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Gender Differences In Thyroid Cancer In A Tertiary Care Hospital Bangladesh

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Abstract:
Background: *The gender disparity in incidence, aggressiveness and prognosis is well established for thyroid cancer but the cause of the disparity is poorly understood.*
Objective: *The main objective of the study was to evaluate the gender difference in thyroid disease.*
Materials and Methods: *This cross sectional study was conducted in the Department of Otolaryngology-Head & Neck Surgery of Bangabandhu Sheikh Mujib Medical University, Dhaka from January 2013 to December 2015. The thyroid gland was assessed by palpation in all patients. Estimation of serum TSH concentrations were performed by automated immune chemiluminescent assay.*
Results: *In this study out of 400 thyroid cancer patients, 327 were females and 73 were males. The mean age was almost similar between male and female patients (p=0.245). HOMA-IR was significant higher in female patients than male patients (1.9±0.5 vs 1.7±0.6). FT3, FT4 and TPO antibody were significantly higher in male patients than female patients, whereas TSH level was significantly higher in female patients than male patients (5.7±2.9 vs 4.5±2.8 µIU/mL). In multivariate logistic regression analysis abnormal TSH patient had 3.61 (95% CI 1.66 to 7.81) times more likely to have female. Abnormal FT3 patient had 2.56 (95% CI 1.08 to 6.05) times more likely to have female. Abnormal TSH and FT3 were significantly associated with female patients.*
Conclusion: *Serum TSH and FT3 levels were significantly associated with thyroid cancer especially for females. Our results suggest the necessity of monitoring TSH and FT3 in the population for thyroid cancer risk assessment, especially female.*
Keywords: *Gender, Thyroid cancer, Serum TSH, FT3 levels, Low-density lipoprotein cholesterol (LDL-C).*

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I. Introduction:

Thyroid cancer is the most commonly diagnosed non-gynecologic human endocrine malignancy.[1] Cancer gender disparity in incidence, disease aggressiveness and prognosis has been observed for a variety of cancers. In sex-specific organs, such as the uterus, prostate, ovary and breast, this disparity can easily be explained. However, some sex-shared sites, such as the thyroid, lung and liver, also show clear gender

differences in incidence and/or survival.[2-5] Thyroid cancer is the most common malignancy of the endocrine system and the seventh most common malignancy in women, but it is not among the most common 15 cancers in men.[5] Thyroid cancer had an age-adjusted incidence rate of 11 per 100,000 persons in 2006, with a 2.9-times higher rate in women (female: male ratio 16.3:5.7).[5] However, the incidence of thyroid cancer is significantly higher in women compared with men. The 2002 GLOBOCAN database reports 103,589 female thyroid cancer cases worldwide compared with only 37,424 male thyroid cancer cases, representing a female to male (F:M) ratio of greater than 2:1.[1] The gender disparity in thyroid cancer is also specific to the histologic subtype of thyroid cancer. The more aggressive types of thyroid cancer, anaplastic thyroid cancer and medullary thyroid cancer have similar rates of incidence in men and women.[6] The incidence of differentiated thyroid cancer (DTC; papillary thyroid carcimona [PTC] or follicular thyroid carcinoma [FTC]) is three-times higher in women than in men, while that of anaplastic thyroid carcinoma (ATC) is twice as common in women than men. There is no significant difference in the incidence of medullary carcinomas (MTC) between men and women.[7] Male gender is among the worst independent prognostic factors for papillary thyroid carcinoma. A recent metanalysis found a 50% increase in recurrence in males compared to females, even worse than age. A TSH concentration below the reference range was associated with a significant increase in tumor risk in women but not in men. Another possible explanation for gender differences in thyroid cancer incidence is the greater confidence of women in physician's advice and their more frequent use of diagnostic services.[8] Thyroid disease is associated with various metabolic abnormalities, due to the effects of thyroid hormones on nearly all major metabolic pathways. Thyroid gland function regulates a wide range of metabolic events. Thyroid gland function significantly affects lipoprotein metabolism and as a result the cardiovascular disease (CVD) risk.[9-10] In fact, even within the normal range of thyroid-stimulating hormone (TSH) values, a gradual elevations in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TGs) and a linear depletion in high-density lipoprotein cholesterol (HDL-C) levels has been observed with increasing TSH.[11,12] Nevertheless, thyroxinetherapy for TSH suppression after thyroidectomy for differentiated thyroid carcinomas is independently associated with reduced recurrence and mortality. This trophic effect of TSH on thyroid tissue that promotes neoplasia and carcinogenesis could be a possible explanation for the increased risk associated with serum TSH concentrations in the upper tertile of the normal range.[13] This objective of the present study was to evaluate the gender difference in thyroid disease.

II. Materials And Methods:

This cross-sectional study was conducted in the Department of Otolaryngology-Head & Neck Surgery of Bangabandhu Sheikh Mujib Medical University, Dhaka from January 2013 to December 2015 to evaluate the gender differences in thyroid cancer. A total of 400 thyroid cancer patients were included in this study. Patients were included if they were diagnosed during the period, had well differentiated (papillary or follicular) thyroid cancer diagnosed at age 18 or older, with information on presentation, treatment, and outcomes; patients with incomplete data and patients with persistent disease after initial surgery were excluded. We did not include patients with poorly differentiated histology. We did include aggressive variants such as tall cell and columnar variants and grouped them together as aggressive variants. Patient with metastatic disease at presentation were only included if they had become disease free after initial management. Detailed history and clinical examination was done to determine any obvious clinical feature of malignancy and any feature of thyroid dysfunction. All the data were recorded in a structured questionnaire. The thyroid nodules were first confirmed with ultrasonography at the department of Radiology and Imaging, BSMMU. The serum, FT4, FT3 and TSH concentrations were measured by automated immunochemiluminescent assay (ICMA) (Immulite, California, USA) at the department of Microbiology and Immunology, BSMMU. Specimen was collected in fasting condition, allowed to clot; serum was separated and analyzed for serum total cholesterol, triacylglycerol and HDL cholesterol levels. LDL cholesterol level was calculated by Friedewald's Equation. FNAC was done in the department of Pathology, BSMMU. After surgery a final histological result was attempted in every case by histopathology. All the patients of DTC, revealed by histopathology report were considered as cases. Collected data were compiled and appropriate analyses were done by using computer based software, SPSS version 23.0. The mean values were calculated for continuous variables. The quantitative observations were indicated by frequencies and percentages. Chi square test was used for quantitative observations to assess the significance between two groups. Unpaired 't' test was used for continuous variables to assess the significance between groups. Multivariate analysis on differences in treatment between men and women was performed using regression analysis. 'p' values <0.05 were considered significant.

III. Results:

In this study out of 400 thyroid cancer patients, 327 were females and 73 were males. The mean age at diagnosis was 47.1±13.9 year sin female patients and 49.2±14.1 years in male patients, that was not significant (p=0.245). Smoker was significantly higher in male patients than female patients (11.0% vs 4.3%). Stage T1

tumor was common in both male and female patients (89.0% vs 94.5%), that was significant (p=0.010). However, tumor size, N stage, M stage, thyroid surgical type, pathology, BMI and blood pressure were not significant between male and female patients (p>0.05) (Table-1). Mean WC was found 80.1±9.9 cm in female and 90.7±9.2 cm in male group. The mean triglyceride was found 240.6±38.9 mg/dL in female and 236.8±40.5 mg/dL in male group. The mean HOMA-IR was found 1.9±0.5 in female and 1.7±0.6 in male group. The mean TSH was found 5.7±2.9 µIU/mL and 4.5±2.8 µIU/mL in female and male groups respectively. The mean FT3 was found 4.8±0.7 pg/mL in female and 5.3±0.8 pg/mL in male group. The mean FT4 was found 15.3±3.0 pg/mL and 16.9±2.7 pg/mL in female and male groups respectively. The mean TPO antibody was found 13.2±2.3 IU/ml in female and 14.5±2.6 IU/ml in male group. Which were statistically significant (p<0.05) between two group (Table-2). Multivariate logistic regression analysis, abnormal TSH patient had 3.61 (95% CI 1.66 to 7.81) times more likely to have female. Abnormal FT3 patient had 2.56 (95% CI 1.08 to 6.05) times more likely to have female. Abnormal TSH and FT3 were significantly associated with female patients. However, smoker, T stage (T2 & T3, abnormal WC, TG, HOMA-IR, FT4 and TPO antibody were not significantly associated with female patients (Table-3).

Table 1: Baseline characteristics of the study population

	Female (n=327)	**Male (n=73)**	**P value**
Mean age at diagnosis (years)	47.1±13.9	49..2±14.1	0.245
Smoker			
Yes	14 (4.3%)	8 (11.0%)	**0.031**
No	313 (95.7%)	65 (89.0%)	
Tumor size (cm)			
≤5	196 (59.9%)	46 (63.0%)	0.627
>5	131 (40.1%)	27 (37.0%)	
T stage			
T1	309 (94.5%)	65 (89.0%)	
T2	17 (5.2%)	5 (6.8%)	**0.010**
T3	1 (0.3%)	3 (4.1%)	
N stage			
N0	291 (89.0%)	60 (82.2%)	0.109
N1	36 (11.0%)	13 (17.8%)	
M stage			
M0	105 (32.1%)	29 (39.7%)	0.213
M1	222 (67.9%)	44 (60.3%)	
Thyroid surgical type			
Total thyroidectomy	285 (87.2%)	65 (89.0%)	0.660
Hemithyroidectomy	42 (12.8%)	8 (11.0%)	
Pathology			
Papillary	311 (95.1%)	65 (89.0%)	0.051
Follicular	16 (4.9%)	8 (11.0%)	
Mean BMI (kg/m^2)	24.2±3.4	25.0±3.3	0.068
Mean SBP (mmHg)	126.1±12.7	125.4±13.2	0.673
Mean DBP (mmHg)	76.3±10.9	79.0±11.1	0.057

p value reached from Chi square and unpaired t-test

Table 2: Investigation of the study population

Investigation	**Female (n=327)**	**Male (n=73)**	**P value**
Metabolic			
WC (cm)	80.1±9.9	90.7±9.2	**0.001**
Total cholesterol (mg/dL)	240.6±38.9	236.8±40.5	0.454
Triglycerides (mg/dL)	156.9±42.7	171.3±45.0	**0.010**
HDL cholesterol (mg/dL)	48.6±10.0	49.0±10.7	0.761
LDL cholesterol (mg/dL)	144.7±36.4	135.8±39.5	0.064
FPG (mmol/l)	5.8±0.9	5.7±1.0	0.401
HbA1c (%)	5.5±0.3	5.55±0.4	0.229
HOMA-IR	1.9±0.5	1.7±0.6	**0.003**
Thyroid			
TSH (µIU/mL)	5.7±2.9	4.5±2.8	**0.001**
FT3(pg/mL)	4.8±0.7	5.3±0.8	**0.001**
FT4 (pg/mL)	15.3±3.0	16.9±2.7	**0.001**
TPO antibody (IU/ml)	13.2±2.3	14.5±2.6	**0.001**

p value reached from unpaired t-test

Table 3: Multivariate logistic regression analysis for female patients

Parameter	Regression coefficient (β)	Odds Ratio (OR)	95% CI for OR	P value
Smoker	-0.13	0.87	0.45-1.71	0.696
T stage (T2 & T3)	-0.10	0.90	0.42-1.95	0.796
Abnormal WC	0.02	1.02	0.44-2.35	0.954
Abnormal TG	0.05	1.04	0.13-8.03	0.967
Abnormal HOMA-IR	-1.36	0.26	0.05-1.51	0.257
Abnormal TSH	1.28	3.61	1.66-7.81	**0.001**
Abnormal FT3	0.94	2.56	1.08-6.05	**0.032**
Abnormal FT4	1.11	3.05	0.96-3.82	0.069
Abnormal TPO antibody	-0.19	0.82	0.17-3.99	0.808

P-value reached from multivariate analysis by binary logistic regression analysis

IV. Discussion:

Thyroid cancer is the most common endocrine malignancy with the increasing new patients diagnosed worldwide. The tumor of thyroid has long been established to have an obvious female predominance. It has been ranked fifth in the most common cancer of female, while not in the list of 15 most common male cancers.[2] However male patients with thyroid cancer had poor prognosis than their female counterparts.[14]

In this study out of 400 thyroid cancer patients, 327 were females and 73 were males. The mean age at diagnosis was 47.1±13.9 year sin female patients and 49.2±14.1 years in male patients, that was not significant (p=0.245). In a study of Zahedi et al. where they found at presentation, men tended to be slightly older than women (50.8±14.3 vs. 46.8±14.0 years).[15] Yan et al. reported that the mean±SD age of the patients was 47±12 years in females and 48±13 years in males, respectively.[16] Another study conducted by Liu et al. where they showed mean age was higher in male than female (53.03±15.30 vs 48.68±15.14 years).[17]

In this study tumor size ≤5 cm was found 196(59.9%) in female patients and 46(63.0%) in male patients, that was not significant (p=0.627). Liu et al. consisted that tumor size was larger (22.48±21.79 vs 16.93±17.75 mm, $p < 0.001$) in men than in women.[17]

In the present study tumour stage 1 was found 94.5% and 89.0% in female and male groups respectively, that was significant (p=0.10). Zahedi et al. showed that tumour stage 1 was 52.9% in women group and 36.1% in men group, the difference was significant (p<0.001) between two groups.[15]

We found that N stage, M stage, thyroid surgical type, pathology, BMI and blood pressure were not significant between male and female patients (p>0.05). Meng et al. reported that there were significant differences in all parameters with respect to opposite gender. BMI, MC, SBP, and DBP in males was higher than in females.[18] Castello and Caputo had observed male gender is among the worst independent prognostic factors for papillary thyroid carcinoma.[8] Zahedi et al. consisted that follicular thyroid cancer was more common in men (9.3%) than in women (5.7%, p = 0.002).[15]

In this present study it was observed that mean WC was found 80.1±9.9 cm in female and 90.7±9.2 cm in male group. The mean triglyceride was found 240.6±38.9 mg/dL in female and 236.8±40.5 mg/dL in male group. The mean HOMA-IR was found 1.9±0.5 in female and 1.7±0.6 in male group. The mean TSH was found 5.7±2.9 μIU/mL and 4.5±2.8 μIU/mL in female and male groups respectively. The mean FT3 was found 4.8±0.7 pg/mL in female and 5.3±0.8 pg/mL in male group. The mean FT4 was found 15.3±3.0 pg/mL and 16.9±2.7 pg/mL in female and male groups respectively. The mean TPO antibody was found 13.2±2.3 IU/ml in female and 14.5±2.6 IU/ml in male group. Which were statistically significant (p<0.05) between two group. However, total cholesterol, HDL cholesterol, LDL cholesterol, FPG and HbA1c were not significant between male and female patients (p>0.05). Meng et al. demonstrated that serum TSH was lower in males than in females, while FT3 and FT4 were higher in males than in females.[18] TC and HDL were lower in males than in females, yet TG and LDL were higher in males than in females. Investigations performed in the French Monica cohorts to separate the contributions of different factors to the metabolic syndrome showed a significantly elevated body weight, waist girth, and low HDL cholesterol in women than in men.[19] MS prevalence was significantly higher in males than in females in all thyroid functional status (P<0.01), except for hyperthyroidism when TSH <0.3 mIU/mL. Females had significantly higher overall incidence of hypothyroidism and hyperthyroidism than males. Various forms of thyroid dysfunction and Hashimoto thyroiditis are more common in women, and the overall incidence increases with age in both sexes (TSH distributional shift with age), especially in women.[20,21] Increasing TSH in overt and mild hypothyroidism is also found to be associated with unfavorable lipid concentrations (like hypercholesterolemia and decreased HDL levels), as well as blood pressure.[22-24] Thyroid function also has an effect on the activity of cholesteryl ester transfer protein and hepatic lipase, which alters HDL metabolism.[25] As a result, T3 is negatively associated with HDL.[26] Castello and Caputo had observed low levels of TSH seem to protect males against hyperlipemia; high TSH concentrations in females herald damaging hyperlipidemia.[8] A TSH concentration below the reference

range was associated with a significant increase in tumor risk in women but not in men. Yan et al. also showed that the median TSH in the male group was 1.66, which was significantly lower than that in the female group (2.08).[16]

Regarding multivariate logistic regression analysis in this study it was observed that abnormal TSH patient had 3.61 (95% CI 1.66 to 7.81) times more likely to have female. Abnormal FT3 patient had 2.56 (95% CI 1.08 to 6.05) times more likely to have female. Abnormal TSH and FT3 were significantly associated with female patients. However, smoker, T stage (T2 & T3, abnormal WC, TG, HOMA-IR, FT4 and TPO antibody were not significantly associated with female patients. Yan et al. showed that higher TSH level was related to the DTC occurrence in male or female.[16] However, compared to the group of $0.3 \leq TSH < 1.0$ mUI/L, the patients with $TSH > 0.3$ mUI/L or $1.0 \leq TSH < 1.9$ mUI/L had a significant higher proportion in female. The patients with multiple nodules had a higher proportion of DTC compared to single nodule (OR = 1.185, 95%CI 1.015–1.383, P = 0.031) while no significant differences were found in male or female. Meng et al. reported that binary logistic regression models reveled that aging was much more effective than thyroid function parameters (TSH or FT3) to engender an enhanced risk of MS.[18] Roef et al. showed that in healthy euthyroid middle-aged men and women, higher FT3 levels, lower FT4 levels, and thus a higher FT3-to-FT4 ratio were consistently associated with various markers of unfavorable metabolic profile and cardiovascular risk.[26] Castello and Caputo also consisted that multiple factors and the wide range of gender-related variables impacting on diagnosis and treatment of thyroidal diseases.[8]

V. Conclusion:

In conclusion, we found that serum TSH and FT3 levels were significantly associated with thyroid cancer especially for females. And females had higher risks than males. Moreover, aging is an important risk factor for thyroid cancer. Our results suggest the necessity of monitoring TSH and FT3 in the population for thyroid cancer risk assessment, especially female.

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Conflicts of interest
There are no conflicts of interest.

Ethical approval
The study was approved by the Institutional Ethics Committee.

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