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Original Article

Dietary patterns and thyroid cancer risk: a population-based case-control study

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Abstract: Purpose: Thyroid cancer (TC) incidence has increased greatly during the past decades with a few established risk factors, while the relationship between dietary factors and TC remains unclear. Limited literature has investigated the association with inconsistent findings. Methods: We examined the association between dietary pattern and risk of TC in a population based case-control study conducted in Connecticut (2010-2011). Our study population included 390 historically confirmed incident TC cases and 436 population-based controls who completed baseline dietary history questionnaires (DHQ). We identified 3 distinct dietary patterns ("Starchy Foods and Desserts", "Fruits and Vegetables", "High Protein and Fat") through principal components analysis. Multivariate unconditional logistic regression models were used to investigate the association between each dietary pattern and risk of TC, controlling for potential confounders. Results: A diet rich in fruits and vegetables was significantly associated with a reduced risk of overall TC (OR = 0.60, 95% CI: 0.39, 0.92; P_{trend} = 0.02). Compared to younger women, a stronger protective effect was observed among women ≥ 50 years of age in overall TC and papillary TC risk. A diet rich in starchy foods and desserts was positively and negatively associated with an overall TC risk among men and women respectively. Conclusions: Our study found a significant negative association between diet patterns rich in fruits and vegetables and TC risk, especially among women aged 50 years or older. While high in starchy foods and desserts may be positively and negatively associated with TC risk among men and women respectively, these results require confirmation in other populations.

Keywords: Dietary pattern, thyroid cancer

Introduction

Incidence rates for thyroid cancer (TC), the most common endocrine cancer, have increased greatly during the past decades, making TC the most rapidly increasing cancer in the U.S. [1]. According to an estimate provided by the American Cancer Society, by 2017, there will be approximately 56,870 new cases of TC (42,470 in women, 14,400 in men) in the U.S., with an estimated death count of 2,010 (1,090 women, 920 men) [1]. Despite accounting for increases in diagnosis along with changes in technology and diagnostic criteria, the true increase in incidence still exists [2-4].

TC is caused by multiple factors [5], yet only a few risk factors have been established. These factors include being exposed to diagnostic or therapeutic radiation, having a history of goiter or thyroid nodule, having a family history of TC, being female, and have a low iodine diet [1]. Other potential risk factors of TC have also been investigated by previous studies. For example, menstrual and reproductive factors through mediation of estrogen receptors may play a role in the etiology of TC [6]; autoimmune disorders, excessive iodine intake and diet are also associated with the risk of TC [7-9]. To date, few studies have investigated the relationship between dietary factors and the risk of TC.

Previous studies have investigated dietary factors and risk of TC, but, they mainly focused on individual food items. Only a few investigated dietary data such as food combinations (dietary patterns) but the results were inconclusive [10]. Although five case-control studies and one cohort study investigated the relationship between fish consumption and TC, the results were inconsistent. Among eight case-control studies focused on the association between fruit and vegetable intake and TC, a positive connection was seen between the consumption of cruciferous plants (e.g., brussel sprout and cabbage) and the risk of TC. A study in Norway found that high intake of citrus fruits was positively associated with TC risk. Eating other fruits and vegetables in general showed a significant decreased risk of TC. Five case-control studies and two cohort studies examined the relationship between meat and dairy consumption and TC, and the results were either positive or insignificant [10].

Recent cancer studies on food exposure have advocated for the application of dietary patterns, which considers different combinations of food intake using the principle component analysis method. Dietary patterns analysis has been suggested to overcome limitations of analyzing individual food items with respect to cancer risk [11]. One of the advantages for applying dietary pattern analyses is that the cumulative effect of multiple foods/nutrients in a dietary pattern may be detected while the effect of a single food item may not [12]. Moreover, an examination of dietary patterns would be more representative of people's diet as nutrients and foods are often consumed in combination. Thus, using dietary pattern analyses would capture variation in overall dietary intake and reflect interactions between foods and nutrients [12, 13].

Currently, only three previous studies have investigated dietary patterns and TC risk. A study from Greece found that a dietary pattern rich in fresh fruits and raw vegetables showed a significantly protective association with the risk of TC [14]. Another study from Poland observed that a diet rich in vegetables and fruits, as well as saltwater fish and low-fat meat, could be an important protective factor for differentiated TC [15]. A study conducted in French Polynesia compared traditional Polynesian with Western dietary patterns and found a non-significant negative association between the traditional Polynesian dietary pattern (high consumption of fish, seafood, and fruits) and TC risk. Meanwhile, the Western pattern (high consumption of meat and starchy food) showed no association with the risk of TC [16]. Our study is among the first few to investigate the relationship between dietary patterns and TC and the first effort to examine such associations in the U.S. population.

Materials and methods

Study population

Detailed information regarding the study design is discussed in the previous publication [17]. Cases were histologically confirmed incident TC patients [papillary (ICD-O-3: 8050, 8052, 8130, 8260, 8340-8344, 8450, and 8452), follicular (ICD-O-3: 8290, 8330-8332, and 8335), medullary (ICD-O-3: 8345, 8346, and 8510), or anaplastic (ICD-O-3: 8021)], who were between 21 and 84 years old at the time of diagnosis, and recruited between the year of 2010 and 2011. Eligible patients had no previous cancer diagnosis with the exception of non-melanoma skin cancer and were alive at the time of interview. Cases were recruited through the Yale Cancer Center's Rapid Case Ascertainment Shared Resource, which acts as an agent of the Connecticut Tumor Registry. During the study period, a total of 701 eligible incident TC cases were identified, among which 462 (65.9%) completed in-person interviews. Population-based controls (N = 498) were recruited using a random digit dialing method, yielding a participation rate of 61.5%. Cases and controls were frequency-matched by age (± 5 years). No significant differences were observed in the distributions of age, sex, and race between participants and non-participants for both cases and controls.

Data collection

After approval by the hospitals and by each subject's physician (cancer cases), or following selection through random sampling (controls), potential participants were approached by letter and then by phone. Participants who agreed to participate were interviewed by trained interviewers either at their home or a convenient location. After obtaining written consent, a standardized, structured questionnaire was used to collect demographic variables and general information such as past medical history, tobacco use, alcohol consumption, occupation and residential histories, and other potential confounders. Dietary information was collected via the original version of Diet History Questionnaire (DHQ) provided by the National Institutes of Health for applied research of cancer control and population science. Participants were asked their dietary intake one year before the date of disease diagnosis (cases) or interview (controls). All procedures were performed in accordance to protocols approved by the Human Investigation Committees at Yale University and the Connecticut Department of Public Health.

Dietary patterns

After excluding participants without complete DHQ data, a total of 826 participants (390 cases, and 436 controls) were included in our study. To avoid unnecessary reduction in statistical power, we assigned a value of 0 servings per year for all missing values, as a missing value for a certain food is likely to indicate 0 consumption [18]. We conducted a principal component analysis of the 148 food items and beverages collected by the DHQ to identify the study population's dietary patterns. The principal component analysis was followed by a varimax orthogonal rotation to improve interpretability and minimize correlations between food components. The number of principal components was determined by the eigenvalue-one criterion (also known as the Kaiser criterion retains principal components with eigenvalues greater than 1.00), along with the screen test [19]. Through these criteria, we were able to retain 3 principal components with each component representing a separate, uncorrelated dietary pattern. The dietary patterns were further ranked by eigenvalue and described as "Starchy Foods and Desserts Pattern", "Fruits and Vegetables Pattern", and "High Protein and Fat Pattern", through identification of the major foods contributing to the pattern, based on the loading of each food item. Each individual was given a factor score for each dietary pattern. Scores for each dietary pattern were categorized into quartiles, with higher scores representing greater adherence to that dietary pattern [20, 21].

Statistical analysis

Univariate-analysis (Chi-squared test) was conducted to examine the distributions of selected characteristics for cases and controls. Unconditional logistic regression models were used to calculate the odds ratios (OR) and 95% confidence intervals (CI) for the association between the quartile of a given dietary pattern and risk of TC (lowest quartile as the reference group). We also examined linear trends across quartiles in both unadjusted and adjusted models. Sex (male, female), age (< 40, 40-49.9, 50-59.9, ≥ 60), education level (high school or less, college or trade school, graduate school), BMI (≤ 24.9, ≤ 30, > 30), family income (low, medium, high), alcohol consumption (yes, no), and family history of TC (yes, no) were adjusted for in the multivariable models. Race and smoking were excluded in the final models because these variables did not result in significant changes in the observed associations. Since papillary cancer constituted the majority of the cases, we investigated the association between dietary patterns and the risk of papillary TC. We also examined the association between dietary pattern and overall TC and papillary TC among males and females. We further conducted stratified analyses by age (≥ 50, < 50) among females to investigate whether changes in female endogenous hormones after menopause modify the association between dietary patterns and TC risk [22].A stratified analysis by tumor size (≤ 10 mm, > 10 mm) was performed in both well-differentiated TC (papillary and follicular) and papillary TC alone. All tests of statistical significance conducted were 2-sided and analyses were performed using SAS software (version 9.4; SAS Institute Inc., Cary, North Carolina, USA).

Results

A majority of the 390 cases were diagnosed with papillary TC (N = 329, 84.4%), followed by follicular TC (N = 50, 12.8%), medullary (N = 9, 2.3%), anaplastic (N = 1, 0.3%), and others (N = 1, 0.3%). The mean age of diagnosis was 51 years. Compared with controls, cases were more likely to be female, obtain lower levels of education, be obese, do not drink alcohol, and have a family history of thyroid cancer (**Table 1**). Distributions of race, family income, and smoking were similar between cases and controls.

Table 1. Selected characteristics of the study population (N = 826)

	Cases (n = 390)		Controls (n = 436)		*P values*
	N	%	N	%	
Sex[a]					*< 0.001*
Female	319	81.8	307	70.6	
Male	71	18.2	128	29.4	
Age (years)					*0.002*
< 40	69	17.7	48	11.0	
40-	93	23.9	109	25.0	
50-	126	32.3	121	27.8	
≥ 60	102	26.2	158	36.2	
Race					*0.58*
White	351	90.0	397	91.1	
Black	16	4.1	20	4.6	
Others	23	5.9	19	4.4	
Education					*0.006*
High school or less	108	27.7	77	17.7	
College or trade school	179	45.9	226	51.8	
Graduate school	91	23.3	121	27.8	
Missing	12		12		
Body mass index (kg/m^2)					*< 0.001*
< 24.9	128	32.8	182	41.7	
24.9-29.9	119	30.5	150	34.4	
> 30	143	36.7	104	23.9	
Family income					*0.80*
Low	107	40.2	120	39.1	
Medium	68	25.6	74	24.1	
High	91	34.2	113	26.8	
Confidential or unknown	124		129		
Smoking[b]					*0.46*
No	274	70.3	296	67.9	
Yes	116	29.8	140	32.1	
Alcohol consumption[c]					*< 0.001*
No	224	57.4	197	45.2	
Yes	166	42.6	239	54.8	
Family history of thyroid cancer					*0.001*
No	331	84.9	401	92.0	
Yes	59	15.1	35	8.0	

[a]Total number does not add up due to missing value. [b]Ever smoking was defined as ever smoked a total of 100 cigarettes or more. [c]Ever alcohol consumption was defined as ever had more than 12 drinks of alcoholic beverages such as beer, wine, or liquor. 1 drink of beer = 1 can or bottle; 1 drink of wine = 14 oz glass; 1 drink of liquor = 1 shot.

In the principal component analysis (**Table 2**), the most prominent dietary pattern (eigenvalue: 20.3, total variance explained: 13.7%) was characterized by high consumption of starchy foods and desserts. This pattern had the highest positive loadings for fruit crisp, pasta, syrup, lasagna, and macaroni and cheese. The second most prominent pattern represented a high intake of vegetables and fruits (eigenvalue: 6.3, total variance explained: 4.3%). This pattern had the highest positive loadings for broccoli, lettuce, tomato, sweet pepper, and apple. The third dietary pattern (eigenvalue: 4.9, total variance explained: 3.3%), which had

Table 2. Factor loadings of the three major dietary patterns identified by principal component analysis

Starchy Foods and Desserts Pattern		Fruits and Vegetables Pattern		High Protein and Fat Pattern	
Food items	Factor loading	Food items	Factor loading	Food items	Factor loading
Fruit crisp	0.054	Broccoli	0.084	Beef/cheese burger	0.109
Pasta	0.050	Lettuce	0.079	Ground beef	0.097
Syrup	0.050	Tomato	0.078	Hot dog	0.095
Lasagna	0.049	Other vegetables	0.074	Cold cuts	0.093
Mac & cheese	0.049	Sweet pepper	0.073	Spare ribs	0.091
Liver	0.047	Apple	0.073	Bacon	0.090
Muffin	0.046	Cauliflower	0.071	Sausage	0.080
Doughnut	0.045	Strawberry	0.071	Dumpling	0.079
Pancake or waffle	0.044	Raw greens	0.070	Pork	0.079
Coleslaw	0.044	Onion	0.070	Ham	0.076

high levels of protein and fat, was featured by beef/cheese burger, ground beef, hot dog, cold cuts, and spare ribs.

A protective unadjusted effect for overall TC was observed among individuals in the highest quartile of Fruits and Vegetables Pattern with a significant dose-response relationship (OR = 0.60, 95% CI: 0.41, 0.89; P_{trend} = 0.007, **Table 3**) compared to those in the lowest quartile. After adjusting for confounding factors, the protective effect against overall TC and the dose-response relationship still existed (OR = 0.60, 95% CI: 0.39, 0.92; P_{trend} = 0.02). Those in the second quartile of High Protein and Fat Pattern experienced a protective effect against overall TC, with a borderline significance (OR = 0.65, 95% CI: 0.43, 0.98; OR = 0.65, 95% CI: 0.43, 0.99 after adjusting for total energy intake). Associations between other food patterns and TC were not statistically significant. Since a majority of the cases had papillary TC, we further investigated the association between food patterns and this type of TC (**Table 4**) and observed no significant associations. Due to the small sample size for follicular thyroid cancer and other TC subtypes, we did not analyze the data for these groups.

When stratified by sex, a negative association between Fruits and Vegetables Pattern and overall TC risk (OR = 0.58, 95% CI: 0.38, 0.94 for the highest quartile; P_{trend} = 0.02, **Table 5**) was found among females. Compared to the first quartile, women in the third quartile of Starchy Foods and Desserts Pattern had a significantly decreased risk of overall TC (OR = 0.62, 95% CI: 0.39, 0.99), but no dose-response relationship was observed. Moreover, a negative association between the second quartile of High Protein and Fat Pattern and overall TC risk was observed in women (OR = 0.62, 95% CI: 0.40, 0.96 for the highest quartile; P_{trend} = 0.06). Similar associations were found in papillary TC. In contrast, a positive association was present between a diet rich in starchy foods and desserts and risk of overall TC for males; there was a significant dose-response relationship (P_{trend} = 0.003) when comparing the third quartile (OR = 4.27, 95% CI: 1.57, 11.64) and fourth quartile (OR = 3.26, 95% CI: 1.23, 8.64) to the first quartile. Similar associations were found with papillary TC, when comparing the third quartile (OR = 3.61, 95% CI: 1.28, 10.15) to the first quartile with a borderline significant trend (P_{trend} = 0.05). Similar results were observed after adjusting for total energy intake. Statistically significant interactions between gender and dietary patterns were only seen for a diet rich in starchy foods and desserts (*P* for interaction < 0.001).

We conducted age-stratified analyses in women (**Table 6**). After adjusting for confounders, we noticed that among women aged 50 years or older, consumption of a diet high in fruits and vegetables was associated with a reduced risk of overall TC (OR = 0.48, 95% CI: 0.26, 0.91; P_{trend} = 0.02) and papillary TC (OR = 0.45, 95% CI: 0.23, 0.89; P_{trend} = 0.02). Furthermore, these trends were characterized by significant dose-response relationships. No such associations were observed with overall TC and papillary TC among women younger than 50 years old.

Table 3. Association between dietary pattern and risk of thyroid cancer (N = 826)

	Controls	Cases	OR	95% CI	OR[a]	95% CI	OR[b]	95% CI
Starchy Foods and Dessert Pattern								
Quartile 1	109	102	1.00		1.00		1.00	
Quartile 2	109	75	0.74	0.49, 1.10	0.73	0.48, 1.12	0.77	0.48, 1.18
Quartile 3	108	95	0.94	0.64, 1.38	0.92	0.61, 1.39	1.06	0.61, 1.62
Quartile 4	110	118	1.15	0.79, 1.67	1.03	0.69, 1.53	1.25	0.81, 1.93
P_{trend}[c]				*0.29*		*0.66*		*0.18*
Fruits and Vegetables Pattern								
Quartile 1	109	125	1.00		1.00		1.00	
Quartile 2	109	103	0.82	0.57, 1.20	0.85	0.57, 1.26	0.88	0.59, 1.31
Quartile 3	109	87	0.70	0.48, 1.02	0.74	0.49, 1.12	0.81	0.52, 1.24
Quartile 4	109	75	0.60	0.41, 0.89	0.60	0.39, 0.92	0.68	0.41, 1.11
P_{trend}[c]				*0.007*		*0.02*		*0.12*
High Protein and Fat Pattern								
Quartile 1	109	116	1.00		1.00		1.00	
Quartile 2	109	83	0.72	0.49, 1.05	0.65	0.43, 0.98	0.65	0.43, 0.99
Quartile 3	109	96	0.83	0.57, 1.21	0.78	0.52, 1.18	0.84	0.55, 1.28
Quartile 4	109	95	0.82	0.56, 1.20	0.72	0.47, 1.11	0.87	0.87, 1.39
P_{trend}[c]				*0.42*		*0.21*		*0.66*

[a]Adjusted for sex, age, BMI, education level, family income, alcohol consumption, and family history of thyroid cancer. [b]Adjusted for sex, age, BMI, education level, family income, alcohol consumption, family history of thyroid cancer, and total energy intake. [c]Test for trend across quartiles from logistic regression model.

Table 4. Association between dietary pattern and risk of papillary thyroid cancer (N = 765)

	Controls	Cases	OR[a]	95% CI	OR[b]	95% CI
Starchy Foods and Dessert Pattern						
Quartile 1	109	83	1.00		1.00	
Quartile 2	109	69	0.80	0.52, 1.25	0.83	0.53, 1.29
Quartile 3	108	79	0.93	0.60, 1.43	1.04	0.67, 1.64
Quartile 4	110	98	0.99	0.65, 1.51	1.18	0.75, 1.86
P_{trend}[c]				*0.89*		*0.35*
Fruits and Vegetables Pattern						
Quartile 1	109	100	1.00		1.00	
Quartile 2	109	90	0.94	0.62,1.43	0.97	0.63, 1.48
Quartile 3	109	76	0.83	0.54, 1.28	0.90	0.57, 1.42
Quartile 4	109	63	0.65	0.41, 1.02	0.74	0.44, 1.25
P_{trend}[c]				*0.05*		*0.28*
High Protein and Fat Pattern						
Quartile 1	109	96	1.00		1.00	
Quartile 2	109	69	0.66	0.43, 1.02	0.67	0.43, 1.03
Quartile 3	109	84	0.82	0.53, 1.26	0.88	0.57, 1.37
Quartile 4	109	80	0.71	0.45, 1.12	0.85	0.51, 1.41
P_{trend}[c]				*0.24*		*0.68*

[a]Adjusted for sex, age, education level, BMI, family income, alcohol consumption, and family history of thyroid cancer. [b]Adjusted for sex, age, BMI, education level, family income, alcohol consumption, family history of thyroid cancer, and total energy intake. [c]Test for trend across quartiles from logistic regression model.

We also examined the relationship between food patterns and TC after stratifying by tumor size. Similar, non-statistically significant associations were observed between microcarcinomas and tumors greater than 10 mm (results not shown).

Discussion

In this population-based case-control study, we observed negative associations between a dietary pattern high in fruits and vegetables and risks of both overall TC and papillary TC. A stronger protective effect of this dietary pattern was found among women, particularly those aged 50 years or older. We also observed a positive association between high

Table 5. Associations between food pattern and risk of thyroid cancer subtypes after stratified by sex (N = 826)

Sex	Controls	Overall TC					Papillary TC				
		Cases	OR[a]	95% CI	OR[b]	95% CI	Cases	OR[a]	95% CI	OR[b]	95% CI
Female (N = 627)											
Starchy Foods and Desserts Pattern											
Quartile 1	71	93	1.00		1.00		74	1.00		1.00	
Quartile 2	76	67	0.69	0.41, 1.04	0.73	0.45, 1.18	62	0.79	0.48, 1.30	0.83	0.50, 1.37
Quartile 3	83	69	0.62	0.39, 0.99	0.71	0.44, 1.14	57	0.65	0.39, 1.06	0.73	0.44, 1.21
Quartile 4	78	90	0.78	0.49, 1.23	0.96	0.58, 1.58	79	0.85	0.52, 1.37	1.03	0.61, 1.72
P_{trend}[c]				*0.24*		*0.81*			*0.38*		*0.95*
Fruits and Vegetables Pattern											
Quartile 1	66	97	1.00		1.00		79	1.00		1.00	
Quartile 2	72	82	0.86	0.54, 1.37	0.89	0.55, 1.43	72	0.93	0.57, 1.52	0.96	0.58, 1.57
Quartile 3	81	72	0.69	0.43, 1.11	0.78	0.47, 1.28	64	0.76	0.46, 1.25	0.84	0.50, 1.41
Quartile 4	89	68	0.58	0.36, 0.94	0.72	0.41, 1.27	57	0.60	0.36, 1.00	0.73	0.41, 1.32
P_{trend}[c]				*0.02*		*0.22*			*0.03*		*0.27*
High Protein and Fat Pattern											
Quartile 1	92	110	1.00		1.00		90	1.00		1.00	
Quartile 2	87	74	0.62	0.40, 0.96	0.62	0.40, 0.97	60	0.61	0.38, 0.97	0.83	0.50, 1.37
Quartile 3	72	72	0.63	0.40, 1.01	0.70	0.44, 1.13	67	0.73	0.45, 1.18	0.73	0.44, 1.21
Quartile 4	57	63	0.64	0.39, 1.05	0.81	0.47, 1.40	55	0.65	0.39, 1.10	1.03	0.61, 1.72
P_{trend}[c]				*0.06*		*0.34*			*0.14*		*0.54*
Male (N = 199)											
Starchy Foods and Desserts Pattern											
Quartile 1	38	9	1.00		1.00		9	1.00		1.00	
Quartile 2	33	8	1.02	0.33, 3.11	0.96	0.31, 2.97	7	0.80	0.25, 2.54	0.77	0.24, 2.46
Quartile 3	25	26	4.27	1.57, 11.64	4.54	1.64, 12.54	22	3.61	1.28, 10.15	3.78	1.32, 10.79
Quartile 4	32	28	3.26	1.23, 8.64	3.75	1.34, 10.53	19	1.93	0.69, 5.34	2.13	0.72, 6.30
P_{trend}[c]				*0.003*		*0.003*			*0.05*		*0.05*
Fruits and Vegetables Pattern											
Quartile 1	43	28	1.00		1.00		21	1.00		1.00	
Quartile 2	37	21	0.77	0.34, 1.73	0.76	0.34, 1.72	18	0.95	0.39, 2.30	0.95	0.39, 2.31
Quartile 3	28	15	0.93	0.38, 2.25	0.86	0.34, 2.14	12	1.18	0.45, 3.12	1.12	0.41, 3.05
Quartile 4	20	7	0.63	0.21, 1.96	0.57	0.17, 1.85	6	0.75	0.22, 2.56	0.68	0.18, 2.52
P_{trend}[c]				*0.51*		*0.39*			*0.86*		*0.76*
High Protein and Fat Pattern											
Quartile 1	17	6	1.00		1.00		6	1.00		1.00	
Quartile 2	22	9	1.15	0.30, 4.36	1.17	0.31, 4.47	9	1.35	0.35, 5.16	1.39	0.36, 5.37
Quartile 3	37	24	1.83	0.57, 5.83	1.86	0.58, 5.96	17	1.44	0.43, 4.77	1.48	1.48, 4.95
Quartile 4	52	32	1.41	0.45, 4.43	1.24	0.37, 4.16	25	1.15	0.36, 3.73	0.98	0.28, 3.44
P_{trend}[c]				*0.53*		*0.63*			*0.95*		*0.93*

[a]Adjusted for age, education level, BMI, family income, alcohol consumption, and family history of thyroid cancer. [b]Adjusted for sex, age, BMI, education level, family income, alcohol consumption, family history of thyroid cancer, and total energy intake. [c]Test for trend across quartiles from logistic regression model.

starchy foods and desserts intake and overall TC risk among men.

Our study characterized dietary patterns through a principle component analysis, which used matrix algebra to identify the principal components in the data based on a correlation or covariance matrix of the food variables. The resulting components are linear combinations of the observed variables that explain the data variance [23]. The three dietary patterns we selected accounted for 21.3% of the total variability in the original food variables.

Our study found a significant protective effect against overall TC and papillary TC for a diet rich

Table 6. Associations between food pattern and risk of thyroid cancer subtypes in women after stratified by age group (N = 626)

Age Group	Controls	Overall TC					Papillary TC				
		Cases	OR[a]	95% CI	OR[b]	95% CI	Cases	OR[a]	95% CI	OR[b]	95% CI
Age ≥ 50											
Starchy Foods and Desserts Pattern											
Quartile 1	43	52	1.00		1.00		40	1.00		1.00	
Quartile 2	40	38	0.84	0.45, 1.56	0.92	0.49, 1.74	34	0.95	0.49, 1.83	1.04	0.53, 2.04
Quartile 3	50	46	0.74	0.41, 1.33	0.94	0.45, 1.55	36	0.73	0.38, 1.37	0.83	0.43, 1.61
Quartile 4	46	46	0.75	0.42, 1.37	0.92	0.48, 1.76	38	0.81	0.43, 1.52	1.01	0.51, 2.01
P_{trend}[c]				*0.31*		*0.74*			*0.38*		*0.86*
Fruits and Vegetables Pattern											
Quartile 1	36	49	1.00		1.00		39	1.00		1.00	
Quartile 2	41	48	0.88	0.47, 1.66	095	0.50, 1.80	40	0.86	0.44, 1.69	0.94	0.47, 1.87
Quartile 3	45	45	0.75	0.40, 1.40	0.84	0.43, 1.65	37	0.75	0.38, 1.46	0.86	0.42, 1.75
Quartile 4	57	40	0.48	0.26, 0.91	0.56	0.26, 1.23	32	0.45	0.23, 0.89	0.54	0.23, 1.24
P_{trend}[c]				*0.02*		*0.16*			*0.02*		*0.16*
High Protein and Fat Pattern											
Quartile 1	57	72	1.00		1.00		57	1.00		1.00	
Quartile 2	46	40	0.66	0.37, 1.17	0.72	0.41, 1.28	31	0.66	0.36, 1.21	0.72	0.39, 1.33
Quartile 3	44	39	0.57	0.32, 1.03	0.63	0.35, 1.15	36	0.68	0.37, 1.24	0.75	0.41, 1.40
Quartile 4	32	31	0.63	0.33, 1.21	0.80	0.39, 1.64	24	0.61	0.31, 1.23	0.81	0.37, 1.74
P_{trend}[c]				*0.08*		*0.30*			*0.14*		*0.46*
Age < 50											
Starchy Foods and Desserts Pattern											
Quartile 1	28	41	1.00		1.00		34	1.00		1.00	
Quartile 2	36	29	0.50	0.23, 1.06	0.51	0.24, 1.08	28	0.60	0.27, 1.29	0.51	0.24, 1.08
Quartile 3	33	23	0.55	0.25, 1.19	0.62	0.28, 1.37	21	0.62	0.28, 1.39	0.62	0.28, 1.37
Quartile 4	31	44	0.96	0.47, 1.99	1.11	0.50, 2.45	41	1.11	0.52, 2.37	1.10	0.50, 2.45
P_{trend}[c]				*0.99*		*0.77*			*0.70*		*0.50*
Fruits and Vegetables Pattern											
Quartile 1	30	48	1.00		1.00		40	1.00		1.00	
Quartile 2	31	34	0.76	0.37, 1.58	0.77	0.37, 1.60	32	0.85	0.40, 1.81	0.77	0.37, 1.60
Quartile 3	35	27	0.52	0.25, 1.09	0.54	0.26, 1.16	27	0.63	0.30, 1.33	0.54	0.26, 1.16
Quartile 4	32	28	0.71	0.34, 1.51	0.81	0.33, 2.01	25	0.73	0.33, 1.59	0.81	0.33, 2.01
P_{trend}[c]				*0.22*		*0.34*			*0.29*		*0.34*
High Protein and Fat Pattern											
Quartile 1	35	38	1.00		1.00		33	1.00		1.00	
Quartile 2	41	34	0.64	0.32, 1.30	0.64	0.31, 1.30	29	0.64	0.31, 1.35	0.64	0.31, 1.30
Quartile 3	28	33	1.01	0.47, 2.16	1.10	0.50, 2.43	31	1.15	0.52, 2.55	1.10	0.50, 2.43
Quartile 4	24	32	0.89	0.41, 1.95	1.06	0.44, 2.53	31	0.99	0.44, 2.21	1.06	0.44, 2.53
P_{trend}[c]				*0.97*		*0.72*			*0.69*		*0.72*

[a]Adjusted for education level, BMI, family income, alcohol consumption, and family history of thyroid cancer. [b]Adjusted for sex, age, BMI, education level, family income, alcohol consumption, family history of thyroid cancer, and total energy intake. [c]Test for trend across quartiles from logistic regression model.

in fruits and vegetables. The health beneficial effect of fruits and vegetables is well established. Fruits and vegetables may reduce risk of cancer via antioxidant mechanisms, by serving as substrates for the formation of anti-neoplastic agents, by inhibiting nitrosamine formation, or by altering hormone metabolism [24]. Previous studies indicated a high intake of fruits and vegetables containing active micronutrients, such as vitamins, folate, and minerals, and phytochemicals could protect against cancers through individual or combination of bioactive components from fruits and vegetables [10]. The three earlier studies investigating food patterns examined the association between high intake of fruits and vegetables and TC. The studies from Greece and Poland suggested intake of fruits and vegetables had a decreased risk of TC [14, 15]. Similarly, the French Polynesian study showed that a high cassava intake had an inverse association with TC risk [16]. Thus, our results were consistent with those from previous studies.

We further observed that the protective effect against papillary TC of diet rich in fruits and vegetables was stronger among women older than 50 years old. The reason for this cutoff age is that 50 years old is the average age of menopause onset and the start of worsening TC prognosis [22]. It is plausible that changes during menopause in either estrogen or luteinizing hormone/follicle-stimulating hormone affect the growth and extension of tumor size of thyroid cancer [22]. Although not reported in other thyroid cancer studies, a stronger inverse association was observed between high fruits and vegetables intake and breast cancer among postmenopausal women [25]. We assume that fruits and vegetable intake may be more influential with the change of female endogenous hormonal status. More studies are needed to explain the precise mechanism behind the observation.

Our study also suggested that a diet rich in carbohydrate increased TC risks specifically among men. Few studies have analyzed the relationship between high carbohydrate intake and TC risk. Sartorius et al. found indirect evidence that different carbohydrates had specific effects on the risk of obesity and increased BMI. This is particularly interesting because increased BMI is associated with thyroid cancer in meta-analysis [26-28]. A previous study investigating the association between high carbohydrate intake and the risk of TC found that excess carbohydrate consumption was associated with an increased risk of differentiated thyroid cancer (OR = 4.905, 95% CI: 2.593, 9.278) [29]. This observation is consistent with ours. While the underlying mechanisms of the association are not fully understood, multiple cancer studies suggested that the insulin pathway may play a key role [30]. The ingestion of carbohydrates leads to a rapid rise in blood glucose level and provokes insulin secretion. Elevated insulin level reduces plasma and tissue levels of the insulin-like growth factor (IGF) binding proteins 1 and 2, which could then increase the availability of IGF-I. Previous studies have indicated that insulin and IGF-I act as cancer-promoting agents when interacting with the thyroid-stimulating hormone (TSH), which is the main growth factor for thyroid cells. IGF-I also has the ability to inhibit apoptosis and stimulate vascular endothelial growth factor (VEGF) synthesis in thyroid tumors [31, 32]. Another possible explanation is that individuals with a diet rich in carbohydrates could consume less fruits and vegetables, which was associated with a protective effect against the risk of TC. We found a weak negative correlation between starchy foods and desserts pattern and fruits and vegetables pattern among men (Pearson's correlation coefficient = -0.097), but not among women (Pearson's correlation coefficient = 0.049). Because of the relatively small sample size of male participants in our study, the results could be due to chance alone. Future studies with sufficient statistical power are needed to confirm our findings.

One of the strengths of our study was that all cases were histologically confirmed, which minimized the likelihood of disease misclassification. We also conducted statistical analyses based on the histologic subtype and tumor size, which were not conducted in previous studies [14, 16]. Our study collected detailed information on potential confounding variables and controlled them in the models. Despite these efforts, potential residual confounding from unknown or uncollected variables cannot be completely ruled out. Compared to previous studies, our study had a relatively large sample size. When we performed subgroup analyses, the numbers were limited, particularly for males and younger age groups. Therefore, it is possible that some of our findings could be due to chance. Another potential limitation could be that the dietary information used in the study was collected through DHQ, and thus susceptible to recall bias. All previous studies that investigated this association utilized dietary questionnaires to obtain dietary information. Thus, we believe that even if recall bias was present in our study, it would be similar among cases and controls [14-16].

In conclusion, our study found a significant negative association between diet patterns rich in fruits and vegetables and TC risk, especially among women aged 50 years or older. While a dietary pattern high in starchy foods and desserts may be positively and negatively associated with TC risk among men and women respectively, these results require confirmation in other populations, especially in future prospective studies.

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Disclosure of conflict of interest

None.

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