

Thyroid nodules in centenarians: prevalence and relationship to lifestyle characteristics and dietary habits

Yao Yao^{1,*}
 Xianghui Chen^{2,*}
 Shengzheng Wu²
 Liang Guo³
 Hao Zhang⁴
 Qiao Zhu⁵
 Jie Tang³
 Fuxin Luan⁵
 Yali Zhao⁵
 Faqin Lv²
 Yao He¹

¹Institute of Geriatrics, Beijing Key Laboratory of Aging and Geriatrics, National Clinical Research Center for Geriatric Disease, Chinese PLA General Hospital, Beijing, People's Republic of China; ²Department of Ultrasonography, Hainan Branch of PLA General Hospital, Sanya, People's Republic of China; ³Department of Ultrasonography, Chinese PLA General Hospital, Beijing, People's Republic of China; ⁴Department of Health Policy and Management, Texas A&M University, College Station, TX, USA; ⁵Central Laboratory, Hainan Branch of Chinese PLA General Hospital, Sanya, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yao He
 Institute of Geriatrics, Chinese PLA General Hospital, Fuxing Road 28, Beijing 100853, People's Republic of China
 Email yhe301@x263.net

Faqin Lv
 Department of Ultrasonography, Branch of PLA General Hospital, Jianglin Road 9, Sanya 572000, People's Republic of China
 Email lvjin8912@163.com

Background: Thyroid nodules (TNs) are common thyroid lesions in older population. Few studies have focused on the prevalence of TNs and their relationship to lifestyle characteristics and dietary habits in centenarians. The current study aimed at determining the prevalence of TNs in Chinese centenarians by using high-resolution ultrasound (US) equipment and at investigating its relationship to lifestyle characteristics and dietary habits.

Participants and methods: The current study was part of the China Hainan Centenarian Cohort Study that was conducted in Hainan, an iodine-sufficient region in People's Republic of China. A total of 874 permanent residents aged ≥ 100 years (mean age = 102.8 ± 2.8 years) without any missing data were included in the analysis.

Results: Among the participants, 649 of them were detected at least one TN under the US examinations. The overall prevalence rate of TNs was 74.3%. The prevalence of TNs was higher in participants who were women, had hypertension, had diabetes, and were underweight compared with their counterparts. Multivariate logistic regression analyses showed that being female, hypertensive, and diabetic; betel quid consumption; and red meat consumption were independent risk factors, while being underweight and nut consumption were independent protective factors for TNs.

Conclusion: Our findings indicate that the presence of TNs was highly prevalent in Chinese centenarians, particularly in women. In addition to gender, having hypertension, having diabetes, and being underweight, the presence of TNs was independently associated with betel quid, red meat, and nut consumption. Further prospective studies are warranted to verify these associations in populations from different age strata, races, cultures, and iodine supplementation.

Keywords: thyroid nodules, ultrasound, lifestyle, dietary, betel quid, red meat, nut, centenarians

Introduction

Thyroid nodules (TNs) are common thyroid lesions in older population. High-resolution ultrasonography has made the detection of asymptomatic and nonpalpable TNs possible.¹ The prevalence of TNs detected by high-resolution ultrasonography was 19%–68% in randomly selected individuals, with annually increasing trends worldwide.^{2,3} The clinical importance of TN 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 the widespread application of high-resolution ultrasound (US) and early diagnosis. In addition, recent studies also proposed that several risk factors could be attributed to TNs. Among these risk factors, some factors were nonmodifiable, such as age, gender, and the 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 TN studies. Therefore, further investigations into the relationship between the prevalence of TNs and potential lifestyle characteristics, as well as dietary habits, are of epidemiological and clinical significance.

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

Participants and methods

Study population

The sample for this study was obtained from the CHCCS, one of the largest centenarian health interdisciplinary studies

conducted in People's Republic of 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 People's Republic of China, and an iodine-sufficient region with abundant seafood provided.¹⁰ Based on the 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 the Hainan branch of Chinese People's Liberation Army General Hospital (Number: 301hn11201601; Sanya, Hainan, People's Republic of China). The participants were informed about the research contents and signed the informed consent form.

Thyroid US procedure

The US scans of the thyroid glands and neck areas were operated using standard procedure by sonographers who were board-certified with >3 years of experience in thyroid US. A TN 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 was Philips CX50 (Philips Medical Systems, Andover, MA, USA) instrument with 3–12-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

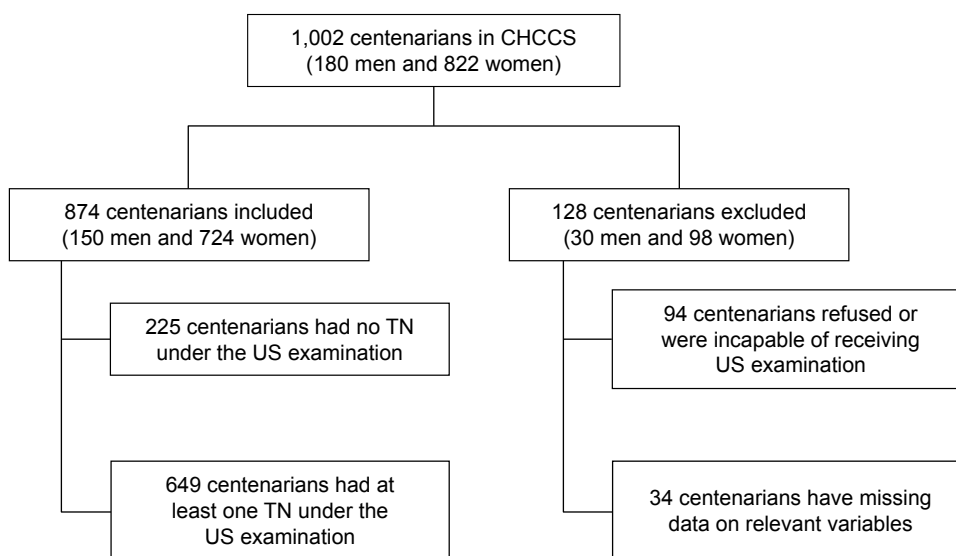


Figure 1 Diagram of the study population.

Abbreviations: CHCCS, China Hainan Centenarian Cohort Study; TN, thyroid nodule; US, ultrasound.

12 years of experience. The participants were dichotomized into TN+ (have at least one nodule) and TN- (normal thyroid gland without nodule).

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. Ethnicity was categorized into Han and non-Han. Given that the majority of centenarians received no education, the 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, moderate manual work, and intellectual work. Health-related variables included body mass index (BMI), hypertension, diabetes, dyslipidemia, anemia, and self-rated health. Height and weight were measured according to the standard procedures, and BMI was calculated as the weight in kilograms divided by the square height in meters. BMI was dichotomized into underweight ($<18.5 \text{ kg/m}^2$) and normal or overweight ($\geq 18.5 \text{ kg/m}^2$) according to the World Health Organization (WHO) criteria.¹¹ Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured two times consecutively, with at least 1-minute intervals between the 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 the 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 $\geq 140 \text{ mmHg}$ and DBP $\geq 90 \text{ mmHg}$ or who were treated with antihypertensive agents were considered to have hypertension.¹² The centenarians who had FBG $\geq 7.0 \text{ mmol/L}$ or who were treated with antidiabetic agents/insulins were considered to have diabetes.¹³ The centenarians who had TG $\geq 1.7 \text{ mmol/L}$, TC $\geq 5.18 \text{ mmol/L}$, LDL-c $\geq 3.37 \text{ mmol/L}$, HDL-c $< 1.04 \text{ mmol/L}$ or who were treated with lipid-regulating agents were considered to have dyslipidemia.¹⁴ Anemia was defined as an Hb level $< 12 \text{ g/dL}$ in women and $< 13 \text{ g/dL}$ in men according to the WHO criteria.¹⁵ Self-rated health was defined as the

subjective perception of health status and was classified as good, fair, and poor.¹⁶

Lifestyle characteristics and dietary habits

Data regarding lifestyle characteristics and dietary habits, including smoking; alcohol drinking; tea drinking; passive smoking; taste preference; and red meat, poultry, seafood, vegetable, fruit, betel quid, egg, milk, and nut consumption, 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.¹⁷ Passive smoking exposure was dichotomized as yes (at least once per week for >1 year) and no.¹⁸ Taste preferences were divided into three groups: salty, average, and bland according to the subjective evaluation. Consumption of red meat, poultry, seafood, vegetable, fruit, egg, milk, and nut was 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.¹⁹ Given that most of the centenarians were incapable of chewing betel quid in their 100s, this habit was dichotomized as yes (in the present or the past) and no.

Statistical analysis

The 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. The counts and percentages were reported for the categorical variables. Differences in the continuous variables were explored using the unpaired Student's *t*-test, Mann-Whitney *U* test, and one-way analysis of variance; χ^2 test or Fisher's exact test was used to compare categorical variables. Multivariate logistic regression analyses were used to determine the independent factors correlated to TNs. All the analyses were carried out by using SPSS software (Version 19.0 for windows, serial number: 5087722; IBM Corporation, Armonk, NY, USA). A *P*-value < 0.05 was considered statistically significant.

Results

General characteristics

A total of 874 individuals aged ≥ 100 years were included in this study. Mean age of the participants was 102.8 ± 2.8 years. As shown in Table 1, the majority of the participants were female (82.8%), illiterate (90.8%), and of Han ethnicity (87.3%). More than 42% of the study participants did heavy

Table 1 General characteristics of the participants by thyroid nodules

Variables	Total n=874	TN+ n=649	TN- n=225	P-value
Age, years	102.8±2.8	102.9±2.8	102.8±2.7	0.724
Women, %	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	

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

Abbreviation: TN, thyroid nodule.

manual work before retirement. 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 anemic. 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.

Prevalence of TNs

Among the 874 centenarians interviewed, 649 centenarians had at least one detected TN under the US procedure. The overall prevalence rate of TNs was 74.3% (Table 1). Female gender was more frequent in subjects who had TNs than in those who did not have TNs (86.6% vs 72.0%; $P<0.001$). In addition to gender, the comparison of age, level of education, ethnicity, and work type before retirement in the participants with or without TNs showed insignificant variations. Figure S1 shows the US images of the TNs. When examining the health-related factors, the prevalence of TNs was significantly more common among those who had hypertension and diabetes (all $P<0.05$). Proportions of underweight and dyslipidemia were higher in participants who had TNs than in those who did not have TNs, but with no statistical significance. The patterns of self-rated health between the participants with and without TNs were not significantly different.

Analyses of TNs with lifestyle characteristics and dietary habits

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

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

Discussion

According to the results of the present study, the hypothesis was accepted that the presence of TNs was highly prevalent in Chinese centenarians, particularly in female subjects. In addition, this study also determined that several lifestyle characteristics and dietary habits, including betel quid, red meat, and nut consumption, were independent factors related to the presence of TNs. This study first reported the prevalence of TNs in a population-based sample of centenarians in People's Republic of China using high-resolution US equipment. Furthermore, this study provided a comprehensive look at the correlation between the prevalence of TNs and lifestyle characteristics 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 women to 58.0% in men. This result indicated a relatively high prevalence of TNs in this exceptionally aged population. To the best of our knowledge, this is the first study to report the prevalence of TNs among centenarians. According to the previous studies, the prevalence of TNs in the senior population was 73.7% in People's Republic of China, 54.9% in Korea, and 46.2% in Cameroon.^{5,20,21} The differences in the prevalence may be due to age, gender, race, culture, dietary patterns, and iodine supplements.^{7,22,23}

The prevalence of TNs was higher in the members of the study population who were female, hypertensive, diabetic, and underweight compared with their counterparts. The gender disparity of the presence of TNs was in accordance

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

Variables	Total n=874	TN+ n=649	TN- n=225	P-value
Smoking, %				0.373
Current	5.9	5.4	7.6	
Former	4.9	4.6	5.8	
Never	89.1	90.0	86.7	
Alcohol drinking, %				0.865
Current	11.9	11.9	12.0	
Former	5.9	5.7	6.7	
Never	82.2	82.4	81.3	
Tea drinking, %				0.397
Frequent	5.5	6.0	4.0	
Occasional	7.2	7.6	6.2	
Never	87.3	86.4	89.8	
Passive smoking, %				0.739
Yes	44.5	44.8	43.6	
No	55.5	55.2	56.4	
Taste preference, %				0.647
Salty	13.8	14.5	12.0	
Average	19.3	19.3	19.6	
Bland	66.8	66.3	68.4	
Red meat consumption, %				0.125
Frequent	77.5	77.5	77.3	
Occasional	17.7	18.5	15.6	
Never	4.8	4.0	7.1	
Poultry consumption, %				0.850
Frequent	36.3	36.1	36.9	
Occasional	58.6	58.6	58.7	
Never	5.1	5.4	4.4	
Seafood consumption, %				0.108
Frequent	63.2	61.2	68.9	
Occasional	32.2	34.1	26.7	
Never	4.7	4.8	4.4	
Vegetable consumption, %				0.471
Frequent	92.9	92.4	94.2	
Occasional	2.5	2.5	2.7	
Never	4.6	5.1	3.1	
Fruit consumption, %				0.263
Frequent	39.0	37.8	42.7	
Occasional	57.0	57.8	54.7	
Never	4.0	4.5	2.7	
Betel quid consumption, %				0.019
Yes	5.8	6.9	2.7	
No	94.2	93.1	97.3	
Egg consumption, %				0.515
Frequent	36.3	36.4	36.0	
Occasional	54.3	53.6	56.4	
Never	9.4	10.0	7.6	
Milk consumption, %				0.217
Frequent	28.7	29.7	25.8	
Occasional	53.7	51.9	58.7	
Never	17.6	18.3	15.6	
Nut consumption, %				0.057
Frequent	3.7	3.2	4.9	
Occasional	66.5	64.9	71.1	
Never	29.9	31.9	24.0	

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

Abbreviation: TN, thyroid nodule.

Table 3 Significant factors of TNs by logistic regression analysis

Variables	β	SE	OR	95% CI	P-value
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	–	–

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

with previous studies.^{5,20,21} Interestingly, this study found a higher odds ratio (OR) of TNs (3.36, 95% confidence interval [CI]=1.97–5.75; $P<0.001$) in women compared with previous studies, which indicates a potentially increasing trend of gender disparity on TNs with age. Further studies are needed to verify this trend. In addition to gender, other age-related conditions, including hypertension, diabetes, and underweight, were independently correlated to TNs. The associations between TNs and hypertension, as well as diabetes, have been reported in the general population.^{8,24,25} 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 compared with those who were not.^{5,22,26} In centenarians, approximately half of them were underweight (53.0%) and another half were of normal weight (47.0%). Participants who were underweight were less likely to have TNs compared with those who were not (0.71, 95% CI =0.50–0.99; $P=0.045$). The combination of the previous findings and this finding may suggest that the prevalence of TNs is positively correlated to BMI. Further studies are necessary to elaborate the mechanisms of the association between BMI and TNs.

Considering that only a few modifiable factors associated with TNs have been identified, this study conducted a comprehensive analysis on the relationship between TNs and 14 modifiable factors regarding the lifestyle characteristics and dietary habits.⁶ The results showed that betel quid intake and red meat consumption were independent risk factors, while nut intake was a protective factor in multivariate logistic analyses. The associations between the prevalence of TNs and smoking, as well as alcohol drinking, were reported in several studies,^{5–7} yet these associations were not found in

the present study. The discrepancy might be explained by differences in iodine status, as the associations seem to be stronger in iodine-deficient regions.²⁷ The betel quid was affirmed as carcinogenic to humans (group 1) by the International Agency for Research on Cancer (IARC).²⁸ There was sufficient evidence that betel quid and the areca nut cause oral and esophageal cancer.^{19,29} However, no evidence supports that betel quid consumption is associated with TNs 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 chronic arecoline treatment caused light degenerations of thyroid follicular cells.³⁰ Further studies are required to examine the association between betel quid and TNs.

Red meat was considered as a 2A-level carcinogen by the IARC.³¹ Previous studies reported that red meat consumption is associated with increased thyroid cancer risk.^{32,33} To the best of our knowledge, however, there is no study on the association between red meat and TNs. Interestingly, the OR of occasional consumption for red meat was higher compared with frequent consumption in this study. We hypothesize that the subjects who frequently consumed red meat in their 100s have better ingestive function and healthier conditions and thus might have a lower prevalence of TNs. Further studies are necessary to verify this association. The logistic regression analyses also showed that nut intake was a potential protective factor of TNs. In addition, the nut intake was inversely correlated to the prevalence of TNs in this study. The main hypothesis is that nut consumption is inversely associated with BMI and the risk of obesity, and higher BMI was associated with an increased frequency of TNs.^{34,35} Thus, the prevalence rate of TNs was lower in participants who frequently consumed nuts compared with those who did not. This finding provided a novel insight that frequent nut consumption is associated with lower odds of TNs under US. Further studies on nut consumption and TNs are needed to examine this association cross-sectionally and prospectively.

As there is little knowledge regarding the prevalence of TNs and their correlation to lifestyle characteristics and dietary habits 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 these key confounders. Nevertheless, there are several limitations that should be acknowledged. First, this study was cross-sectionally designed, and thus, causality could not be

inferred. Further prospective studies are required to verify the association between lifestyle characteristics and dietary factors and the prevalence of TNs. Second, the indices of thyroid function including thyroid stimulating hormone, triiodothyronine, and thyroxine could not be measured. Hence, potential confounders may remain unrecognized.³⁶ However, this study was conducted in the iodine-sufficient region, and the population in this region was more likely to have a normal range of thyroid function.³⁷

Conclusion

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

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

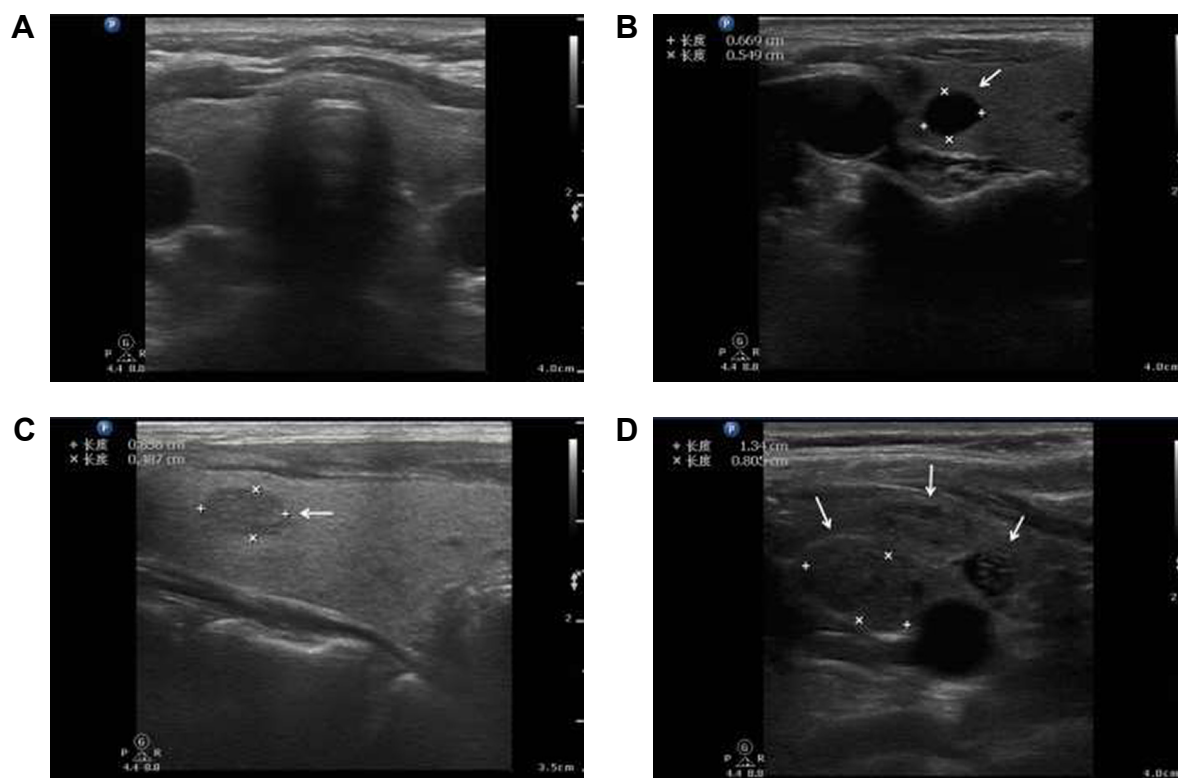


Figure S1 Ultrasound images of thyroid glands with or without nodule in centenarians. **(A)** Normal thyroid gland without TN, female, 104 years old; **(B)** a solitary cystic thyroid nodule in the right lobe of thyroid gland, female, 101 years old; **(C)** a solitary solid nodule in the right lobe of thyroid gland, female, 103 years old; **(D)** multiple nodules including solid and mixed mass in the left lobe of thyroid gland, female, 101 years old. Arrows point to the three thyroid nodules.

Abbreviation: TN, thyroid nodule.

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