Original Article

Prevalence of malignancy in thyroid nodules with AUS cytopathology: A retrospective cross-sectional study

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Abstract

Background: Category III (AUS; Atypia of Undetermined Significance) of The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) was established to describe thyroid nodule features that are neither benign nor cancerous. **Objectives:** This study aims to evaluate the rate of thyroid malignancy in patients diagnosed with AUS at the Armed Forces Hospital Southern Region (AFHSR), Saudi Arabia. **Method:** The patients (508) diagnosed with AUS in their thyroid nodules underwent fine-needle aspiration cytology (FNAC). Data were collected through a chart-based approach, reviewing patients' medical records and relevant information. **Results:** Among the cases, the majority were females (84.6%). Among the different age groups, individuals between 40 and 50 years had the highest prevalence of thyroid nodules (32.5%). Approximately 27% of patients exhibited tumor sizes larger than 4 cm. FNAC results revealed 16.5% benign, 26% AUS, and 22.4% follicular neoplasm cases. Histopathology indicated 54.1% of benign and 37.2% of malignant cases. Papillary carcinoma accounts for 80.4% of all malignant cases. A significant correlation was observed between FNAC and postoperative histopathology (P value < 0.05). Hypoechoic nodules exhibited 33.9% of malignant cases, and calcification was observed in 25% of the cases. A significant association was found between malignancy and echogenicity and between malignancy and calcification (P value = 0.003 and 0.001, respectively). **Conclusion:** The findings of this study identify malignancy in thyroid nodules with AUS cytopathology, particularly in the Southern region of Saudi Arabia. The correlation between pre-surgery FNAC and postoperative histopathology supports FNAC's diagnostic value. Additionally, echogenicity and calcification can potentially contribute to predicting nodule malignancy.

Keywords: Atypia of undetermined significance, Bethesda classification, fine-needle aspiration, malignant, thyroid cancer, thyroid nodules

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Introduction

Thyroid cancer is a highly prevalent endocrine tumor worldwide, and it stands as the second most frequent cancer among females in Saudi Arabia. Studies undertaken in the Kingdom of Saudi Arabia

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have found a notable increase, ranging from 9 to 11.7% in thyroid cancer rates, with significant geographical variation.[1,2] Several studies indicate that approximately 50% of patients aged 50 exhibit nodules, with a relatively low risk of malignancy ranging from 5 to 7%.[3,4] Thyroid ultrasound and fine-needle aspiration cytology (FNAC) remained the most important diagnostic tools to guide the management of thyroid nodules.[5] FNAC plays a crucial role in the evaluation and treatment of thyroid nodules.

Primary care practitioners commonly face thyroid nodules in family medicine clinics. A lot of the time, confusion can occur about whether to keep monitoring these nodules closely or reassure patients not to worry about them.[6] Therefore, it is relevant to discuss among the primary care physicians this topic.

FNA results are classified into six categories based on The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC): Nondiagnostic (Bethesda I), Benign (Bethesda II), Atypia of Undetermined Significance (AUS) (Bethesda III), Follicular Neoplasm (Bethesda IV), Suspicious for Malignancy (Bethesda V), and Malignant (Bethesda VI).[7,8] Each category has an implied cancer risk of malignancy (ROM) that averages from 4% for the "Benign" category to virtually 100% for the "Malignant" category and subsequent recommended management guidelines. The purpose of this system is to simplify the diagnosis of thyroid cytopathology.[8] Moreover, many studies have reported the usefulness of thyroid ultrasound in improving the ability to predict nodular malignancy categorized as undetermined cytology in the initial FNAC.[9-12]

Studies have reported high malignancy rates of up to 48%, suggesting diagnostic lobectomy for all AUS/FLUS nodule cases.[13] Others suggested further dividing AUS/FLUS into a two-tiered subclassification consisting of low cellularity with predominant microfollicular architecture and the absence of colloid and nuclear atypia (nonbenign characteristics), which is attributable to the strict probability of cancer evaluation.[14-16] In a study by Pasha *et al.* (2020),[17] out of 495 FNAC samples, 81 samples (16.4%) were categorized as AUS/FLUS (Pasha *et al.*, 2020).[17] On the other hand, (Raparia *et al.* 2009),[18] reported that among 108 cases deemed suspicious for follicular neoplasm based on cytological evaluation, histological follow-up revealed malignancy in 26 patients. Furthermore, among the 37 cases that were suspected of Hürthle cell neoplasm, 15 cases (41%) were found to be malignant.

Studies conducted in Saudi Arabia showed considerable geographical variations in thyroid cancer rates.[2,19-21] This study investigates the malignancy rate in thyroid nodules of Bethesda category III classification among adult patients at the Armed Forces Hospital Southern Region (AFHSR), Saudi Arabia.

Materials and Methods

Study design and area

This cross-sectional retrospective study was conducted at Armed Forces Hospital Southern Region, Saudi Arabia (AFHSR), from January 2013 to December 2021. The research was approved by the Research Ethics Committee (AFHSRMREC/2022/Internal Medicine/629), Armed Forces Hospital Southern Region, Saudi Arabia (AFHSR), on July 3, 2022. Furthermore, the study was conducted according to the Declaration of Helsinki guidelines for human research.

Study population

The study involved 508 adult patients who underwent fine-needle aspiration (FNA) of thyroid nodule (s) and were subjected to thyroid surgery at AFHSR. It included all patients aged >18 years. Patients who underwent thyroidectomy for other reasons or thyroidectomy without FNA were excluded.

Data collection and management

A chart-based approach was applied in this study. A thorough review of patients' medical records focused on individuals diagnosed with thyroid nodules categorized as AUS according to the BSRTC, who had undergone ultrasound and subsequent FNAC. The primary investigators collected the data using a structured data collection sheet. This sheet encompassed various aspects, including patient demographics and sonographic features of thyroid nodules, such as size, number, consistency, echogenicity, the presence of calcifications, margins, halo, vascularity, lymph node enlargement, and risk stratification according to ultrasonographic features into benign, very low suspicion, intermediate suspicion, and high suspicion. The data collection sheet also incorporated FNAC results based on the Bethesda classification, details regarding the type of thyroidectomy performed, and the postoperative histological diagnosis. The FNAC results were then correlated with the final histopathology findings.

Statistical analysis

The data analysis was carried out using the SPSS version 25.0. Descriptive statistics were performed to present the frequency of variables in terms of percentages. A bivariate analysis was conducted to determine the associations between outcome variables and other relevant factors, utilizing the Chi-square test for categorical variables and the *t* test for quantitative variables. A *P* value of 0.05 or less was considered statistically significant.

Results

A total of 508 patients diagnosed with thyroid nodules and subsequently underwent thyroid FNAC followed by thyroidectomy were included in the study. Among the participants, the majority were females, accounting for 84.6% (430) of the cases, and males accounted for only 15.4% (78) (N = 508) [Figure 1].

Among the 508 patients, 140 (27.6%) individuals diagnosed with thyroid nodules were over the age of 50. The most highly diagnosed age group was between 40 and 50, representing 165 (32.5%) patients. The age group between 30 and 40 years accounted for 138 (27.2%) occurrences. Patients in the

20–30-year range constituted 51 (10%) cases, while those below 20 years comprised 14 (2.8%) patients [Figure 2]. The study population's distribution based on tumor size is illustrated in Figure 3. A total of 137 (27%) cases had tumors larger than 4 cm. A total of 108 (21.3%) cases had tumors ranging from 1 to 2 cm, 108 (21.3%) had tumors measuring 3 to 4 cm, and 81 (15.9%) had tumors sized between 2 and 3 cm.

Analysis of the FNAC results revealed that 16.5% (84) of the cases had benign tumors, 26% (132) of patients were classified as AUS, and 22.4% (114) were diagnosed with follicular neoplasm. Moreover, 4.5% (23) showed a suspicion of malignancy, suggesting a potential risk of cancer. 3.5%[18] of the patients were diagnosed with malignancy, while 27.0% (137) were not mentioned [Table 1].

Figure 4 provides a clear overview of the distribution of patients who underwent surgery. A total of 200 (39.4%) patients underwent surgery on the basis of FNAC results and 160 (31.5) required surgery due to obstructive symptoms.

After surgery, a histopathological examination was conducted. Out of the 508 patients, 275 (54.1%) cases were diagnosed as benign after surgery, while 189 (37.2%) were determined to have malignancy. Furthermore, 17 (3.3%) cases were classified as reactive, indicating inflammatory changes in the thyroid tissue, and 19 (3.7%) were categorized as others, representing specific findings that are distinct from benign or malignant conditions. The diagnosis of 8 (1.6%) cases was not mentioned [Table 2].

As depicted in Figure 5, the histopathology results revealed that 152 (80.4%) of 189 malignant tumors were diagnosed as papillary thyroid carcinoma. Additionally, 32 (16.9%) malignant tumors were classified as follicular thyroid carcinoma, 4 (2.1%) as medullary carcinoma, and 1 (0.5%) as anaplastic thyroid carcinoma ($N = 189$).

Table 1: Classification of thyroid tumors based on FNAC results

Classification	Frequency	Percentage (%)
Benign	84	16.5
AUS	132	26.0
Follicular neoplasm	114	22.4
Suspicion of malignancy	23	4.5
Malignancy	18	3.5
Others	137	27.0
Total	508	100.0

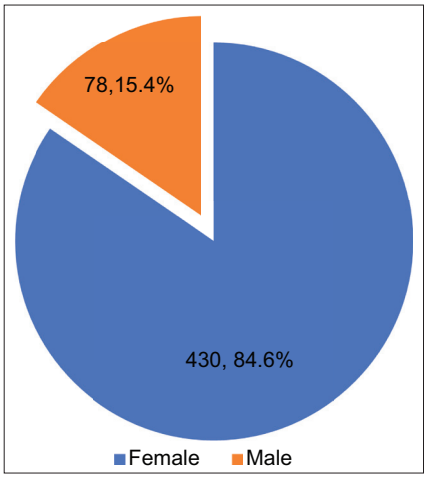

Figure 1: Distribution of the study population by gender

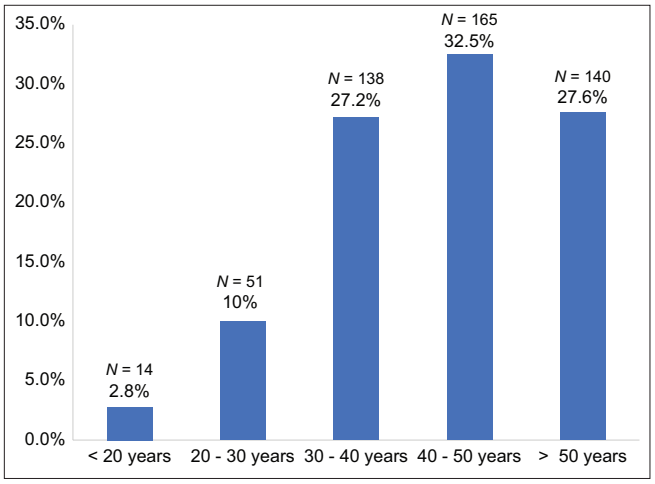

Figure 2: Distribution of the study population by age group

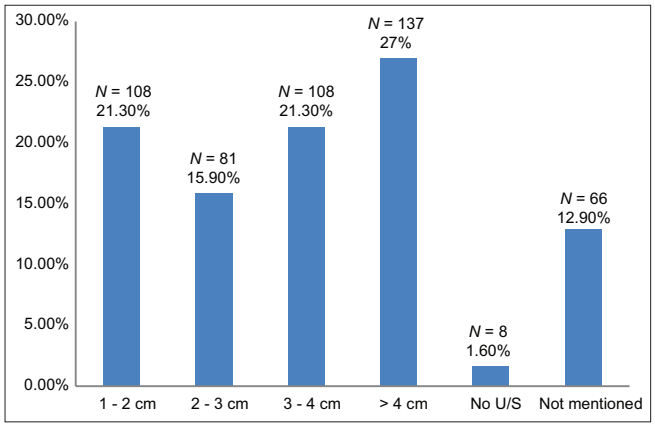

Figure 3: Distribution of the study population by tumor size

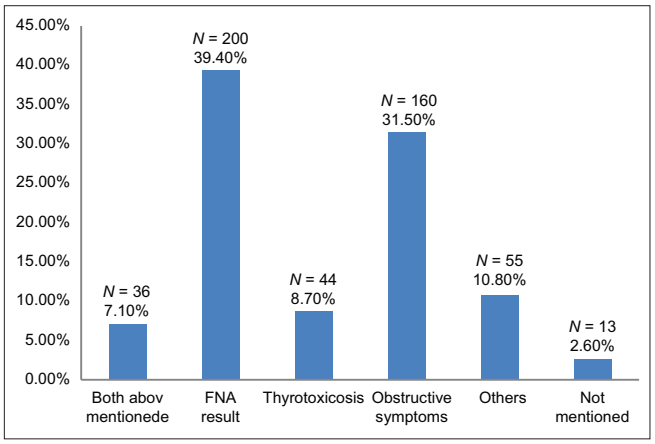

Figure 4: Distribution of the study population by indication for surgery

Subsequent histopathological examination following surgery showed a malignancy rate of 23.8% for patients with benign nodules, 27.3% for patients initially diagnosed with AUS by FNAC, 49.1% for those diagnosed with follicular neoplasm, 87% for those suspicious of malignancy, and 100% for patients with malignant nodules [Table 3].

A noteworthy finding in our study was the substantial correlation between the histopathological results obtained after surgery and the pre-surgery FNA results in identifying benign lesions, AUS/FLUS, suspicion of malignancy, and malignancy. This correlation was supported by a statistically significant *P* value of less than 0.05. However, we did not find a significant association between the FNA results of follicular neoplasm and its post-surgery histopathology results.

Regarding the ultrasound characteristics of the nodules, 115 (22.6%) of 508 cases of nodules were found to be hypoechoic, 100 (19.7%) were heterogenous, 89 (17.5%) were complex, 64 (12.6%) were isoechoic, 46 (9.1%) contained cysts, and 30 (5.9%) were hyperechoic [Figure 6]. Calcification was absent in 325 (64%) cases and present in 127 (25%) cases, while it was not mentioned in 56 (11%) cases (*N* = 508) [Figure 7].

Table 4 displays the relationship of thyroid nodule malignancy, as determined by histopathology results, with echogenicity variables and calcification. The analysis revealed significant associations between malignancy and echogenicity (*P* value = 0.003) and malignancy and calcification (*P* value = 0.001).

Regarding echogenicity, the study observed different patterns in malignant nodules. Most malignant nodules, comprising 33.9%, showed a hypoechoic pattern. 24.0% of the malignant cases exhibited a heterogenous echotexture. 18.7% of the malignant nodules were complex homogenous, 10.5% were isoechoic, 8.2% were hyperechoic, and 4.7% were cysts. Furthermore, nodules without calcifications accounted for 65.5% of all cases, whereas those with calcifications represented 34.5%. The presence of calcifications demonstrated a significant association with malignancy, as indicated by the *P* value of 0.001. These findings

Table 2: Classification of thyroid tumor based on histopathology results after surgery

Classification	Frequency	Percentage (%)
Benign	275	54.1
Malignancy	189	37.2
Reactive	17	3.3
Others	19	3.7
Not mentioned	8	1.6
Total	508	100.0

Table 3: Correlation between FNAC and post-surgery histopathology results

FNAC Results		Histopathology after surgery		*P*
Classification	Frequency	Malignancy	Benign	
Benign	84	20 (23.8%)	57 (67.9%)	0.000*
AUS	132	36 (27.3%)	89 (67.4%)	0.000*
Follicular neoplasm	114	56 (49.1%)	44 (38.6%)	0.230
Suspicion of malignancy	23	20 (87.0%)	3 (13.0%)	0.000*
Malignancy	18	18 (100.0%)	0 (0.0%)	0.000*

*Significant correlation

Table 4: Association of thyroid nodule malignancy with echogenicity and calcification

Sonographic features	Malignant		*P*
	n	%	
Echogenicity			
Complex homogenous	32	18.7	0.003*
Cysts	8	4.7	
Heterogenous echotexture	41	24.0	
Hyperechoic	14	8.2	
Hypoechoic	58	33.9	
Isoechoic	18	10.5	
Calcification			
Absent	112	65.5	0.001*
Present	59	34.5	

*Significant correlation

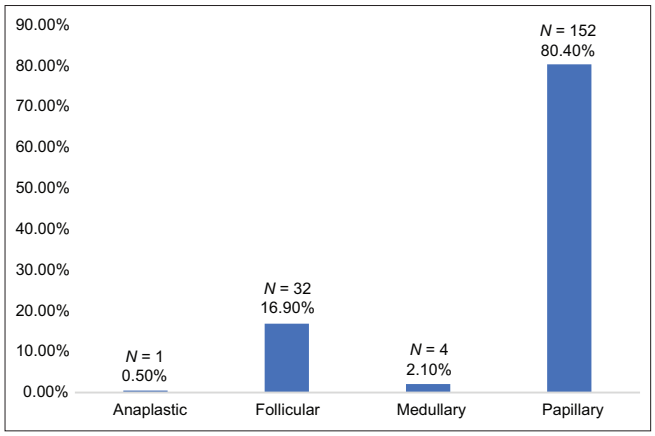

Figure 5: Categorization of tumors based on histopathological studies

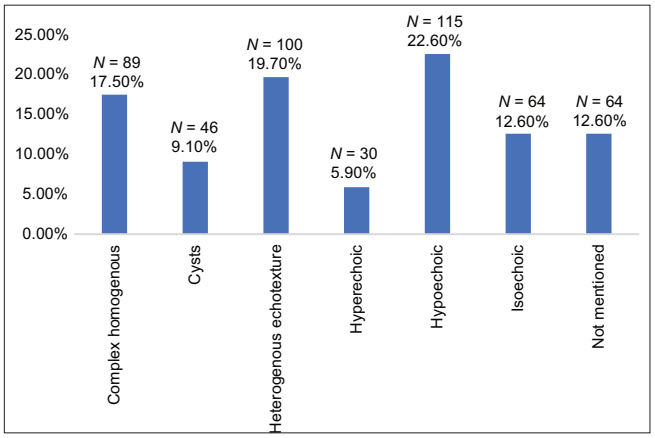

Figure 6: Categorization of tumor based on echogenicity

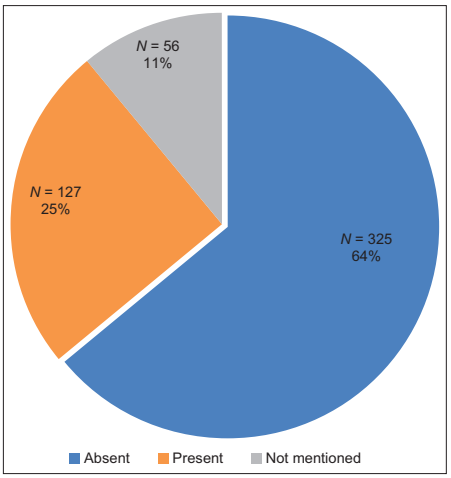

Figure 7: Population presented with tumor calcification

suggest that both echogenicity patterns and calcifications are essential factors to consider in assessing the potential malignancy of thyroid nodules.

Discussion

Prevalence

This retrospective cross-sectional study was conducted in a hospital setting and involved 508 patients diagnosed with thyroid nodules. Our findings revealed that the most prevalent age group affected by thyroid nodules was between 40 and 50 years, with a higher incidence among females which is reflected in other studies as well.[22,23] These results agree with previous studies.[24-26] The high prevalence of thyroid nodules in the 40–50 age group underscores the importance of age-related screening and monitoring in this population.

Size and malignancy

This study assessed the size distribution of thyroid nodules in the studied population. A significant proportion of patients (27%) had tumors larger than 4 cm, indicating the presence of relatively large nodules. This finding raises concerns about the potential for malignancy, as larger nodules are generally associated with a higher risk of malignancy and are frequently referred for surgical removal.[27] The various sizes of tumors in our study samples highlight the diverse range of nodule sizes encountered in clinical practice and their careful evaluation and management.

FNA

Based on the Bethesda classification, the occurrence of AUS/FLUS revealed after FNAC was 26%. The study findings are consistent with reported data from the eastern region of Saudi Arabia (Johns Hopkins Aramco Healthcare). According to this, 42.74% of FNAC samples in that region were labeled AUS/FLUS.[20] The results of our study revealed higher prevalence rates of indeterminate cytology (AUS/FLUS) compared to data reported from different regions of Saudi Arabia.[1,19,28,29]

Moreover, our data showed high malignancy rates of thyroid in the AUS (27.3%) and FLUS group (49.1%), which is considerably higher than cases reported from different regions of Saudi Arabia and globally.[17,19,20,28] Our study showed a high prevalence of AUS/FLUS compared to cases reported from Pakistan, where the prevalence was 16.4%[17,30] reported 29% of cases with AUS/FLUS, and the malignancy rate diagnosed by FNA was 20%.[30]

Histopathology

Histopathological findings demonstrate that most malignant tumors were identified as papillary carcinoma, accounting for 80.4% of all cases. This finding is consistent with the research conducted by Zarif (2018),[29] where papillary carcinoma was also reported as the most prevalent tumor, observed in 23.5% of the histopathology samples.[29]

Correlation between FNA and histopathology

Our study revealed a significant correlation between the results of FNAC and the histopathology findings of thyroid nodules, with a P value < 0.05, indicating that FNAC has high specificity in detecting thyroid cancer. In other words, when FNAC results indicate malignancy, there is a high likelihood that the nodule is indeed cancerous. This finding strengthens the validity and reliability of FNAC as a valuable diagnostic tool for identifying thyroid cancer. The study by Lew *et al.* (2011)[25] also reported significant results similar to our findings (Lew *et al.*, 2011).[25] Similarly, the study by Cheung *et al.* (2007)[31] also had significant results, providing additional evidence of the effectiveness of FNAC in identifying thyroid malignancies.[31]

Ultrasound features and malignancy

In this study, we observed various echogenicity patterns in malignant thyroid nodules, with a significant number of cases (33.9%) showing a hypoechoic pattern. Our study is relevant to Anil *et al.* (2011),[32] who explained that thyroid nodules with a hypoechoic pattern highly indicate malignancy, as 92% of nodules diagnosed without hypoechoic waves were benign. The overall performance of this feature in correctly classifying nodules as either malignant or benign suggests that approximately 92% of nodules without a markedly hypoechoic pattern are indeed benign (Anil *et al.*, 2011).[32] It is crucial to remember that no single ultrasound feature can definitively diagnose malignancy, some malignant nodules may not show a markedly hypoechoic pattern, and some benign nodules may exhibit this feature, leading to misclassifications. Therefore, the ultrasound findings should be considered with other clinical and imaging features.[32,33]

Furthermore, our study showed calcifications in 34.5% of malignant cases, while 65.5% of malignant nodules did not exhibit calcifications. The significant association between calcifications and malignancy (P value = 0.001) was observed highlighting the role of calcification assessment in the diagnosis of thyroid cancer. Our results align with those of Zahir *et al.* (2016),[34] who also found a significant relationship between the type of nodule

and calcification detected in ultrasound views ($P = 0.001$).[34,35] also reported that ultrasonographic calcification of thyroid nodules significantly predicts malignant nodules. This suggests that calcification assessment can serve as a reliable indicator in identifying suspicious nodules and aiding in the early detection of thyroid cancer.[35] Therefore, we emphasize the clinical significance of incorporating calcification assessment into thyroid nodule evaluation.

Conclusion

Our findings revealed a significant increase in the thyroid cancer rate among patients diagnosed with AUS/FLUS in the Southern region of the Kingdom of Saudi Arabia. This highlights the importance of vigilance and thorough evaluation in cases presenting with AUS/FLUS cytopathology, as these patients may have an elevated risk of thyroid malignancy. Furthermore, our research identified echogenicity and calcification as valuable indicators for predicting malignancy in thyroid nodules. The significant associations observed between malignancy and these sonographic features may offer valuable insights to healthcare professionals, leading to improved diagnostic accuracy and better-informed patient management decisions.

Study limitations and recommendations

The study employed a retrospective design and did not encompass the assessment of thyroid gland functional status or the investigation of risk factors associated with thyroid malignancy. We recommend conducting prospective studies to explore the prevalence of atypia in thyroid nodules and the local risk factors that lead to high rates of thyroid cancer in the southern region. In addition, we recommend conducting further studies, explicitly focusing on the local risk factors that may contribute to the higher incidence of thyroid cancer in the southern region. By investigating these regional risk factors in depth, we can better understand the factors that may be influencing the elevated rates of thyroid cancer in this area. This knowledge will aid in developing targeted preventive strategies and better management approaches for thyroid nodules and malignancies in the region.

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Conflicts of interest

There are no conflicts of interest.

References

1. Alyousif H, Adam I, Alamin NA, Sid Ahmed MA, Al Saeed A, Hassoni AH, *et al.* The prevalence and associated predictors for Bethesda III-VI for reporting thyroid cytopathology in Royal Commission Hospital, Kingdom of Saudi Arabia. Ther Adv Endocrinol Metab 2022;12:20420188221122486.
2. Hussain F, Iqbal S, Mehmood A, Bazarbashi S, ElHassan T, Chaudhri N. Incidence of thyroid cancer in the Kingdom of Saudi Arabia, 2000-2010. Hematol Oncol Stem Cell Ther 2013;6:58-64.
3. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer; Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, *et al.* Revised American thyroid association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2000;19:1167-214.
4. Cibas ES, Ali SZ; NCI Thyroid FNA State of the Science Conference. The Bethesda system for reporting thyroid cytopathology. Am J Clin Pathol 2009;132:658-65.
5. Martin HE, Ellis EB. Biopsy by needle puncture and aspiration. Ann Surg 1930;92:169-81.
6. Ruhaiyem ME, Al Khenizan A, Hussain A. The yield of thyroid fine-needle aspiration in a primary care setting in Riyadh, Saudi Arabia. J Family Med Prim Care 2022;11:7602-6.
7. Ali SZ, Baloch Z, editors. The Bethesda System for Reporting Thyroid Cytopathology. 3rd ed. Cham: Springer; 2023. Available from: https://link.springer.com/book/10.1007/978-3-031-28046-7.
8. Cibas ES, Ali SZ. The 2017 Bethesda system for reporting thyroid cytopathology. Thyroid 2017;27:1341-6.
9. Akın Ş, Helvacı N, Çınar N, Önder S, Bayraktar MJA. Atypia of undetermined significance in thyroid fine-needle aspiration cytology: Pathological evaluation and risk factors for malignancy. South Clin Ist Euras 2017;28:82-6.
10. Hong SH, Lee H, Cho MS, Lee JE, Sung YA, Hong YS. Malignancy risk and related factors of atypia of undetermined significance/follicular lesion of undetermined significance in thyroid fine needle aspiration. Int J Endocrinol 2018;30:4521984.
11. Horne MJ, Chhieng DC, Theoharis C, Schofield K, Kowalski D, Prasad ML, *et al.* Thyroid follicular lesion of undetermined significance: Evaluation of the risk of malignancy using the two-tier sub-classification. Diagn Cytopathol 2012;40:410-5.
12. Mendez W, Rodgers SE, Lew JI, Montano R, Solorzano CC. Role of surgeon-performed ultrasound in predicting malignancy in patients with indeterminate thyroid nodules. Ann Surg Oncol 2008;15:2487-92.
13. Vázquez YL, Álvarez MP, Fraile PSM, Pérez MB. Riesgo de malignidad de los nódulos tiroideos con atipia de significado incierto/Risk of malignancy in thyroid nodules with atipia of undetermined significance. Endocrinol Nutr 2015;62:507-10.
14. Eisa N, Khan A, Akhter M, Fensterwald M, Saleem S, Fananapazir G, *et al.* Both ultrasound features and nuclear atypia are associated with malignancy in thyroid nodules with atypia of undetermined significance. Ann Surg Oncol 2018;25:3913-8.
15. Kim SJ, Roh J, Baek JH, Hong SJ, Shong YK, Kim WB, *et al.* Risk of malignancy according to sub-classification of the atypia of undetermined significance or follicular lesion of undetermined significance (AUS/FLUS) category in the Bethesda system for reporting thyroid cytopathology. Cytopathology 2017;28:65-73.
16. Luu MH, Fischer AH, Stockl TJ, Pisharodi L, Owens CL. Atypical follicular cells with equivocal features of papillary thyroid carcinoma is not a low-risk cytologic diagnosis. Acta Cytol 2011;55:526-30.
17. Pasha HA, Dhanani R, Mughal A, Ahmed KS, Suhail A. Malignancy rate in thyroid nodules with atypia or follicular lesion of undetermined significance. Int Arch Otorhinolaryngol 2020;24:e221-6.

18. Raparia K, Min SK, Mody DR, Anton R, Amrikachi M. Clinical outcomes for "suspicious" category in thyroid fine-needle aspiration biopsy: Patient's sex and nodule size are possible predictors of malignancy. Arch Pathol Lab Med 2009;133:787-90.
19. Al-Shraim MM, Kaood OM, Hussain M, Al-Ahmary AM, Al-Shehri GY, Jastania RA, *et al.* Assessment of malignancy rate in thyroid nodules according to the Bethesda system of fine-needle aspiration. Saudi Med J 2012;33:167-71.
20. Alhashem MH, Alabidi A, Aly MG. The Bethesda system for reporting thyroid cytopathology: A retrospective review of its diagnostic utility at Johns Hopkins Aramco Healthcare, Saudi Arabia. Am J Otolaryngol 2021;42:103088.
21. Bazarbashi S, Al Eid H, Minguet J. Cancer incidence in Saudi Arabia: 2012 Data from the Saudi cancer registry. Asian Pac J Cancer Prev 2017;18:2437-44.
22. Alshahrani AS, Alamri AS, Balkhoyor AH, Mahzari MM, Alshieban SS, Majed, PM, *et al.* The prediction of malignancy risk in thyroid nodules classified as Bethesda system category III (AUS/FLUS) and the role of ultrasound finding for prediction of malignancy risk. Cureus 2021;13:e17924.
23. Cakir B, Ersoy R, Cuhaci F, Aydin C, Polat B, Kılıc M, *et al.* Elastosonographic strain index in thyroid nodules with atypia of undetermined significance. J Endocrinol Invest 2014;37:127-33.
24. Kwong N, Medici M, Angell TE, Liu X, Marqusee E, Cibas ES, *et al.* The influence of patient age on thyroid nodule formation, multinodularity, and thyroid cancer risk. J Clin Endocrinol Metab 2015;100:4434-40.
25. Lew JI, Snyder RA, Sanchez YM, Solorzano CC. Fine needle aspiration of the thyroid: Correlation with final histopathology in a surgical series of 797 patients. J Am Coll Surg 2011;213:188-94.
26. Li Y, Jin C, Li J, Tong M, Wang M, Huang J, *et al.* Prevalence of thyroid nodules in China: A health examination cohort-based study. Front Endocrinol (Lausanne) 2021;12:676144.
27. Kamran SC, Marqusee E, Kim MI, Frates MC, Ritner J, Peters H, *et al.* Thyroid nodule size and prediction of cancer. J Clin Endocrinol Metab 2013;98:564-70.
28. Al Dawish MA, Robert AA, Muna A, Eyad A, Al Ghamdi A, Al Hajeri K, *et al.* Bethesda system for reporting thyroid cytopathology: A three-year study at a tertiary care referral center in Saudi Arabia. World J Clin Oncol 2017;8:151-7.
29. Zarif HA, Ghandurah SE, Al-Garni MA, Binmahfooz SK, Alsaywid BS, Satti MB. Thyroid nodules cytopathology applying the Bethesda system with histopathological correlation. Saudi J Med Med Sci 2018;6:143-8.
30. Broome JT, Solorzano CC. The impact of atypia/follicular lesion of undetermined significance on the rate of malignancy in thyroid fine-needle aspiration: Evaluation of the Bethesda system for reporting thyroid cytopathology. Surgery 2011;150:1234-41.
31. Cheung Y, Poon C, Mak S, Suen MW, Leong H. Fine-needle aspiration cytology of thyroid nodules-how well are we doing? Hong Kong Med J 2007;13:12-5.
32. Anil G, Hegde A, Chong FV. Thyroid nodules: risk stratification for malignancy with ultrasound and guided biopsy. Cancer Imaging 2011;11:209-23.
33. Desser TS, Kamaya A. Ultrasound of thyroid nodules. Ultrasound Clin 2009;4:87-103.
34. Zahir ST, Vakili M, Ghaneei A, Heidari F. Ultrasound assistance in differentiating malignant thyroid nodules from benign ones. J Ayub Med Coll Abbottabad 2016;28:644-9.
35. Kim BK, Choi YS, Kwon HJ, Lee JS, Heo JJ, Han YJ, *et al.* Relationship between patterns of calcification in thyroid nodules and histopathologic findings. Endocr J 2013;60:155-60.