Thyroid Nodules in Centenarians: Prevalence and Relationship to Lifestyle Characteristics and Dietary Habits

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Abstract: Thyroid nodules (TNs) are common thyroid lesions in older population. Few studies focused on the prevalence of TNs and its relationship to lifestyle characteristics and dietary habits in centenarians. The current study aimed to determine the prevalence of TNs in Chinese centenarians using high-resolution ultrasound equipment and investigate its relationship to lifestyles and dietary habits. The current study was part of China Hainan Centenarian Cohort Study (CHCCS) which conducted in Hainan, an iodine sufficient region in China. A total of 874 permanent residents aged 100 years or older (mean age, 102.8 ± 2.8 years) without any missing data were included in the analysis. Among the participants, 649 of them were detected at least one thyroid nodule under the ultrasound examinations. The overall prevalence rate of TNs was 74.3%. The prevalence of TNs was higher in participants who were females, hypertension, diabetes, and underweight than their counterparts. Multivariate logistic regression analyses showed that being female, hypertension, diabetes, betel quid consumption, red meat consumption were independent risk factors, while being underweight, and nut consumption were independent protective factors for TNs. Our findings indicate that the presence of thyroid nodules was highly prevalent in Chinese centenarians, particularly in females. In addition to gender, hypertension, diabetes, and underweight, the presence of TNs was independently associated with betel quid, red meat, and nut consumptions. Further prospective studies are warranted to verify these associations in population from different age strata, races, cultures, and iodine backgrounds.

Keyword: thyroid nodules; ultrasound; lifestyle; dietary; betel quid; red meat; nut; centenarians

1. Introduction

Thyroid nodules (TNs) are common thyroid lesions in older population. High-resolution ultrasonography has made possible the detection of asymptomatic and non-palpable thyroid nodules [1]. The prevalence of TNs detected by high-resolution ultrasonography was 19-68% based on randomly selected individuals, with annual increasing trends worldwide [2,3]. The clinical importance of TNs detection rests with the need to exclude thyroid cancer, which occurs in 5-15% of TN cases [1,4]. A recent study reported that the occurrence of TNs increased as people age, with a prevalence of 74% in a community-based sample of Chinese senior adults [5]. However, the prevalence of this lesion in centenarians remained understudied. Considering the issues mentioned above, there is a need to specifically determine the prevalence of TNs in late life, particularly in centenarians.
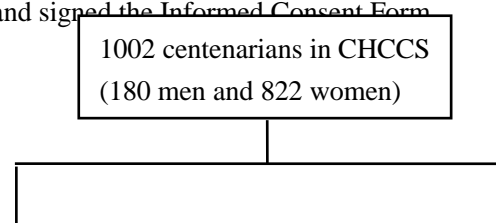
The high prevalence rate of TNs was partly due to widespread application of high-resolution ultrasound and early diagnosis. In addition, recent studies also proposed that several risk factors could attribute to TNs. Among those risk factors, some factors were non-modifiable such as age, sex, and history of irradiation exposure, while others were modifiable including iodine intake, smoking, alcohol drinking, obesity and metabolic syndrome [5-8]. However, some other modifiable factors, including passive smoking, red meat consumption, and nut intake which were related to lifestyle and dietary habits, were seldom regarded in TNs' studies. Therefore, further investigations on the relationship between prevalence of TNs and potential lifestyle characteristics as well as dietary habits are of epidemiological and clinical significance.

The aim of this study was to determine the prevalence of TNs in Chinese centenarians and investigate its relationship to lifestyle characteristics and dietary habits. Data from the China Hainan Centenarian Cohort Study were used in this study. It was hypothesized that (1) TNs were highly prevalent in centenarians; (2) occurrence of TNs were correlated to several lifestyle characteristics and dietary habits such as betel quid consumption, red meat consumption, and nut intake.

2. Subjects and Methods

2.1. Study population

The sample for this study was obtained from the China Hainan Centenarian Cohort Study (CHCCS), one of the largest centenarian health interdisciplinary studies conducted in China from June 2014 to December 2016. Details of this study have been described elsewhere [9]. The CHCCS is located in Hainan province, which is both a longevity area with the highest density of centenarians in China and an iodine sufficient region with abundant seafood provided [10]. Based on National Civil Registry, 1,002 centenarians were recruited in the present study. Age was ascertained from national identification cards. There were 874 centenarians including 150 men and 724 women without any missing data in the final analysis (Figure 1). The present study was approved by the Ethics Committee of Hainan branch of Chinese People's Liberation Army General Hospital (Sanya, Hainan; Number: 301hn11201601). Participants were informed about the research contents and signed the Informed Consent Form.
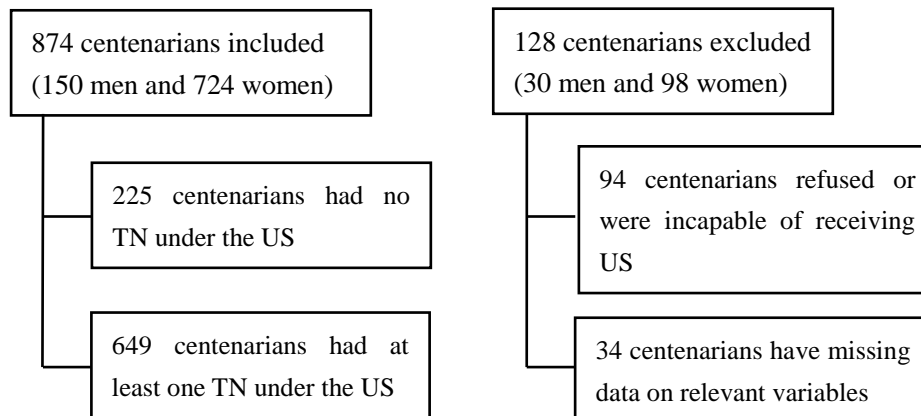

1002 centenarians in CHCCS
(180 men and 822 women)

874 centenarians included (150 men and 724 women)	128 centenarians excluded (30 men and 98 women)

225 centenarians had no TN under the US	94 centenarians refused or were incapable of receiving US

649 centenarians had at least one TN under the US	34 centenarians have missing data on relevant variables

Figure 1: Diagram of the study population. US: ultrasonography

2.2. Thyroid ultrasound procedure

The ultrasound (US) scans of thyroid glands and neck areas were operated using standard procedure by sonographers who were board-certified with more than 3 years of experience in thyroid US. A thyroid nodule is a discrete lesion within the thyroid gland that is radiologically distinct from the surrounding thyroid parenchyma [4]. The US equipment used in the study were Philip CX50 (Philip Medical System, Andover, MA, USA) instruments with3-12 MHz linear-array transducers. All the US examinations complied with the same protocol for thyroid scanning. US images were stored in separate hard drives and separately reviewed by two radiologists with 5 and 12 years of experience. Participants were dichotomized into TN+ (have at least one nodule) and TN- (normal thyroid gland without nodule).

2.3. Demographic and health-related variables

Home interviews were conducted to collect data on the demographic details (age, gender, ethnicity, level of education, and work type before retirement). Health examinations were performed and blood samples were obtained from each participant. Ethnicities were categorized into Han and non-Han. Given that the majority of centenarians received no education, participants were categorized into illiterate and primary school or above. Considering that only 2.7% of centenarians were doing manual works such as farming before retirement, work types before retirement were classified as heavy manual work and moderate manual or mental work. Health-related variables contained BMI, hypertension, diabetes, dyslipidemia, anemia, and self-rated health. Height and weight were measured according standard procedures, and body mass index (BMI) was calculated as the weight in kilograms divided by square height in meters. BMI was dichotomized into underweight (<18.5 kg/m^2) and normal or overweight (≥18.5 kg/m^2). Systolic and diastolic blood pressures (SBP and DBP) were measured two times consecutively, with at least 1 minute interval between measurements, and the reported blood pressures were the average of the two measurements. Samples of venous blood were obtained from the centenarians in a seated position and transported in cold storage (4°C) to Central Laboratory within 4 hours. Serum concentrations of triglyceride (TG), total cholesterol (TC), low density lipoprotein cholesterol (LDL-c), high density lipoprotein cholesterol (HDL-c), fasting blood glucose (FBG), and hemoglobin (Hb) were measured using enzymatic assays (Roche Products Ltd, Basel, Switzerland) on a fully automatic biochemical autoanalyzer (COBAS c702; Roche Products Ltd).

The centenarians who had SBP ≥140 mmHg, DBP ≥90 mmHg or were treated with anti-hypertensive agents were considered having hypertension [11]. The centenarians who had FBG ≥7.0 mmol/L or were treated with anti-diabetic agents/insulins were considered having diabetes [12]. The centenarians who had TG ≥1.7 mmol/L, TC ≥5.18 mmol/L; LDL-C ≥3.37 mmol/L, HDL-C <1.04 mmol/L or were treated with lipid-regulating agents were considered have dyslipidemia [13]. Anemia was defined as a hemoglobin level below 12 g/dL in women and below 13 g/dL in men according to the WHO criteria [14]. Self-rated health was defined as subjective perception of health status and was classified as good, fair, and poor [15].

2.4. Lifestyle characteristics and dietary habits

Data regarding lifestyle characteristics and dietary habits, including smoking, alcohol drinking, tea drinking, passive smoking, taste preference, red meat, poultry, seafood, vegetable, fruit, betel quid, egg, milk, and nut consumptions, were collected. Habits of smoking, alcohol drinking, and tea drinking were categorized as current, former and never. Passive smoking was defined as involuntary inhalation of smoke by persons other than the intended 'active' smoker [16]. Exposure of passive smoking was dichotomized as yes (at least once per week for longer than 1 year) and no [17]. Taste preferences were divided into three groups: salty, average, and bland according to subjective evaluation. Consumptions of red meat, poultry, seafood, vegetable, fruit, egg, milk, and nut were categorized into three groups: frequent (≥ 3 times/week), occasional (< 3 times/week), and never. Betel quid generally consists of areca nut, betel leaf, catechu, slaked lime, and often tobacco [18]. Given that most of centenarians were incapable of chewing betel quid in their 100s, habits of betel quid chewing were dichotomized as yes (in the present or past) and no.

2.4. Statistical Analysis

Data were reported as mean values and standard deviations for normally distributed variables or as median values and corresponding 25th and 75th percentiles for non-normally distributed variables. Counts and percentages were reported for categorical variables. Differences in continuous variables were explored with the unpaired *t* test, Mann-Whitney *U*-test and one-way analysis of variance (ANOVA). Chi-square test or Fisher's exact test were used to compare categorical variables. Multivariate logistic regression analyses were used to determine the independent factors correlated to TNs. All analyses were carried out using SPSS software (version 19.0 for windows; IBM co., NY, USA; No. of serial: 5087722). A *P* value <0.05 was considered statistically significant.

3. Results

3.1. General Characteristics

A total of 874 individuals aged 100 years and over were included in this study. Mean age of the participants was 102.8 ± 2.8 years. As Table 1 shows, majority of the participants were female (82.8%), illiterate (90.8%), and Han ethnic (87.3%). More than 42% of study participants did heavy manual works before retirements. Fifty-three percent of the study participants were underweight. The prevalence of chronic conditions was 67.3%, 10.2%, and 23.7% for hypertension, diabetes, and dyslipidemia, respectively. About one third of the study participants were anemia. The proportions of self-rated health were 23.6%, 60.3%, and 16.1% for good, fair, and poor, respectively. None of the participants declared that they had iodine supplementation in

the present and the past. Besides, there was no radiation exposure before and after retirement of the participants.

Table 1. General characteristics of the participants by thyroid nodules

Variables	Total n=874	TN+ n=649	TN- n=225	P
Age, years	102.8 ± 2.8	102.9 ± 2.8	102.8 ± 2.7	0.724
Females, %	82.8	86.6	72.0	< 0.001
Illiterate, %	90.8	91.4	89.3	0.361
Han ethnic,%	87.3	87.2	87.6	0.894
Heavy manual work, %	42.7	41.9	44.9	0.436
Underweight, %	53.0	51.5	57.3	0.128
Hypertension, %	67.3	69.8	60.0	0.007
Diabetes, %	10.2	11.6	6.2	0.023
Dyslipidemia, %	23.7	22.8	26.2	0.299
Anemia, %	32.0	33.3	28.4	0.180
Self-rated health, %				0.190
Good	23.6	24.8	20.0	
Fair	60.3	58.6	65.3	
Poor	16.1	16.6	14.7	

TN+: Participants with at least one thyroid nodule under the ultrasound examinations; TN-: Participants without thyroid nodule.

3.2. Prevalence of Thyroid Nodules

Among the 874 centenarians interviewed, 649 of them were detected at least one thyroid nodule under the US procedure. The overall prevalence rate of TNs was 74.3% (Table 1). Female sex was more frequent in subjects who had TNs than those who had not (86.6% *vs.* 72.0%; $P < 0.001$). In addition to gender, comparison of the age, level of education, ethnicity, and work type before retirement in participants with or without TNs showed insignificant variations. When examining the health-related factors, the prevalence of TNs was significantly more common among those who were hypertension and diabetes (all $P < 0.05$). Proportions of Underweight and dyslipidemia were higher in participants who had TNs than those who had no TN, but with no statistical significance. The patterns of self-rated health between participants with and without TNs were not significant different.

3.3. Analyses of Thyroid Nodules with Lifestyle characteristics and Dietary Habits

Comparison analyses on lifestyle and dietary variables between participants with and without the presence of TNs were performed (Table 2). The prevalence of betel quid consumption in participants who had TNs was significant higher than those who had no TN (6.9% *vs.* 2.7%; $P < 0.05$). As for other factors regarding to lifestyle and dietary habits, no significant variation was found between participants with and without the presence of TNs.

Table 2. Lifestyle characteristics and dietary habits of the participants by thyroid nodules

Variables	Total n=874	TN+ n=649	TN- n=225	P	Variables	Total n=874	TN+ n=649	TN- n=225	P
Smoking, %				0.373	Seafood				0.108

	Total	TN-	TN+	p		Total	TN-	TN+	p
					consumption, %				
Current	5.9	5.4	7.6		Frequent	63.2	61.2	68.9	
Former	4.9	4.6	5.8		Occasional	32.2	34.1	26.7	
Never	89.1	90.0	86.7		Never	4.7	4.8	4.4	
Alcohol drinking, %				0.865	Vegetable consumption, %				0.471
Current	11.9	11.9	12.0		Frequent	92.9	92.4	94.2	
Former	5.9	5.7	6.7		Occasional	2.5	2.5	2.7	
Never	82.2	82.4	81.3		Never	4.6	5.1	3.1	
Tea drinking, %				0.397	Fruit consumption, %				0.263
Frequent	5.5	6.0	4.0		Frequent	39.0	37.8	42.7	
Occasional	7.2	7.6	6.2		Occasional	57.0	57.8	54.7	
Never	87.3	86.4	89.8		Never	4.0	4.5	2.7	
Passive smoking, %				0.739	Betel quid consumption, %				0.019
Yes	44.5	44.8	43.6		Yes	5.8	6.9	2.7	
No	55.5	55.2	56.4		No	94.2	93.1	97.3	
Taste preference, %				0.647	Egg consumption, %				0.515
Salty	13.8	14.5	12.0		Frequent	36.3	36.4	36.0	
Average	19.3	19.3	19.6		Occasional	54.3	53.6	56.4	
Bland	66.8	66.3	68.4		Never	9.4	10.0	7.6	
Red meat consumption, %				0.125	Milk consumption, %				0.217
Frequent	77.5	77.5	77.3		Frequent	28.7	29.7	25.8	
Occasional	17.7	18.5	15.6		Occasional	53.7	51.9	58.7	
Never	4.8	4.0	7.1		Never	17.6	18.3	15.6	
Poultry consumption, %				0.850	Nut consumption, %				0.057
Frequent	36.3	36.1	36.9		Frequent	3.7	3.2	4.9	
Occasional	58.6	58.6	58.7		Occasional	66.5	64.9	71.1	
Never	5.1	5.4	4.4		Never	29.9	31.9	24.0	

TN+: Participants with at least one thyroid nodule under the ultrasound examinations; TN-: Participants without thyroid nodule.

Table 3 shows the results from the logistic regression analyses. After adjusting for all related factors, the multivariate model revealed that being female, hypertension, diabetes, underweight, consumption of betel quid, red meat, and nut were significantly independent correlates of the presence of TNs. Among these correlates, being female, hypertension, diabetes, consumption of betel quid and red meat were risk factors, while being underweight, consumption of nut were protective factors for TNs.

Table 3. Significant factors of TNs by logistic regression analysis

Variables	β	SE	OR	95%CI	*P*
Female	1.21	0.27	3.36	1.97-5.75	< 0.001
Hypertension	0.49	0.18	1.63	1.16-2.30	0.005
Diabetes	0.94	0.33	2.55	1.35-4.83	0.004
Underweight	-0.35	0.17	0.71	0.50-0.99	0.045
Betel quid consumption	1.12	0.48	3.08	1.21-7.85	0.019
Red meat consumption					
Frequent	1.03	0.40	2.80	1.28-6.09	0.010
Occasional	1.23	0.44	3.43	1.45-8.15	0.005
Never (Reference)	-	-	1.00	-	-
Nut consumption					
Frequent	-0.97	0.46	0.38	0.15-0.94	0.037
Occasional	-0.58	0.23	0.56	0.35-0.89	0.013
Never (Reference)	-	-	1.00	-	-

TNs: thyroid nodules; β: logistic regression coefficient; SE: standard error; OR: odds ratio; CI: confidence interval.

4. Discussion

According to the results of this study, the hypothesis was accepted that the presence of thyroid nodules was highly prevalent in Chinese centenarians, particularly in female subjects. In addition, this study also found out that several lifestyles and dietary habits including betel quid, red meat, and nut consumptions were independent factors related to the presence of TNs. This study firstly reported the prevalence rate of TNs in a population-based sample of centenarians in China using high-resolution ultrasound equipment. Furthermore, this study provided a comprehensive look at the correlation between prevalence of TNs and lifestyles as well as diet habits in this population.

The findings of this study showed that the overall prevalence of TNs in centenarians was 74.3%, ranging from 77.6% in females to 58.0% in males. This result indicated a relatively high prevalence of TNs in this exceptional aged population. To our best knowledge, this is the first study to report prevalence of thyroid nodules among centenarians. According to the previous studies, the prevalence of TNs in senior population was 73.7% in China [5], 54.9% in Korea [19], and 46.2% in Cameroon [20]. The differences in the prevalence may be due to age, gender, race, culture, dietary patterns, and iodine supplements [7,21,22].

The prevalence of TNs was higher in study population who were female sex, hypertension, diabetes, and underweight than their counterparts. The gender disparity of the presence of TNs was in accordance with previous studies [5,19,20]. Interestingly, this study found a higher odds ratio of TNs (3.36, 95%CI = 1.97-5.75; *P* < 0.001) in females than previous studies, which indicates a potentially increasing trend of gender disparity on TNs with aging. Further studies are needed to verify this trend. In addition to gender, other age-related conditions including hypertension, diabetes, and underweight were found to independently correlate to TNs. The associations between TNs and hypertension as well as diabetes have been reported in general population [8,23,24]. Previous studies have investigated the relationship between obesity and TNs, indicating that people who were overweight and with a higher BMI were more likely to have TNs than those who were not [5,21,25]. In centenarians, approximately half of them were underweight

(53.0%) and another half were mainly normal weight (47.0%). Participants who were underweight were less likely to have TNs than those who were not (0.71, 95%CI = 0.50-0.99; *P* = 0.045). The combination of previous findings and this finding may suggest that prevalence of thyroid nodules is positively correlated to BMI. Further studies are necessary to elaborate the mechanisms of the association between BMI and TNs.

Considering that only few modifiable factors associated with TNs have been identified [6], this study conducted a comprehensive analysis on the relationship between TNs and fourteen modifiable factors regarding to lifestyle characteristics and dietary habits. The results showed that betel quid and red meat consumption were independent risk factors, while nut intake was protective factor in multivariate logistic analyses. The betel quid was affirmed as carcinogenic to humans (Group 1) by International Agency for Research on Cancer (IARC) [26]. There was sufficient evidence that betel quid or areca nut cause oral and oesophagus cancer [18,27]. However, no evidence supports that betel quid consumption is associated with thyroid nodules or thyroid cancer. One previous study on rat experiments found that arecoline, a carcinogenic element of betel quid, initially stimulated the thyroid and eventually inhibited the activity; and the chronic arecoline treatment caused light degenerations of thyro-follicular cells [28]. Further studies are required to examine the mechanisms of the association on betel quid and thyroid nodules.

Red meat was considered as a 2A-level carcinogen by IARC [29]. Previous studies reported that red meat consumption is associated with increased thyroid cancer risk [30,31]. To our knowledge, however, there is no study on the association between the red meat and thyroid nodules. Thus further studies are necessary to illuminate this association. In addition to risk factors of TNs, the logistic regression analyses also showed that nut intake was potential protective factors of TNs. The main hypothesis is that nut consumption is inversely associated with body mass index (BMI) and risk of obesity [32], and higher BMI was associated with an increased frequency of TNs [33]. Thus the prevalence rate of TNs was lower in participants who were frequent in nut consumption than those who were not. This finding provided a novel insight that frequent nut consumption is associated with lower odds of TNs under the US. Further studies on nut consumption and thyroid nodules are needed to examine this association cross-sectionally and prospectively.

As there is little knowledge in prevalence of thyroid nodules and its correlation to lifestyle and dietary factors in centenarians, this study addressed the knowledge gap and provided novel insight into this correlation in a population-based sample of Chinese centenarians. In addition, the participants were from iodine-sufficient areas and were free from iodine intake and radiation exposure, which enhances the reliability of the findings by excluding the key confounders. Nevertheless, there are several limitations that should be acknowledged. First, this study was cross-sectional designed, and thus causality could not be inferred. Further prospective studies are acquired to verify the association between lifestyle and dietary factors and the prevalence of TNs. Second, the indices of thyroid function including thyroid stimulating hormone (TSH), triiodothyronine (T3), tyroxine (T4) could not be measured, and hence, potential confounders may remain unrecognized [34]. However, this study was conducted in iodine sufficient region and the population here were more likely to have normal range of thyroid function [35].

5. Conclusions

In summary, this study determined the prevalence of TNs and its association to lifestyle

characteristics and dietary habits in a population-based sample of Chinese centenarians. The results showed that presence of TNs by ultrasound is highly prevalent in centenarians. Female sex, hypertension, diabetes, and underweight were independently associated with the prevalence of TNs. Betel quid and red meat consumption were independent lifestyle and dietary risk factors, while nut intake was protective factor. Considering that the TNs were common among elder populations, these findings may provide some insights for intervention strategies for thyroid nodules. Further prospectively designed population studies and clinical trials are needed to clarify the roles of betel quid, red meat, and nut consumptions in thyroid nodules progression and prevention.

Author Contributions: Yao He, Faqin Lv, Yao Yao, Xianghui Chen, Jie Tang, Fuxin Luan, and Yali Zhao conceived and designed the project; Yao Yao, Xianghui Chen, Shengzheng Wu, Liang Guo, and Qiao Zhu performed the study; Yao He, Faqin Lv, Yao Yao, and Hao Zhang analyzed and interpreted the data; Shengzheng Wu, Liang Guo, Qiao Zhu, Fuxin Luan, Yali Zhao coordinated the study; Yao Yao, Xianghui Chen wrote the paper.

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Abbreviations:
The following abbreviations are used in this manuscript:
TNs, thyroid nodules; US, ultrasound; CHCCS, China Hainan Centenarian Cohort Study; ORs, odds ratios; 95% CIs, 95% confidence intervals; BMI, body mass index; SBP, systolic blood pressures; DBP, diastolic blood pressures; TG, triglyceride; TC, total cholesterol; LDL-c, low density lipoprotein cholesterol; HDL-c, high density lipoprotein cholesterol; FBG, fasting blood glucose; Hb, hemoglobin; IARC, International Agency for Research on Cancer.

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