency. In this series, TC made up 4.9% of all cancers, implying that the incidence of TC may be slightly higher than the figures noted earlier. The highest rate of TC was from the Perak study conducted by Htwe et al in 2009 (unpublished data). However,

Table V. Observed findings of thyroid cancers in the five studies in Malaysia and Myanmar.

Study; year	Comments and discussions
Sarawak; 2000–2004	• Incidence significantly higher in males (p = 0.01) • Highest prevalence in the age range 21–40 yrs • Highest by ethnicity: Ibans and Malays • Highest by histological type: PTC
Kelantan; 1994–2004	• 28.1% of 1,480 thyroid lesions were neoplastic • Incidence of cancer was 3.5 per 100,000 admission • TC made up 4.9% of all cancers seen in hospital admission • Most common was PTC (76.6%) • The majority (59.9%) occurred in the background of nodular hyperplasia • Study suggests TC arising from MNG are high in iodine-deficient areas
Kuala Lumpur; 1995–2000	• FCA in Malay patients was higher than Chinese, Indians and other races • Median age was 36 yrs in Malays, 37 yrs in Chinese and 33 yrs in Indians • FCA is more common in Malays (56%) • WD TC forms the largest percentage
Perak; 2004–2007	• Not an endemic area; sample size was small, but TC rate was higher than other regions (11%); PTC (57.5%) • Age 21-60 yrs; highest in Malays, followed by Indians and Chinese
Myanmar; 1996–1998	• Occurrence of TC among total cases was highly significant; p < 0.0001 • Significantly higher frequency in patients aged 21–60 yrs; p < 0.008 • PTC and FCA were significantly higher than other types; p = 0.003 • Increasing incidence by yr; p > 0.034

PTC: papillary thyroid carcinoma; TC: thyroid cancer; MNG: multinodular goitre; FCA: follicular carcinoma; WD TC: well-differentiated thyroid cancer

Table VI. Observed findings of thyroid cancers in five studies in Europe and the USA.

Study; duration; location	Comments and discussions
Enewold et al;[20] 25 yrs (1980–2005); USA	• A rising incidence of TC in the USA • Rate varied by histological types, gender and race/ethnicity • Consistent increase, especially PTC in females • Increasing rates of very small cancer size (< 1.0 cm) • Medical surveillance and more sensitive diagnostic procedures cannot completely explain the reason • Other possible explanations should be explored
Kilfoy et al;[21] 30 yrs (1973–2002); USA	• Across continent study of TC in 5 continents: from 19 populations in the Americas, Asia, Europe and Oceania • TC rates have increased from 1973–1977 to 1998–2002 worldwide, except in Sweden • Recently, the age-adjusted TC incidence from 1998–2002 varied 5-fold for males and nearly 10-fold for females by geographic regions • Incidence rates were low in Africa • Iodine supplementation was implemented in countries by World Summit for Children in 1990. Findings in 1999 showed that when such supplementation occurs in iodine-deficient regions, the proportion of PTC often increases, although the overall rates tend to stay the same
Kilfoy et al;[22] 14 yrs (1992–2006); USA	• Using National Cancer Institute's surveillance, Epidemiology and End Results (SEER): variations were found in race/ethnicity, gender and age • Cannot be completely explained as the amount or quality of healthcare provided varied • Recommended future aetiologic investigation to focus on exogenous and endogenous exposures; especially with race, age and gender specifications
Yu et al;[23] 13 yrs (1992–2004); USA	• PTC incidence significantly increased among the 5 major races/ethnicity groups (REGs) • In small or large tumors, in both genders • Difference in diagnostic scrutiny alone was not applicable in all cases
Olaleye et al;[24] 19 yrs (1987–2006); South East England	• TC was more common among females than males (2.7:1) • Mean age 53 yrs (range 5–99 yrs) • Increasing incidence trend was observed in early stage disease (p < 0.001) in young adults < 49 yrs (p-0.001) and in WD types (PTC and FCA)

PTC: papillary thyroid carcinoma; TC: thyroid cancer; MNG: multinodular goitre; FCA: follicular carcinoma; WD TC: well-differentiated thyroid cancer

the data may also be biased, as the results were based on cases admitted into hospitals only, which may hence not reflect the true incidence.

DISCUSSION

This review article compares studies on TC conducted in different states of Malaysia as well as in Myanmar, another Southeast Asian country. The author herself was involved in three out of the five studies, which spanned from 1996 to 2007. The occurrence of TC among admitted cases of goitrous thyroid swelling reflects the general trend in epidemiological studies worldwide. The salient findings in these studies are shown in Table V. A significantly higher incidence in male subjects was noted in the Sarawak study. The incidence of TC was 3.5 per 100,000 admissions in the Kelantan study, with the majority (59.5%) arising in the background of nodular hyperplasia. FCA was more commom (56%) among the Malay population in the Kuala Lumpur study. The Myanmar study revealed a significantly high percentage of TCs among cases of goitrous thyroid swelling and an increasing incidence with advancing years, although this was not a significant finding (Table V). The above findings were compared to the observations from five different studies conducted in Europe and the USA (Table VI).[20-24] The study durations of the European and USA studies ranged from 13 to 30 years. Kilfoy et al's studies in 2009 and 2011 revealed an increasing trend of TC worldwide and observed that its epidemiological variations could not be completely explained by the amount or quality of healthcare provided. This observation supports the finding that medical surveillance and sensitive diagnostic procedures could not account for the increasing incidence of PTC, and that further exploration is necessary.[20,23,24]

It is recommended that a thorough long-term surveillance study be implemented in Asia in view of the rising trend in TC incidence. Due to the association between radiation exposure and risk of TC, a systematic epidemiological study should be conducted in the Asian continental in order to identify the multifactorial risks and aetiology of the disease. With the recent natural disaster in Japan and the accidental radiation exposure in the Fukushima region, there is a need for preventive measures to be put in place and for clinicians to be on the alert for the possible emergence of TC. In addition, studies should explore the effect of iodine deficiency on multinodular goitrous thyroid swelling, as well as reassess the role of iodine supplementation in iodine-deficient areas and genetic influences on TC among different races and ethnicities.

REFERENCES

1. Pacini F, DeGroot LJ. Thyroid neoplasia. In: DeGroot LJ, Jameson JL, eds. Endocrinology. 4th ed. Philidelphia: WB Saunders, 2001:1541-66.
2. Sugitani I, Kasai N, Fujimoto Y, Yanagisawa A. A novel classification system for patients with PTC: addition of the new variables of large (3cm or greater) nodal metastases and reclassification during the follow-up period. Surgery 2004; 135:139-48.
3. Riccabona G. Thyroid cancer and endemic goiter. In: Stanbury JB, Hatzel BS, eds. Endemic goiter and endemic cretinism. Chichester: John Wiley and Sons Inc, 1980: 333-50.

4. Bakiri F, Djemli FK, Mokrane LA, Djidel FK. The relative roles of endemic goiter and socioeconomic development status in the prognosis of thyroid carcinoma. Cancer 1998; 82:1146-53.
5. Jemal A, Tiwari RC, Murray T, et al. Cancer Statistics, 2004. CA Cancer J Clin 2004; 54:8-29.
6. WHO reaffirms goal for sustainable IDD elimination. In: International Centre for the control of Iodine Deficiency Disorders (ICCIDD). IDD Newsletter 1996; 12:1-3.
7. Mafauzy M, Mohamad WB, Anum MY, Musalmah M. Urinary iodine excretion in the northeast of Peninsular Malaysia. Southeast Asian J Trop Med Public Health 1995; 26:138-42.
8. Annual report. Ministry of Health Malaysia; 1999.
9. Ogihara T, Oki K, Iida Y, Hayashi S. Endemic goitre in Sarawak, Borneo island; prevalence and pathogenesis. Endocrinol Jpn 1972; 19:285-93.
10. Chen CC, Lim PP. The prevalence of endemic goitre in the Tinjar area, Sarawak. Med J Malaysia 1982; 37:265-9.
11. Htwe TT, Hamdi MM, Swethadri GK, et.al. Incidence of thyroid malignancy among goitrous thyroid lesions from the Sarawak General Hospital 2000-2004. Singapore Med J 2009; 50:724-8.
12. Othman NH, Omar E, Naing NN. Spectrum of thyroid lesions in hospital Universiti Sains Malaysia over 11 years and a review of thyroid cancers in Malaysia. Asia Pac J Cancer Prev 2009; 10:87-90.
13. Marsden AT. The geographical pathology of cancer in Malaya. Br J Cancer 1958; 12:161-76.
14. Lim HH. The epidemiology of cancers in the Universiti Hospital Kuala Lumpur. Med J Malaysia 1962; 37:52-9.
15. Armstrong RW, Ahluwalia HS. Cancer incidence in Malaysia. Natl Cancer Inst Monogr 1979; 53-7.
16. Abdullah M. Thyroid cancer: The Kuala Lumpur experience. ANZ J Surg 2002; 72:660-4.
17. Htwe TT, Ko M. Thyroid cancer: a three years retrospective histopathological study. J Myanmar Acad Tech 2001; 1:23-30.
18. Machens A, Hauptmann S, Dralle H. Disparities between male and female patients with thyroid cancers: sex difference or gender divide? Clin Endocrinol (Oxf) 2006; 65:500-5.
19. Dos Santos Silva I, Swerdlow AJ. Sex differences in the risks of hormone-dependent cancers. Am J Epidemiol 1993; 138:10-28.
20. Enewold L, Zhu K, Ron E, et.al. Rising thyroid cancer incidence in the United States by demographic and tumor characteristics, 1980-2005. Cancer Epidemiol Biomarkers Prev 2009; 18:784-91.
21. Kilfoy BA, Zheng T, Holford TR, et.al. International patterns and trends in thyroid cancer incidence, 1973-2002. Cancer Causes Control 2009; 20:525-31.
22. Kilfoy BA, Ward MH, Sabra MM, Devesa SS. Thyroid cancer incidence patterns in the United States by histologic type, 1992-2006. Thyroid 2011; 22:125-34.
23. Yu GP, Li JC, Branovan D, McCormick S, Schantz SP. Thyroid cancer incidence and survival in the national cancer institute surveillance, epidemiology, and end results. race/ethnicity groups. Thyroid 2010; 20:465-73.
24. Olaleye O, Ekrikpo U, Moorthy R, et.al. Increasing incidence of differentiated thyroid cancer in South East England: 1987-2006. Eur Arch Otorhinolaryngol 2011; 268:899-906.