MALIGNANT THYROID LESIONS: A HISTOPATHOLOGICAL PERSPECTIVE

ABSTRACT

Introduction: Thyroid cancer incidence is increasing globally. This increase has been attributed to improvement in diagnostic methods. This study has as its aim the analysis of the pattern of thyroid gland malignancies seen at the Jos University Teaching Hospital, Jos, Nigeria, between January 2008 and December 2018.

Methodology: A descriptive retrospective study of consecutive cases of thyroid specimens analyzed at our center was done. Data was obtained from the Histopathology Department Records. The diagnosis of each case was confirmed by reviewing archival slides.

Results: There were 70 cases of thyroid carcinomas during the period of the study. The histological types of thyroid cancers seen were: follicular carcinoma, papillary carcinoma, medullary carcinoma and anaplastic carcinoma, respectively accounting for 36(51.4%), 23(32.9%), 4(5.7%) and 7(8.6%) cases. There was only 1 case of follicular carcinoma in 2012, and non between 2013 and 2018. The male to female ratio was 1: 3.1. The mean age of thyroid carcinoma was 42.7 years, with an age range of 13-80 years.

Conclusion: The histological pattern of thyroid cancers has changed over the last two decades in our environment with the erstwhile predominant follicular carcinoma receding to near disappearance. The papillary carcinoma histotype is currently overwhelmingly the commonest type diagnosed. The former is relatively commonly seen in the older age group, in a sharp contrast with the later. The female gender remains the most afflicted group.

KEY WORDS: Thyroid, cancer, iodine.

INTRODUCTION

Cancer of the thyroid is not uncommon, and is a differential diagnosis in patients presenting with enlargement of the anterior neck region. It accounts for 1.0% to 2.1% of all cancers globally [1,2]. It is also the commonest malignancy of the endocrine system [2,3,4].

The incidence of thyroid cancer exhibits variation worldwide [3]. This incidence has increased globally [5,6,7,8,9]. The rate of increase has been alarming as it is greater than that of any other cancer [6,7]. The reason for this is unclear but might not be unconnected to improvement in diagnostic methods [9].

The clinical presentations of benign and malignant thyroid pathologies are similar [8]. Inter-alia, goiter represents the swelling of the thyroid gland from any cause, and is one of the prominent

features of thyroid disease [5,10]. Although thyroid cancer shows good prognosis owing to its slow progression, it has a mortality rate higher than other endocrine malignancies [2].

This study has as its aim the analysis of the pattern of thyroid gland malignancies seen at the Jos University Teaching Hospital, Jos, Nigeria, in relation to age and sex, and comparing these findings with other studies.

MATERIALS AND METHODS

We undertook a descriptive retrospective study of consecutive cases of thyroid specimens analyzed at our center between January 2008 and December 2018. Data was obtained from the Histopathology Department Records. The diagnosis of each case was confirmed by reviewing archival slides. Cases of missing, broken or faded slides were resolved by selecting corresponding archival tissue blocks, and sectioning same into 5µm slides, staining with Haematoxylin and Eosin stain, and reviewed microscopically to confirm the diagnosis of the disease. Histologically confirmed cases were included in the study, while those with inadequate records were excluded. The data was analyzed using SPSS soft ware and presented in tables, simple frequencies, and percentages.

RESULTS

There were 71 cases of thyroid cancers during the period of the study. Seventy (98.6%) cases were primary thyroid carcinomas, while 1 (1.4%) case was a stromal tumor (fibrosarcoma) which occurred in a 20 years old female.

Of these carcinomas, 43(61.4%) cases occurred between 1997 and 2007, while 27(37.6%) were seen between 2008 and 2018 (Table 1). The histological types of thyroid cancers seen were: follicular carcinoma, papillary carcinoma, medullary carcinoma and anaplastic carcinoma, respectively accounting for 36(51.4%), 23(32.9%), 4(5.7%) and 7(8.6%) cases (Table 1 and 2).

Between 1997 and 2007 (with 43 cases), there were 28(65.1%) cases of follicular carcinomas, 6(14.0%) cases of papillary carcinomas, 3(7.0%) cases of medullary carcinomas and 6(14.0%) cases of anaplastic carcinomas. The corresponding number of cases for these histotypes between 2008 and 2018 (27 cases) were, 8(29.6), 17(63.0%), 1(3.7%), and 1(3.7%) respectively (Table 1). There was only 1 case of follicular carcinoma in 2012, and none between 2013 and 2018.

There was an overwhelming female population accounting for 75.7% (53) of cases (the male female ratio was 1: 3.1) (Table 1). The preponderance of female cases was seen in all histological types safe for medullary carcinoma with equal number of case.

The mean age of thyroid carcinoma was 42.7 years, with an age range of 13-80 years. The respective mean ages and age ranges in years for follicular, papillary, medullary and anaplastic carcinoma were: 45.2, 30-67; 37.9, 13-65; 32.0, 19-60; and 52.0, 35-80. It was seen that 69.6% (16) cases of papillary carcinomas occurred before the age of 40 years, while 66.7% (24) cases of follicular carcinomas were seen from age 40 years and beyond. The peak age incidence of both papillary and follicular carcinomas was 30-39 years, with 11 cases each.

Year	Histological Types Of Thyroid Cancers								Total
	Follicular		Papillary		Medullary		Anaplastic		
	F	M	F	M	F	M	F	M	
1997-2007	21	7	5	1	1	2	3	3	43(61.4%)
2008-2018	8	-	13	4	1	0	1	-	27(37.6%)
Total	29	7	18	5	2	2	4	3	
	36(51.4%)		23(32.9%)		4(5.7%)		7(8.6%)		70(100%)

Table 1. Showing distribution of thyroid carcinoma between 1997-2018 according to gender and histological type

Age (years)	Histological Types Of Thyroid Cancers								Total
	Follicular		Papillary		Medullary		Anaplastic		
	F	M	F	M	F	M	F	M	
10-19	-	-	2	-	-	1	-	-	3(4.3%)
20-29	1	-	3	-	2	1	-	-	7(10.0%)
30-39	9	2	8	3	-	-	1	-	23(32.9%)
40-49	7	1	2	-	-	-	-	2	12(17.1%)
50-59	7	-	3	-	-	-	2	-	12(17.1%)
60-69	4	3	1	-	-	-	-	1	9(12.9%)
70-79	1	1	1	-	-	-	-	-	3(4.3%)
80-89	-	-	-	-	-	-	1	-	1(1.4%)
Total	29	7	20	3	2	2	4	3	
	36(51.4%)		23(32.9%)		4(5.7%)		7(10.0%)		70(100%)

Table 2. Showing the age distribution of thyroid carcinoma according to gender and histological type

DISCUSSION

Thyroid cancer is on a steady but dramatic increase globally over the last three [11] to four [12] decades. In the United States (USA), the annual increase is reported to be 6.5% and 5.4% in men

and women respectively [13]. It is estimated that between 2014 and 2035 in the United Kingdom (UK), there would be a rise of 74% in the incidence of thyroid cancers, and that by 2035 there would be 11 cases per 100,000 people [14]. This projected rise within this time frame in this locale would be 77% (7 cases per 100,000) in males, and 74% (16 cases per 100,000) in females.

In this study, we found a decline in the frequency of thyroid cancer in our center. There were 43(61.4%) cases of the malignancy between 1997 and 2007, and 27(37.6%) cases between 2008 and 2018. This might be due to the proliferation of centers offering histopathology services in the North-Central region of Nigeria, as the Jos University Teaching Hospital has earlier been the only facility offering this service. This might not be the true reason owing to the accompanying population explosion over this time [15]. Additionally, thyroid disease is fairly and relatively a common and constant pathology that shows no seasonal variation or time dependent changes.

A possible reason for this decrease is the disparity in the advancement and availability of diagnostic technology between developed climes and Africa. It has been documented that there is no increase in thyroid cancer in Africa due to insufficient diagnostic capacity [11]. According to the World Health Organization (WHO), as much as 2/3rd to 3/4th of the world's populace experience complete lack or inadequate access to medical imaging [16].

The increase in thyroid cancer across the globe has been attributed to increase in diagnostic intensity with modern imaging leading to over diagnosis of small tumors [17,18,19,20]. This small tumors have been tagged "clinically unimportant" as they pose little or no immediate/long term risk to patient, but rather leads to avoidable anxiety, overtreatment (drastic therapy of otherwise indolent tumor) and it adverse effects, and unnecessary financial burden [11,20]. However, the debate over whether small carcinomas of the thyroid should be treated is currently still raging [21]. A US postmortem study reported that more than 38 million people were unknowingly living with papillary thyroid carcinoma [21]. This staggering figure raises more questions than answers about the burden on these individuals, if they had ante-mortem diagnosis.

The most common thyroid carcinomas arise from two cell types: follicular epithelial cells giving rise to follicular carcinoma, papillary carcinoma, and anaplastic carcinoma and para-follicular (c) cells generating medullary carcinomas [21,22,23]. These four histotypes were the only ones seen in this study. Follicular and papillary carcinomas were the most common cancers in this study, a finding that has been consistently reported by researchers [24-48].

In a dramatic twist, we found a changing pattern in the relative frequencies of these two dominant thyroid malignancies over time: 65.1% of the cancers in the first half of this study (1997-2007) were follicular carcinomas, constituting 77.8% of follicular carcinomas, while in the

second half (2008-2018), 63.0% were papillary carcinomas constituting 73.9% of all papillary carcinoma. In other words, as the incidence of follicular carcinoma wanes, there is seen the waxing of that of papillary carcinoma with the passage of time. A review of thyroid carcinomas on the African continent in 20 literatures, [28-47] published between 1952 and 2014, corroborated this finding (Table 3). In these studies, cancers occurring between 1952 and 1998 were predominantly of the follicular subtype, while those occurring between1999 and 2014 were predominantly papillary carcinomas (Table 3).

The reason for this change in pattern can be attributed to iodination. Iodine deficiency has been implicated in the higher frequency of thyroid disease [49,50,51] and follicular carcinoma (not papillary) [22]. Owing to the high prevalence of iodine deficiency in the past, a global action was initiated by the United Nation incorporating it into the millennium development goals [52]. This resulted to the launching of the USI (Universal Salt Iodization) program, an exceptional cost effective community health intervention strategy [53]. This program recorded remarkable success worldwide in reducing the incidence of thyroid disease [54,55,56].

The finding in this study can be said to be one of the success story of the iodization program, as "high proportion of aggressive follicular and anaplastic tumors are seen in iodine deficiency while the more benign papillary type is common in iodine-rich populations" [57]. This work would serve as a follow-up to a study by Okosieme et al, who reviewed available literature in Africa and concluded in a review publication in 2006 that Follicular carcinoma is the predominant histological type in Africa, attributing this to persistent iodine deficiency [58].

The pathogenic mechanism of iodine deficiency stems from the stimulatory growth on thyroid epithelial cells [59,60,61]. Deficiency of iodine leads to decrease synthesis and thereby low levels of serum thyroid hormones (T_3 and T_4), leading to increase synthesis/release of thyroid stimulating hormone (TSH) [61]. TSH hyper stimulation of the thyroid with persistent iodine deficiency leads to the growth of thyroid epithelial cells with resultant hyperplasia. Pathologic hyperplasia, as occurs in other organs (breast and ovaries) is a fertile soil for malignant transformation [62]. Additionally, tumor promotive factors in this milieu include increased proliferation of thyroid cells due to EGF-induction, decreased TGF-β1 production and increased angiogenesis [61].

The changing pattern, with a shift from follicular to papillary carcinoma with wide scale iodine supplementation has not clearly shown an increase in incidence owing to this intervention [61]. Furthermore, high levels of iodine consumption have been associated with an increased risk of BRAF mutation in thyroid epithelial cells, an important mutation in the pathogenesis of papillary thyroid carcinoma [63]. Studies have shown that up-to 97% of thyroid cancers in iodine sufficient areas are papillary carcinomas, and equal to or greater than 80% of these have BRAF mutation [64-66]. Additionally, exposure to environmental pollutants which are thyroid

endocrine disruptors such as Polychlorinated biphenyls, Polybrominated Diphenyl Ethers, Bisphenols, and Pthalates, play an important role in tumorigenesis in this gland [67].

Additionally, papillary carcinoma has been reported to have a different aetio-pathology from follicular cancer with exposure to radiation being an important risk factor [22]. A study of our environment (the Nigeria Jos Plateau Tin-Mining Region) carried out on sample of soils from abandoned mines from different locations showed traces of X-ray, beta-ray and gamma-ray as well as the heavy metals (such as Pb, As, Cu, Cr and Ni) exceeding international standards [68]. This suggests that mining activities might be contributory to the risk of papillary carcinoma in our environment.

In agreement with literature reviewed in this study, there was a preponderance of female cases over males for thyroid cancer. This wide gap to the best of our knowledge is reported as the rule across the globe. We have in an earlier study suggested for future research, investigating the possible stimulatory and inhibitory role of estrogen and androgens respectively on the pathogenesis of thyroid disorders [69]. Many studies have documented the presence of estrogen receptors on the thyroid and direct effects of estrogen in inducing proliferation of thyroid epithelial cells [70].

Although thyroid carcinomas can occur throughout life, papillary carcinomas are seen generally at an earlier age than follicular carcinomas. This is true in our study as papillary carcinoma recorded a mean age, and age range of 37.9, and 13-65 years in contrast to that of follicular carcinoma which was 42.5 and 30-67 years respectively. Also 69.6% of cases of papillary carcinomas occurred before the age of 40 years, while 66.7% of cases of follicular carcinomas were seen from this age onwards. Solomon et al., corroborated this pattern in a study with a mean age of 38.1 years for papillary carcinomas, and 42.9 years for follicular carcinomas, with respective age range of 17-70 years and 17-80 years [71]. Der et al, also found a similar mean age of 38.2 years, with an exact peak age of incidence of 30-39 years for papillary carcinoma [72].

Finally, although race and ethnicity has an important role to play in the outlook of thyroid cancers [73-75], our study was not primarily aimed at studying these influences. However, all our patients were of African black population and of Nigerian descent. Magreni et al, in a study, reported that, no significant difference was observed between the increase in incidence for whites and blacks, but incidence for non-Hispanics was significantly higher than that for Hispanics [73]. Keane et al, in a review of eight retrospective cohort studies, with a total of 611 777 patients, found out that black and white patients have a higher proportion of follicular cancer, than Hispanics, though the later have a younger age at diagnosis[74]. Also, Week et al, reported that the white population has a greater proportion of diagnosed small tumors (papillary microcarcinomas) than

non whites, attributable to their being more medical insured, and thereby susceptible to "unnecessary" investigations and overtreatment [75].

Reference Number, and Author	Location and period of study (1999-2014)	Histological types of thyroid carcinomas			
		Follicular	Papillary	Medullary	Anaplastic
28. Selzer et al.	Capetown, South Africa, 1952-1975	31	27	4	10
29. Olurin et al.	Ibadan, Nigeria, 1957-1970	16	16	0	10
30. Thomas et al.	Ibadan, Nigeria, 1965-1984	45	45	5	4
31. Gitau et al.	Nairobi, Kenya, 1968-1973	55	30	0	15
32. Bakiri et al.	Algiers,Algeria, 1966-1981	36	39	4	16
33. Omran et al.	Khartoum, Sudan, 1982-1989	42	22	2	21
34. Lawal et al.	Ile-Ife, Nigeria, 1983-1993	69	11	6	3
35. Nkanza	Harare,Zimbabwe, 1985-87	70	12	2	12
36. Tsegaye et al.	Addis Ababa, Ethiopia, 1994-1998	16	77	6	2
37. Mulaudzi et al.	Durban, South Africa, 1990-1997	68	16	13	3

Table 3a. Showing the frequency of various histological types of thyroid cancer on the African continent, in 10 studies, between 1952 and 1975.

Reference Number, and Author	Location and period of study (1999-2014)	Histological types of thyroid carcinomas			
		Follicular	Papillary	Medullary	Anaplastic
38. Hill et al.	Kijabe, Kenya, 1999-2001	10	15	-	-
39. Ijeomone et al.	Port-Harcourt, Nigeria, 1999-2008	6	11	2	1
40. Ukekwe et al.	Enugu, Nigeria, 2000-2014	23	26	3	2
41. Der et al.	Accra, Ghana, 2004-2010	9	33	2	-
42. Salami et al.	Sagamu, Nigeri , 2004-2014	2	2	-	-
43. Raheen et al.	Zaria, Nigeria, 2005-2014	2	10	1	-
44. Dodiyi-Manuel et al.	Port-Harcourt, Nigeria, 2006 -2011	3	5	-	1
45. Rahman et al.	Savar, Dhaka, 2006-2012	2	6	-	1
46. Chalya et al.	Mwanza, Tanzania 2008-2010	5	4	-	-

47. Guidoum et al.	El-Taref and Guelma, Algeria 2008-2012	28	213	2	2

Table 3b. Showing the frequency of various histological types of thyroid cancer on the African continent, in 10 studies, between 1999-2014.

CONCLUSION

The histological pattern of thyroid cancers has changed over the last two decades in our environment with the erstwhile predominant follicular carcinoma receding to near disappearance. The papillary carcinoma histotype has been on a relative rise and is currently overwhelmingly the commonest type diagnosed. This pattern is attributable to the success of the iodization program, as deficiency of iodine is a trigger for follicular carcinoma, and its sufficiency increasing risk of papillary carcinoma. Follicular carcinoma is seen in older age occurring predominantly in the fourth decade and beyond, in a sharp contrast to papillary carcinoma. The female gender remains the most afflicted group.

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