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ORIGINAL ARTICLE

Observational Study

Environmental mineral density and thyroid malignancy: A multicenter cross-sectional study

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Abstract

BACKGROUND
Several trace minerals have been shown to be associated with thyroid cancer. Democratic Republic of Congo (DRC) is deemed the most mineral-rich country globally. Data on the characteristics of thyroid nodules in various mineral-rich regions of the DRC is scarce.

AIM
To analyze the differential spectrum of thyroid nodules based on locoregional variance in mineral density.

METHODS
We conducted a cross-sectional study on 529 patients with thyroid nodules residing in Katanga, South Kivu and Kinshasa between 2005 and 2019. Of these three provinces, Katanga and South Kivu have the highest mineral density with the DRC.

RESULTS
Mean patient age was 44.2 years ± 14.6 years with a female predominance, with a female to male ratio of 5.4. The 66.5% of patients had a family history of thyroid disease. Total 74 patients had simple nodules, and the remaining 455 patients had multiple nodules. The 87.7% of patients were euthyroid. The nodules exhibited varying characteristics namely hypoechogenicity (84.5%), solid echostructure (72.2%), macronodular appearance (59.8%), calcifications (14.4%) and associated lymphadenopathy (15.5%). The 22.3% of the nodules were malignant. Factors independently associated with malignancy were older age (≥ 60 years) [adjusted odds ratio (aOR) = 2.81], Katanga province (aOR = 8.19), solid echostructure (aOR = 7.69), hypoechogenicity (aOR = 14.19), macronodular appearance (aOR = 9.13), calcifications (aOR = 2.6) and presence of lymphadenopathy (aOR = 6.94).

CONCLUSION
Thyroid nodules emanating from the mineral-laden province of Katanga were more likely to be malignant. Early and accurate risk-stratification of patients with thyroid nodules residing in high-risk areas could be instrumental in optimizing survival in these patients.

Key Words: Thyroid; Cancer; Nodules; Minerals; Heavy metals

Core Tip: Geographical variation in mineral density can potentially impact the prevalence of thyroid malignancies. Our study demonstrated that a higher environmental mineral burden was associated with an increased prevalence of thyroid cancer after adjusting for other covariates. More studies utilizing sophisticated assays to measure serum and environmental levels of various heavy metals could reinforce our study findings. This association holds significant potential in accurate risk-stratification and early detection of thyroid neoplasms amongst patients residing in mineral-laden provinces within the Democratic Republic of Congo.

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INTRODUCTION

Thyroid cancer incidence has increased by 20% in the past two decades globally[1]. Notably this rise in thyroid cancer incidence has impacted certain geographic areas more profoundly compared to others. This discrepancy was initially attributed to advancement in diagnostic testing. However, recent literature has highlighted the role of additional factors namely environmental pollutants, ionizing radiation, obesity, *etc.*[2-5]. Geographic variance in thyroid cancer incidence is indeed an interesting correlation derived from numerous studies conducted in Hawaii, French Polynesian islands, Iceland, and Sicily. All these places, with active volcanic activity, have disproportionately higher rates of thyroid cancer. Heavy metals have an affinity for thyroidal tissue. A study comparing two cohorts with comparable genetic, ethnic and lifestyle profiles found that the cohort in proximity to an active volcano named Mount Etna had a two-fold risk of papillary thyroid cancer[6-9]. It is possible that higher mineral content of the vegetation and water bodies at these locations translates to greater exposure to heavy metals in local residents. Soil contamination from unsafe dumping of hazardous wastes can also lead to substantial exposure to heavy metals, especially in developing countries where stringent regulatory checks pertaining to waste management do not exist.

Some elements are crucial to optimal functioning of the thyroid gland, whereas others are either known endocrine disruptors or carcinogenic. Meta-analyses have shown higher levels of copper but lower levels of serum zinc and selenium in patients with thyroid cancer when compared to controls[10,11]. Nonetheless, the majority of literature is derived from small, retrospective studies, and has yielded conflicting findings. The most recent study on thyroid nodules in the Democratic Republic of Congo (DRC) was conducted in a single institution located in a province that is not known to have soil rich in trace minerals[12]. We conducted a multi-provincial retrospective analysis, assessing regions with high mineral densities in the DRC. To the best of our knowledge, there are currently no studies on thyroid nodules in the DRC involving patients residing in mineral-rich provinces. The objective of this study is to establish the spectrum of thyroid nodules and ascertain risk factors for malignancy amongst patients living in mineral-abundant regions within the DRC.

MATERIALS AND METHODS

Study design

This is a multi-center cross-sectional study of 529 patients who were diagnosed with thyroid nodules *via* an ultrasound and histopathological examination across 35 hospitals in Kinshasa, two in Bukavu and one in Katanga between 2005 to 2019. The sampling process was exhaustive and all case records were manually reviewed. Data was de-identified to anonymize study participants and protect their privacy. Institutional Review Board approval was granted by all the participating hospitals across the three provinces.

Variables of interest

Investigators collected information about following variables: (1) Province of residence; (2) Age; (3) Gender; (4) Marital status; (5) Clinical parameters (history of thyroid cancer in the family, reason for consultation, parity, gestation, abortion, duration of the mass, arterial pressure, heart rate, lymphadenopathy); (6) Clinical diagnosis; (7) Ultrasound parameters (total volume of the thyroid gland, echostructure, echogenicity, presence of nodule, size, calcification, lymphadenopathy on ultrasound, ultrasound diagnosis); and (8) Histopathological diagnosis. Patient records containing information regarding all the variables of interest were retained for eventual analyses. Study protocol recommended that the participating study centers use standardized ultrasonographic equipment, produced by a particular manufacturer to prevent discrepancies in assessments due to calibration errors. However, only 60% of centers were able to comply with this recommendation. We also aimed to minimize inter-operator bias, which is historically deemed implicit in radiological assessments. To mitigate operator and measurement biases, the results of all ultrasound examinations were independently reviewed by two radiologists who were masked to patients' malignancy status. Ultrasound characteristics that were indicative of malignancy included the presence of a solid hypoechoic nodule or a partially cystic nodule with solid hypoechoic component along with irregular margins, rim calcifications with extrusive soft tissue, microcalcifications, taller than wider configuration, or extrathyroidal involvement. Each reviewer separately analyzed the ultrasonographic features of nodules. Kappa coefficient was between 0.78 to 1, indicating strong inter-observer agreement. Discordant cases were resolved by arriving at mutual consensus. Subsequent histopathological examination also assisted with diagnostic confirmation. The histopathologist served as an unblinded reviewer, and verified the ultrasonographic and histopathological findings to attest to the malignant nature of nodules in affected patients. Patients with indeterminate biopsy results were excluded from the analyses.

Statistical analysis

Statistical analyses were carried out using Statistical Package for the Social Sciences for Windows version 24 software. Descriptive summary statistics include mean and standard deviation for quantitative data, and the absolute (n) and relative (%) frequencies for categorical data. Pearson's χ^2 or Fisher's exact test was used to compare proportions (%) and student's t test was used to compare the means of two groups. Logistic regression was used to ascertain factors associated with thyroid malignancy in univariate and multivariate analyses. Odds ratio (OR) and their respective 95%CI yielded the strength of association. A P value < 0.05 was considered statistically significant.

RESULTS

Characteristics of thyroid nodules

Amongst our study group consisting of 529 patients, 74 (14%) had a single nodule whereas 455 patients (86%) had multiple nodules. The socio-demographic characteristics of nodules are illustrated in Table 1. Mean age of patients was 44.2 years ± 14.6 years. Study group was primarily composed of female patients (84.4%; female to male ratio of 5.4). The 75.1% of patients were married and 85.5% of patients resided in Kinshasa. Patients with single and multiple nodules did not differ significantly in terms of their sociodemographic characteristics (P > 0.05). The 53.6% of patients were multiparous, and 66.5% of patients had a family history of thyroid pathology. The 58.2% of the latter subgroup consisted of first-degree relatives. On clinical examination, 95.1% of patients had an anterocervical mass, 35.3% were obese, 8.7% had lymphadenopathy and 87.7% were euthyroid. No significant differences were noted amongst patients with single *vs* multiple nodules with respect to aforementioned clinical features (Table 2). Sonographic characteristics of nodules

Table 1 Sociodemographic characteristics of the study participants according to the type of nodule, *n* (%)

Variables	All (*n* = 529)	Single (*n* = 74)	Multiple (*n* = 455)	*P* value
Age (years)	44.2 ± 14.6	45.0 ± 14.9	44.0 ± 14.2	0.21
≤ 20	35 (6.6)	8 (10.8)	7 (5.9)	
21-30	54 (10.2)	2 (2.7)	52 (11.4)	
31-40	135 (25.5)	19 (25.7)	116 (25.5)	
41-50	127 (24.0)	19 (25.7)	108 (23.7)	
51-60	96 (18.1)	14 (18.9)	82 (18.0)	
> 60	82 (15.5)	12 (16.2)	70 (15.4)	
Sex				0.36
Male	82 (15.6)	13 (17.6)	69 (15.3)	
Female	444 (84.4)	61 (82.4)	383 (84.7)	
Marital status				0.63
Married	373 (75.1)	51 (77.3)	322 (74.7)	
Single	115 (23.1)	13 (19.7)	102 (23.7)	
Divorced/widowed	9 (1.8)	2 (3.0)	7 (1.6)	
Province of residence				0.28
Kinshasa	468 (88.5)	64 (86.5)	404 (88.8)	
Katanga	18 (3.4)	1 (1.4)	17 (3.7)	
South Kivu	43 (8.1)	9 (12.2)	34 (7.5)	

(Table 3) revealed a predominance of solid echostructure (72.2%), hypoechogenicity (84.5%), macronodular configuration (59.8%) amongst the study population. Microcalcifications and adenopathy were noted in 14.4% and 15.5% of patients respectively. Histopathological analyses (Table 4) revealed that 77.7% of nodules were benign and 22.3% malignant in nature. Colloid goiter was the predominant type of benign nodule (73.5%) and papillary carcinoma was the most commonly encountered malignant nodule (66.9%). Anaplastic carcinoma, on the other hand, represented 7.6% of malignant nodules.

Factors associated with increased risk for malignancy

Table 5 compares the sociodemographic and clinical characteristics based on nodular histopathology. Variables associated with malignancy included older age [> 60 years; (P = 0.003)], residence within Katanga province (P = 0.044), family history of thyroid pathology (P = 0.002) and cervical lymphadenopathy (P < 0.001). Table 6 indicates varying ultrasound characteristics of benign and malignant nodules. Nodular size, echostructure, echogenicity, and presence of lymphadenopathy and calcifications statistically differed between the two groups.

Factors associated with malignancy in univariate analyses were age ≥ 60 years, residence within Katanga province, family history of thyroid pathology, presence of calcifications, clinical or sonographic lymphadenopathy, solid echostructure, hypoechogenicity, and macronodules. Multivariate analyses yielded an independent association between thyroid malignancy and following variables: (1) Age ≥ 60 years [adjusted OR (aOR) = 2.81; 95%CI: 1.14-6.94, P = 0.025]; (2) Residence within Katanga (aOR = 8.19; 95%CI: 1.14-12.45, P = 0.036); (3) Presence of sonographic lymphadenopathy (aOR = 6.94; 95%CI: 2.79-17.25, P < 0.001); (4) Calcifications (aOR = 2.60; 95%CI: 1.19-5.7, P = 0.017); (5) Solid echostructure (aOR = 7.69; 95%CI: 2.40-24.58, P = 0.001); (6) Hypoechogenicity (aOR = 14.19; 95%CI: 1.60-25.93, P = 0.017); and (7) Macronodule (aOR = 9.13; 95%CI: 4.19-19.89, P < 0.001) (Table 7).

DISCUSSION

Our nationally representative study revealed a female predominance in the distribution of thyroid nodules, with the majority of patients being euthyroid. Solid echostructure, hypoechogenicity, macronodules, microcalcifications and lymphadenopathy were common ultrasound features found in our study population. Advanced age, residence in Katanga province, solid echostructure, hypoechogenicity, macronodules, microcalcifications and adenopathy independently predicted the malignant potential of thyroid nodules.

Meticulous thyroid nodule evaluation is imperative to definitively rule out thyroid cancer, which is prevalent in 4% to 6.5% of thyroid nodules[12]. Female gender and iodine deficiency are two well-recognized risk factors for development of thyroid nodules[8,13]. Our study also revealed a female predominance in thyroid nodule prevalence within the DRC.

Table 2 Clinical characteristics of the study participants according to the type of nodule, *n* (%)

Variables	All (*n* = 529)	Single (*n* = 74)	Multiple (*n* = 455)	*P* value
Parity				0.67
Nulliparous	65 (14.6)	10 (16.4)	55 (14.3)	
Primiparous	40 (9.0)	5 (8.2)	35 (9.1)	
Pauciparous	102 (22.9)	17 (27.9)	85 (22.1)	
Multiparous	239 (53.6)	29 (47.5)	210 (54.5)	
Gravida				0.51
Nulligravid	71 (16.0)	11 (18.0)	60 (15.6)	
Primigravid	40 (9.0)	3 (4.9)	37 (9.6)	
Multigravid	334 (75.1)	47 (77.0)	287 (74.7)	
Abortion	83 (18.7)	15 (24.6)	68 (17.7)	0.14
Family history of thyroid pathology	352 (66.5)	51 (68.9)	301 (66.2))	0.37
First degree	205 (58.2)	30 (60.0)	175 (57.9)	
Second degree	147 (41.8)	20 (40.0)	127 (42.1)	
Anterior-cervical mass	503 (95.1)	71 (95.9)	391 (95.8)	0.1
Overweight	195 (36.9)	23 (31.1)	172 (37.8)	0.16
Obesity	187 (35.3)	28 (37.8)	159 (34.9)	0.36
Clinical lymphadenopathy	46 (8.7)	10 (13.5)	36 (7.9)	0.09
Systolic blood pressure	135.6 ± 58.6	131.4 ± 13.8	135.8 ± 65.5	0.79
Diastolic blood pressure	72.6 ± 8.9	73.9 ± 8.5	72.3 ± 9.2	0.48
Body mass index	29.8 ± 12.1	29.5 ± 3.1	29.9 ± 13.6	0.96
Heart rate	83.0 ± 11.0	82.0 ± 11.6	83.1 ± 10.6	0.56
Total volume	70.9 ± 31.5	68.5 ± 30.8	70.8 ± 32.2	0.6
Thyroid function				0.63
Euthyroid	464 (87.7)	63 (85.1)	401 (88.1)	
Hyperthyroid	50 (9.5)	9 (12.2)	41 (9.0)	
Hypothyroid	15 (2.8)	2 (2.7)	13 (2.9)	

Furthermore, previous literature states that thyroid nodules are common amongst the Congolese population due to the lack of adequate iodine in the typical Congolese cuisine[8]. Prevalence of cancer is higher in several groups such as children, adults younger than 30, patients with a history of head and neck irradiation, and/or family history of thyroid cancer[12,14,15]. Our study, however, revealed a higher prevalence of thyroid cancer in patients older than 60 years of age which is in line with the findings of the study by Kwong *et al*[16] but in contrast to the Sicilian study conducted by Belfiore *et al*[15]. The latter found that adults younger than 30 years old were at highest risk of developing malignant nodules.

Exposure to trace minerals and heavy metals has also been associated with thyroid cancer development[9-11]. A study by Petrosino *et al*[17] revealed that all patients with head and neck cancer had at least twice the upper limit of reference range of heavy metals and polychlorinated biphenyls (PCB) in their blood and hair tissue. In contrast, all healthy volunteers did not have significant levels of either metals or PCBs. A study done at Yale University found that urinary cadmium, antimony and tungsten were significantly associated with increased odds of thyroid dysfunction, including cancer[18]. A similar study done in South Korea among residents living near industrial complexes revealed that urinary mercury concentration was associated with increased risk of thyroid cancer[19]. No such study has been carried out in the DRC. Furthermore, no studies have been done to evaluate the frequency of thyroid cancer in different regions of the country that are rich in heavy metals. DRC is endowed with exceptional natural resources, including minerals such as cobalt, copper, coltan, mercury, tantalum, tin, gold, lithium, tungsten, manganese, uranium, and many others[20]. The natural resources are not equally distributed within the country, with some regions having a remarkably higher concentration than others.

Katanga province is one of the wealthiest regions across the globe in terms of natural resources. It has 34% of the world's cobalt reserve and 10% of the world's copper reserve. It is also rich in zinc, lead, uranium, tin, manganese, chromium, mercury, cadmium, silver, gold, germanium, and coal. A 2009 study in the province found substantial

Table 3 Ultrasonographic features of thyroid nodules, *n* (%)

Variables	All (*n* = 529)	Simple (*n* = 74)	Multiple (*n* = 408)	*P* value
Echostructure				0.84
Solid	382 (72.2)	53 (71.6)	329 (72.3)	
Liquid	12 (2.3)	1 (1.4)	11 (2.4)	
Mixed	135 (25.5)	20 (27.0)	115 (25.3)	
Echogenicity				0.33
Hypoechoic	447 (84.5)	59 (79.7)	388 (85.3)	
Isoechoic	81 (15.3)	15 (20.3)	66 (14.5)	
Anechoic	1 (0.2)	0 (0.0)	1 (0.2)	
Size				0.36
Macronodule	315 (59.8)	50 (67.6)	265 (58.5)	
Micronodule	82 (15.6)	9 (12.2)	73 (16.1)	
Mixed	130 (24.7)	15 (20.3)	115 (25.4)	
Microcalcifications				0.5
No	453 (85.6)	64 (86.5)	389 (85.5)	
Yes	76 (14.4)	10 (13.5)	66 (14.5)	
Adenopathy				0.35
No	447 (84.5)	61 (82.4)	386 (84.8)	
Yes	82 (15.5)	13 (17.6)	69 (15.2)	

exposure to several metals, especially affecting children. Urinary Cobalt concentrations in this population are the highest ever reported for a general population[21]. In 2016, researchers discovered enormous metal contamination affecting marine life in Katanga's Lake Tshangalele, near mining and other metallurgical operations in Likasi. Affected fish species are commonly consumed by the local population[22]. However, no studies have been carried out in the country to compare the frequency of malignant thyroid nodules in this area *vs* lower mineral density regions. Our study found that 44.4 % of nodules in the Katanga region were malignant, in contrast with 22.2% nodules in patients from Kinshasa. This trend shows a plausible role of heavy metal contamination in carcinogenesis amongst this population.

Ultrasonography yields extremely valuable information about the thyroid gland and adjacent structures. Cumulative ultrasonographic evidence, in appropriate clinical context, can increase diagnostic accuracy and assist with treatment through surgical, radiation, and/or ablation based modalities[23-25]. Malignant thyroid nodules often have a hypoechoic appearance on ultrasound[26,27]. Microcalcifications may be present in both benign and malignant nodules and are therefore only partially predictive of histopathology, however, in a Greek study by Kakkos *et al*[28], the prevalence of cancer was significantly higher in the presence of microcalcifications. Our study revealed that hypoechogenicity and microcalcifications were associated with malignancy, which is in accordance with the current literature. The uniformity of the internal structure of a nodule is not a useful indicator for diagnosis of cancer; cancers may be either entirely solid or contain some component of cystic content. In general, the larger the cystic component, the higher is the likelihood of the nodule being benign[29]. In addition, a large nodule diameter and volume is predictive of malignant potential and clinical prognosis[30-32]. In a large study, conducted by Angell *et al*[23], that assessed 20000 thyroid nodules, for every centimeter increase in size of a nodule over 1 cm, there was a 15% to 30% escalation in malignancy risk. Our study also found that a solid echostructure and greater nodule size were associated with greater odds of malignancy.

Thyroid follicular epithelial-derived cancers are divided into three categories namely papillary (85%), follicular (12%) and anaplastic (< 3%). Papillary and follicular cancers are considered differentiated cancers. Most anaplastic (undifferentiated) cancers appear to arise from differentiated cancers[33]. Papillary followed by follicular cancers were the most prevalent malignancies in our study population. Anaplastic cancers occurred at a higher frequency when compared with existing literature (7.6% *vs* < 3%). This could be explained by the paucity of healthcare resources and accessibility, and absence of routine patient follow-up in the DRC that permits progression of longstanding differentiated carcinomas into undifferentiated lesions.

This study has several limitations, such as missing data variables, multiplicity of types of ultrasound devices and operators, and the lack of a validated thyroid ultrasound examination protocol. Also, we excluded case records that didn't have a definitive histopathological diagnosis on file. Determination of causality and temporality in the association between mineral exposure and thyroid cancer development is an existing limitation of our study, inherent to its retrospective study design. Moreover, several unknown variables contributing to an increased risk of malignancy were unaccounted for. Recruitment of patients from the three provinces was not equal due to dearth of healthcare access in certain regions of the country. Additionally, lack of accessibility to sensitive analyses to measure blood and environ-

Table 4 Histopathological characteristics of thyroid nodules, *n* (%)

Variables	Number (*n* = 529)
Histopathology	
Benign nodules	441 (77.7)
Malignant nodules	118 (22.3)
Benign nodules	
Colloid goiter	302 (73.5)
Adenomatoid goiter	36 (8.8)
Follicular adenoma	20 (4.9)
Macrofollicular adenoma	18 (4.4)
Follicular cyst	8 (1.9)
Adenomatoid nodule	5 (1.2)
Thyroid abscess	3 (0.7)
Follicular adenoma	3 (0.7)
Microfollicular adenoma	3 (0.7)
Reactive lymphadenopathy	3 (0.7)
Chronic strumitis	3 (0.7)
Grave's disease	2 (0.5)
Non toxic adenoma	1 (0.2)
Toxic adenoma	1 (0.2)
Granulomatous thyroid	1 (0.2)
Dequervain's subacute thyroiditis	1 (0.2)
Hashimoto's thyroiditis	1 (0.2)
Malignant nodules	
Papillary carcinoma	79 (66.9)
Follicular carcinoma	26 (22.0)
Anaplastic carcinoma	9 (7.6)
Lymphoma	3 (2.5)
Medullary carcinoma	1 (0.8)

mental levels of the various minerals is a potential drawback of our study. Our analyses didn't elucidate the malignancy risk imparted by different heavy metals individually. Rather we based our conclusions on the differences in geographical mineral density, which took into account the effect of a mixture of heavy metals. The latter is invariably an accurate representation of real-world impact of heavy metal exposure, and hence, it could also be deemed as a strength of our study in lieu of a shortcoming. Nevertheless, it is necessary to delineate the individualistic risk posed by these heavy metals as some elements may confer protection against malignant transformation. Ecological studies comparing the soil and urinary concentrations of various heavy metals against thyroid cancer prevalence in specific geographical locations could lend valuable information. Urinary concentration of heavy metals concentrations and serum levels of thyroid-related antibodies serve as reliable surrogate markers for heavy metal exposure and malignancy risk, respectively. Prospective studies should be designed to obtain these estimates and assess for thyroid cancer incidence. Given the increasing global burden of environmental pollutants and thyroid cancer incidence, it is worthwhile to ascertain the correlation between these two variables in mineral dense regions as public health measures can be implemented to mitigate heavy metal exposure in at-risk populations.

To the best of our knowledge, this is the first study to demonstrate that residence within the mineral-dense province of Katanga was associated with higher odds of having a thyroid malignancy. Although we can't draw any causal inference from this peculiar finding, it provides us with preliminary data to conduct and/or fund studies testing similar hypotheses. We hope to conduct future studies to further elucidate the association between heavy metal exposure and thyroid cancer in the DRC based on our current study findings. We would like to systematically analyze this relationship by utilizing objective parameters quantifying the environmental and serum levels of various heavy metals and testing surrogate markers predictive of thyroid malignancy.

Table 5 Sociodemographic and clinical characteristics of thyroid nodules, based on histopathology, *n* (%)

Variables	*N*	Benign nodule	Malignant nodule	*P* value
Age (years)				0.003
≤ 20	35	31 (87.1)	4 (12.9)	
21-60	412	333 (80.8)	79 (19.2)	
> 60	82	47 (57.3)	35 (42.7)	
Sex				0.061
Male	82	58 (70.7)	24 (29.3)	
Female	444	352 (79.3)	92 (20.7)	
Residential province				0.044
Kinshasa	468	364 (77.8)	104 (22.2)	
Katanga	18	10 (55.6)	8 (44.4)	
South Kivu	43	37 (86.0)	6 (14.0)	
Marital status				0.26
Married	373	293 (78.6)	80 (21.4)	
Single	115	85 (73.9)	30 (26.1)	
Divorced/widowed	9	7 (77.8)	2 (22.2)	
Parity				0.16
Nulliparous	65	46 (70.8)	19 (29.2)	
Primiparous	40	32 (80.0)	8 (20.0)	
Pauciparous	102	87 (85.3)	15 (14.7)	
Multiparous	239	187 (78.2)	52 (21.8)	
Gravida				0.311
Nulligravid	71	51 (71.8)	20 (28.2)	
Primigravid	40	32 (80.0)	8 (20.0)	
Multigravid	334	268 (80.2)	66 (19.8)	
Family history of thyroid pathology				0.022
No	177	147 (83.1)	30 (16.9)	
Yes	352	264 (75.0)	88 (25.0)	
Body mass index				0.51
Normal	25	22 (88.0)	3 (12.0)	
Overweight	195	150 (76.9)	45 (23.1)	
Obesity	187	146 (78.1)	41 (21.9)	
Lymphadenopathy				< 0.001
No	100.0	397 (82.2)	86 (17.8)	
Yes	100.0	14 (30.4)	32 (69.6)	

CONCLUSION

This is the first study to demonstrate that differential provincial mineral density in the DRC impacts the odds of thyroid malignancy. We believe that our study unlocks a significant association between environmental mineral density and thyroid malignancy in the DRC, and this relationship should be tested robustly in future studies based on our premise. Albeit routine screening for thyroid cancer in a low-risk population might not be cost effective, it still holds public health relevance in areas of mineral abundance, given the higher frequency of undifferentiated cancers in this subset. This association needs to be substantiated further in future, well-funded studies to accurately delineate the effect of heavy metal exposure on the risk of thyroid cancer development.

Table 6 Ultrasound characteristics of benign and malignant thyroid nodules, *n* (%)

Variables	*N*	Benign nodule	Malignant nodule	*P* value
Echostructure				< 0.001
Solid	382	268 (70.2)	114 (29.8)	
Liquid	12	12 (100.0)	0 (0.0)	
Mixed	135	4 (97.0)	4 (3.0)	
Echogenicity				< 0.001
Hypoechoic	447	330 (73.8)	117 (26.2)	
Isoechoic	81	80 (98.8)	1 (1.2)	
Anechoic	1	1 (100.0)	0 (0.0)	
Number				0.284
Single	74	55 (74.3)	19 (25.7)	
Multiple	455	356 (79.2)	99 (20.8)	
Size				< 0.001
Macronodule	315	211 (67.0)	104 (33.0)	
Micronodule	82	81 (98.8)	1 (1.2)	
Mixed	130	119 (91.5)	11 (8.5)	
Calcifications				< 0.001
No	453	376 (83.0)	77 (17.0)	
Yes	76	35 (46.1)	41 (53.9)	
Adenopathy				< 0.001
No	447	382 (85.5)	65 (14.5)	
Yes	82	29 (35.4)	53 (64.6)	

Table 7 Sociodemographic, clinical and ultrasonographic features associated with malignancy in thyroid nodules

Variables	Univariate analysis		Multivariate analysis	
	P value	OR (95%CI)	*P* value	Adjusted OR (95%CI)
Age (years)				
≤ 20		1		1
21-60	0.319	1.52 (0.67-3.46)	0.614	1.32 (0.26-2.24)
> 60	0.003	2.81 (1.37-5.78)	0.025	2.81 (1.14-6.94)
Province of origin of the sample				
South Kivu		1		1
Kinshasa	0.212	1.76 (0.72-4.29)	0.116	2.47 (0.80-7.62)
Katanga	0.014	4.93 (1.39-17.54)	0.036	8.19 (1.14-12.45)
Family history of thyroid pathology				
No		1		1
Yes	0.022	1.63 (1.03-2.59)	0.105	1.65 (0.90-3.34)
Clinical LAD				
No		1		1
Yes	< 0.001	10.55 (5.40-20.62)	0.760	1.20 (0.38-3.82)
Echostructure				

Liquid		1		1
Solid	< 0.001	15.21 (5.50-42.07)	0.001	7.69 (2.40-24.58)
Echogenicity				
Isoechoic		1		1
Hypoechoic	< 0.001	18.72 (3.95-28.68)	0.017	14.19 (1.60-25.93)
Size				
Micronodule		1		1
Macronodule	< 0.001	5.33 (2.75-10.33)	< 0.001	9.13 (4.19-19.89)
Calcification				
No		1		1
Yes	< 0.001	5.72 (3.42-9.55)	0.017	2.60 (1.19-5.70)
Sonographic LAD				
No		1		1
Yes	< 0.001	10.74 (6.36-18.13)	< 0.000	6.94 (2.79-17.25)

LAD: Lymphadenopathy; OR: Odds ratio.

FOOTNOTES

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