January 2016

Dietary Patterns And Thyroid Cancer Risk: A Population-Based Case-Control Study

Jiaxin Liang
Yale University, jiaxinfrost@gmail.com

Dietary Patterns and Thyroid Cancer Risk:

a Population-Based Case-Control Study

Thesis

Jiaxin Liang, M.P.H. Candidate,

Department of Environmental Health Sciences

Thesis Advisor: Dr. Yawei Zhang

Second Reader: Dr. Shuangge (Steven) Ma

Abstract

Thyroid cancer (TC) incidence has increased greatly during the past decades with a few established risk factors. The relationship between diet factors and TC remains unclear. Limited literature has investigated the association and with inconsistent findings. We examined the association between dietary pattern and risk of TC in a population based case-control study conducted in Connecticut (2010-2011). 390 historically confirmed incident TC cases and 436 population-based controls that completed baseline dietary history questionnaires were included in the analyses. 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 dietary pattern and risk of TC, controlling for potential confounders. A diet rich in fruits and vegetables was significantly associated with a reduced risk of overall TC (OR=0.59, 95%CI: 0.39-0.90, P_{trend}=0.023). Stronger protective effect with significant dose-response relationship was observed among women ≥ 50 years of age in risk of both overall TC (OR=0.45, 95%CI: 0.24-0.86, P_{trend}=0.036) and papillary TC (OR=0.42, 95%CI: 0.21-0.84, P_{trend}=0.031). A diet rich in starchy foods and dessert is positively associated with overall TC risk among men, and negatively associated with risk of TC among women. No significant associations were found between high protein and fat intake with risk of TC.

Acknowledgements

First and foremost, I would like to express the deepest appreciation to my thesis advisor, Dr. Yawei Zhang, who has been generously and continuously providing me with guidance and support throughout my research and thesis writing. She has been a tremendous mentor for me, none of these would've happened without her help and patience.

I would like to thank my second reader of the thesis, Dr. Shuangge (Steven) Ma, for the help he provided and for reading my thesis.

I would like to acknowledge Dr. Cairong Zhu of Sichuan University, China, for helping me with the statistical analysis methods in my thesis.

I am grateful to my academic advisor, Dr. Mark Russi, who has always been there to provide me with precious advice and encouragement. His patience and support helped me overcome many crisis situations.

I would also like to thank my wife and my parents for been there for me all the time. I couldn't have made this far without their unconditional love and support.

Finally, I am really thankful for the financial support from the Stolwijk Fellowship, which funded my summer internship and my research.

Table of Contents

ABSTRACT 1

ACKNOWLEDGEMENTS 2

TABLE OF CONTENTS 3

LIST OF TABLES 4

INTRODUCTION 12

MATERIALS AND METHODS 14

STUDY POPULATION 14
DATA COLLECTION 15
DIETARY PATTERNS 16
STATISTICAL ANALYSIS 17

RESULTS 18

DISCUSSION 20

CONCLUSION 24

REFERENCES 25

List of Tables

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.

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	
Main food items	**Factor loading**	**Main food items**	**Factor loading**	**Main food items**	**Factor loading**
Fruit crisp	0.069	Broccoli	0.080	Beef/cheese burger	0.099
Pasta	0.065	Lettuce	0.075	Ground beef	0.090
Lasagna	0.064	Tomato	0.073	Hot dog	0.086
Mac & cheese	0.063	Onion	0.073	Bacon	0.086
Liver	0.061	Sweet pepper	0.072	Spare ribs	0.082
Muffin	0.061	Apple	0.071	Cold cuts	0.082
Doughnut	0.059	Raw greens	0.070	Sausage	0.075
Coleslaw	0.057	Cauliflower	0.069	Dumpling	0.074
Pancake or waffle	0.056	Other vegetables	0.069	Butter	0.069
Cake	0.055	Strawberry	0.068	Pork	0.069

Table 3. Association Between Dietary Pattern and Risk of Overall Thyroid Cancer (N=826)

	Unadjusted				Adjusted[a]			
	Cases	Controls	OR	95%CI	Cases	Controls	OR	95%CI
Starchy Foods and Dessert Pattern								
Quartile1	102	103	1.00	Reference	102	103	1.00	Reference
Quartile2	83	123	0.68	0.46, 1.01	83	123	0.69	0.46, 1.05
Quartile3	93	115	0.82	0.56, 1.20	93	115	0.79	0.53. 1.20
Quartile4	112	95	1.19	0.81, 1.75	112	95	1.10	0.73, 1.66
P_{trend}[b]				0.26				0.53
Fruits and Vegetables Pattern								
Quartile1	112	94	1.00	Reference	112	94	1.00	Reference
Quartile2	100	107	0.78	0.53, 1.16	100	107	0.77	0.51, 1.16
Quartile3	93	133	0.69	0.47, 1.02	93	133	0.79	0.52, 1.19
Quartile4	85	122	0.59	0.40, 0.86	85	122	0.59	0.39, 0.90
P_{trend}[b]				0.006				0.023
High Protein and Fat Pattern								
Quartile1	103	103	1.00	Reference	102	103	1.00	Reference
Quartile2	98	109	0.90	0.61, 1.32	83	123	0.88	0.59, 1.33
Quartile3	87	118	0.74	0.50, 1.09	93	115	0.73	0.48, 1.11
Quartile4	102	106	0.96	0.66, 1.42	112	95	0.82	0.53, 1.27
P_{trend}[b]				0.62				0.27

[a] Adjusted for sex, age, BMI, education level, family income, alcohol consumption, and family history of thyroid cancer.

[b] Test for trend across quartiles from logistic regression model.

Table 4. Association Between Dietary Pattern and Risk of Papillary Thyroid Cancer (N=765)

	Cases	Controls	OR[a]	95%CI[a]
Starchy Foods and Dessert Pattern				
Quartile1	84	103	1.00	Reference
Quartile2	74	123	0.74	0.48, 1.14
Quartile3	83	115	0.83	0.54, 1.27
Quartile4	88	95	1.01	0.65, 1.57
P_{trend}[b]			0.85	
Fruits and Vegetables Pattern				
Quartile1	89	94	1.00	Reference
Quartile2	86	107	0.85	0.55, 1.31
Quartile3	84	133	0.92	0.60, 1.43
Quartile4	70	122	0.62	0.40, 0.98
P_{trend}[b]			0.07	
High Protein and Fat Pattern				
Quartile1	84	103	1.00	Reference
Quartile2	83	109	0.94	0.61, 1.45
Quartile3	77	118	0.81	0.52, 1.26
Quartile4	85	106	0.80	0.50, 1.27
P_{trend}[b]			0.27	

[a] Adjusted for sex, age, education level, BMI, family income, alcohol consumption, and family history of thyroid cancer

[b] Test for trend across quartiles from logistic regression model.

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)	Cases	OR[a] (95% CI)
Female					
Starchy Foods and Desserts Pattern					
Quartile1	67	93	1.00	75	1.00
Quartile2	84	68	0.60 (0.38, 0.96)	62	0.68 (0.42, 1.12)
Quartile3	89	69	0.55 (0.34, 0.88)	63	0.61 (0.38, 1.00)
Quartile4	67	89	0.87 (0.54, 1.39)	72	0.86 (0.52, 1.41)
P_{trend}^{b}			0.46		0.45
Fruits and Vegetables Pattern					
Quartile1	59	90	1.00	72	1.00
Quartile2	76	77	0.67 (0.42, 1.09)	68	0.77 (0.47, 1.28)
Quartile3	76	77	0.79 (0.49, 1.29)	69	0.91 (0.54, 1.51)
Quartile4	96	75	0.54 (0.34, 0.88)	63	0.58 (0.35, 0.96)
P_{trend}^{b}			0.030		0.06
High Protein and Fat Pattern					
Quartile1	88	97	1.00	78	1.00
Quartile2	83	88	0.87 (0.56, 1.34)	73	0.90 (0.56, 1.43)
Quartile3	76	67	0.67 (0.42, 1.07)	62	0.80 (0.49, 1.30)
Quartile4	60	67	0.65 (0.39, 1.08)	59	0.69 (0.40, 1.16)
P_{trend}^{b}			0.05		0.14
Male					
Starchy Foods and Desserts Pattern					
Quartile1	36	9	1.00	9	1.00
Quartile2	39	15	1.28 (0.47, 3.48)	12	1.00 (0.36, 2.83)
Quartile3	26	24	3.34 (1.25, 8.91)	20	2.60 (0.96, 7.08)
Quartile4	27	23	3.00 (1.11, 8.13)	16	1.96 (0.69, 5.58)
P_{trend}^{b}			0.007		0.06
Fruits and Vegetables Pattern					
Quartile1	35	22	1.00	17	1.00
Quartile2	31	23	1.01 (0.44, 2.31)	18	1.13 (0.46, 2.78)
Quartile3	36	16	0.68 (0.28, 1.64)	15	0.99 (0.39, 2.52)
Quartile4	26	10	0.74 (0.26, 2.07)	7	0.69 (0.21, 2.24)
P_{trend}^{b}			0.38		0.60
High Protein and Fat Pattern					
Quartile1	15	6	1.00	6	1.00
Quartile2	26	10	1.18 (0.33, 4.29)	10	1.33 (0.36, 4.89)
Quartile3	42	20	1.11 (0.34, 3.62)	15	0.91 (0.27, 3.07)
Quartile4	45	35	1.77 (0.55, 5.65)	26	1.30 (0.39, 4.32)
P_{trend}^{b}			0.25		0.78

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

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

Age		Controls	Overall TC		Papillary TC	
			Cases	OR[a](95% CI)	Cases	OR[a](95% CI)
Age ≥ 50						
Starchy Foods and Desserts Pattern						
	Quartile1	40	54	1.00	42	1.00
	Quartile2	49	36	0.60 (0.33, 1.11)	31	0.66 (0.34, 1.26)
	Quartile3	48	41	0.67 (0.36, 1.23)	37	0.77 (0.40, 1.45)
	Quartile4	42	51	0.83 (0.46, 1.51)	38	0.79 (0.42, 1.50)
	P_{trend}[b]			0.61		0.58
Fruits and Vegetables Pattern						
	Quartile1	31	45	1.00	36	1.00
	Quartile2	44	44	0.65 (0.34, 1.26)	36	0.67 (0.33, 1.33)
	Quartile3	44	50	0.86 (0.45, 1.65)	42	0.86 (0.43, 1.71)
	Quartile4	60	43	0.45 (0.24, 0.86)	34	0.42 (0.21, 0.84)
	P_{trend}[b]			0.036		0.031
High Protein and Fat Pattern						
	Quartile1	56	63	1.00	48	1.00
	Quartile2	49	53	0.94 (0.54, 1.63)	43	1.02 (0.57, 1.83)
	Quartile3	40	34	0.66 (0.36, 1.22)	31	0.83 (0.44, 1.57)
	Quartile4	34	32	0.69 (0.36, 1.33)	26	0.74 (0.37, 1.49)
	P_{trend}[b]			0.16		0.34
Age < 50						
Starchy Foods and Desserts Pattern						
	Quartile1	27	39	1.00	33	1.00
	Quartile2	35	32	0.59 (0.28, 1.24)	31	0.69 (0.32, 1.49)
	Quartile3	41	28	0.53 (0.25, 1.11)	26	0.58 (0.27, 1.27)
	Quartile4	25	38	1.04 (0.49, 2.21)	34	1.09 (0.50, 2.39)
	P_{trend}[b]			0.93		0.98
Fruits and Vegetables Pattern						
	Quartile1	27	39	1.00	33	1.00
	Quartile2	35	32	0.75 (0.36, 1.56)	31	0.98 (0.46, 2.07)
	Quartile3	41	28	0.58 (0.27, 1.22)	26	0.73 (0.34, 1.57)
	Quartile4	25	38	0.67 (0.32, 1.41)	34	0.74 (0.34, 1.61)
	P_{trend}[b]			0.23		0.36
High Protein and Fat Pattern						
	Quartile1	32	34	1.00	30	1.00
	Quartile2	34	35	0.87 (0.42, 1.80)	30	0.82 (0.38, 1.76)
	Quartile3	36	33	0.81 (0.38, 1.73)	31	0.92 (0.42, 2.01)
	Quartile4	26	35	0.85 (0.39, 1.86)	33	0.89 (0.40, 2.00)
	P_{trend}[b]			0.66		0.87

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

Table 7. Associations between food pattern and risk of well-differentiated thyroid cancer subtypes after stratified by tumor size (N=815)

	Controls	Tumor size ≤10mm		Tumor size >10mm	
		Cases	OR[a](95% CI)	Cases	OR[a](95% CI)
Starchy Foods and Desserts Pattern					
Quartile1	103	49	1.00	47	1.00
Quartile2	123	43	0.76 (0.45, 1.28)	40	0.76 (0.45, 1.27)
Quartile3	115	43	0.75 (0.44, 1.26)	49	0.89 (0.53, 1.48)
Quartile4	95	51	1.12 (0.67, 1.87)	57	1.14 (0.69, 1.90)
P_{trend}^{b}			0.71		0.50
Fruits and Vegetables Pattern					
Quartile1	94	45	1.00	59	1.00
Quartile2	107	49	0.92 (0.54, 1.56)	51	0.76 (0.46, 1.24)
Quartile3	113	50	1.06 (0.62, 1.80)	42	0.71 (0.42, 1.19)
Quartile4	122	42	0.65 (0.38, 1.13)	41	0.64 (0.38, 1.07)
P_{trend}^{b}			0.19		0.09
High Protein and Fat Pattern					
Quartile1	103	55	1.00	43	1.00
Quartile2	109	51	0.92 (0.59, 1.52)	44	0.92 (0.54, 1.56)
Quartile3	118	40	0.70 (0.41, 1.18)	46	0.80 (0.47, 1.37)
Quartile4	106	40	0.70 (0.40, 1.24)	60	0.93 (0.54, 1.60)
P_{trend}^{b}			0.14		0.72

[a] Adjusted for sex, age, BMI, education level, family income, alcohol consumption, and family history of thyroid cancer.

[b] Test for trend across quartiles from logistic regression model.

Table 8. Associations between food pattern and risk of papillary thyroid cancer subtypes after stratified by tumor size (N=765)

	Controls	Tumor size ≤10mm		Tumor size >10mm	
		Cases	**OR[a](95% CI)**	**Cases**	**OR[a](95% CI)**
Starchy Foods and Desserts Pattern					
Quartile1	103	45	1.00	39	1.00
Quartile2	123	39	0.76 (0.44, 1.30)	35	0.76 (0.44, 1.33)
Quartile3	115	38	0.69 (0.40, 1.20)	45	0.94 (0.55, 1.60)
Quartile4	95	40	0.92 (0.53, 1.59)	48	1.12 (0.55, 1.60)
P_{trend}[b]			0.68		0.53
Fruits and Vegetables Pattern					
Quartile1	94	39	1.00	50	1.00
Quartile2	107	43	0.97 (0.55, 1.69)	43	0.75 (0.44, 1.26)
Quartile3	113	43	1.08 (0.62, 1.90)	41	0.82 (0.48, 1.41)
Quartile4	122	37	0.68 (0.38, 1.21)	33	0.58 (0.33, 1.01)
P_{trend}[b]			0.25		0.09
High Protein and Fat Pattern					
Quartile1	103	48	1.00	36	1.00
Quartile2	109	45	0.94 (0.56, 1.59)	38	0.98 (0.56, 1.72)
Quartile3	118	36	0.72 (0.42, 1.25)	41	0.89 (0.51, 1.57)
Quartile4	106	33	0.65 (0.35, 1.18)	52	0.94 (0.53, 1.66)
P_{trend}[b]			0.10		0.77

[a] Adjusted for sex, age, BMI, education level, family income, alcohol consumption, and family history of thyroid cancer.

[b] Test for trend across quartiles from logistic regression model.

Introduction

Being the most common endocrine cancer, thyroid cancer (TC) incidence has increased greatly during the past decades, and it is also the most rapidly increasing cancer in the U.S. (American Cancer Society 2016). According to an estimate provided by American Cancer Society (ACS), there will be about 62,450 new cases of TC (49,350 in women, 19,950 in men) in the year of 2016 in the U.S., with a estimated death count of 1,980 (1,070 women, 910 men) (American Cancer Society 2016). Despite the fact that some of the increase may due to more frequent diagnosis or change of technology or criteria for diagnosis, the true increase in incidence still exists (Cramer and others 2010). Based on the morphology and clinical features, TC is traditionally separated into two major groups: differentiated (papillary and follicular) and undifferentiated (medullary and anaplastic) carcinoma (Dal Maso and others 2009; DeLellis 2004).

Thyroid nodules are attributed to multiple factors (Knudsen and Brix 2014), yet few risk factors have been established, including radiation, history of goiter or nodule, family history of TC, being female and diet low in iodine (American Cancer Society 2016). 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 (Caini and others 2015); autoimmune disorders, excessive iodine intake and diet are also associated with risk of TC (Franceschi and others 1991; Kocak and others 2014; Tavani and others 2000). To date, few studies have investigated the relationship between dietary factors and risk of TC.

Previous literature have investigated dietary factor as carcinogen for TC. However, most studies analyzed the food items separately, few of them treated the dietary data as combinations of several food components (dietary patterns), and the results were inconclusive due to other confounders such as ethnic groups, life-styles, eating habits and other environmental factors (Choi and Kim 2014). Five case-control studies and one cohort study have investigated the relationship between fish consumption and TC, yet the results were inconsistent. Eight case-control studies have focused on the association between fruit and vegetable intake and TC. A positive connection was made between cruciferous plants (e.g., brussels sprouts and cabbages) and risk of TC. One study in Norway found high intake of citrus fruits is positively associated with TC risk. Eating other fruits and vegetables in general showed a significantly 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 (Choi and Kim 2014).

Recent cancer studies on food exposure have advocated the application of dietary patterns, which considers different combinations of food intakes using the principle component method. Dietary patterns analysis has been suggested to overcome the limitation of analyzing individual food items and cancer risk (Harris and others 2015). One of the advantages for applying dietary patterns analysis is that it could reflect the interaction among food and nutrients (Lin and others 2014), and the cumulative effect of multiple foods/nutrients included in a dietary pattern may be large enough to be detected while the effect of a single food item may not (Hu 2002). Moreover, an examination of dietary patterns would be closer to the real world, in which nutrients and foods are consumed in combination, and their joint effects could be investigated by analyzing the entire eating pattern (Hu 2002).

To the author's best knowledge, only two previous studies have analyzed dietary data as dietary patterns. One study from Greece examined the association between dietary patterns and risk of TC, and found the dietary pattern rich in fresh fruits and raw vegetables showed a significantly inversed association with risk of TC (Markaki and others 2003). Another study conducted in French Polynesia compared traditional Polynesian and Western dietary patterns. This study found a non-significant negative association between the traditional Polynesian dietary pattern (high consumption of fish, seafood, and fruits) and TC risk, while the Western pattern (high consumption of meat and starchy food) showed no association with risk of TC (Clero and others 2012). Our study is among the first few studies to investigate the relationship between dietary patterns and TC, and also the first effort to examine such association in American population.

Materials and methods

Study population

Detailed information regarding the study design is discussed in the previous publication (Zhang and others 2015). 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)], age between 21 and 84 years at diagnosis, and were recruited between the year of 2010 and 2011. Eligible patients had no previous diagnosis of cancer (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 (RCA), 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%) patients completed in-person interviews. Population-based controls were recruited using a random digit dialing method. 498 individuals were recruited in the study, with 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 the participants and nonparticipants 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 were interviewed by trained interviewers either at the subject's home or at 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. 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 number of 826 participants（390 cases, 436 controls) were included in our study. In order to avoid unnecessarily reduction in statistical power, we assigned a value of 0 servings per year as missing value for a certain food is likely to indicate 0 consumption (Hansson and Galanti 2000). We conducted a principal components analysis of the 146 food items and beverages collected by the DHQ, to identify the dietary patterns of the study population. Dietary patterns are used to investigate the combined effect of dietary items on the risk of the disease, rather than treating them as individual food items, which is closer to the real world scenario. The principal components analysis was followed by a varimax orthogonal rotation to improve interpretability and minimizing correlation between food components. The number of principal components was determined by the eigenvalue-one criterion (also known as the Kaiser criterion, that is to retain and interpret any component with an eigenvalue greater than 1.00), the proportion of variance accounted for, and graphically by the scree test (SAS Institute). We were able to retain 3 principal components following these criteria, and 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 factor-loading coefficient from each food item. Each individual was given a factor score for each dietary pattern. The scores for each dietary pattern were categorized into quartiles, and higher scores represent greater adherence to that dietary pattern (Epstein and others 2015; Link and others 2013).

Statistical analysis

Univariate-analysis (Chi-square test) was conducted to examine the distributions of selected characteristics for cases and controls. Unconditional logistic regression model was used to calculate the odds ratios (OR) and 95% confidence intervals (CI) for the association between quartile of a given dietary pattern and risk of TC (lowest quartile as the reference group). We also examined the 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 in the multivariable models. Race and smoking were also adjusted in the model, but did not result in material changes in the observed associations, thus were not included in the final models. Since papillary cancer constituted the most part of the cases, we therefore 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 and by age (≥ 50, <50) among females, to investigate whether change in the female endogenous hormone after menopausal period modifying the association between dietary patterns and TC risk (Haymart 2009). We also conducted a stratified analysis by tumor size (≤10mm, >10mm) in both well-differentiated TC (papillary and follicular) and papillary TC alone. All tests of statistical significance were conducted 2 sided. All analyses were carried out using SAS software (version 9.3; SAS Institute Inc., Cary, North Carolina, USA).

Results

The 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 women, of lower level of education, obese, nondrinkers, and have family history of thyroid cancer (Table 1). Distributions of race, family income, and smoking were similar between cases and controls.

With the use of principal component analysis and judging graphically by the scree test, we were able to identify three distinct dietary patterns (Table 2). The most prominent dietary pattern, which is the pattern that explained the greatest amount of total variance (eigenvalue: 16.2, total variance explained: 11.1%), is characterized by high consumption of starchy foods and desserts. The Starchy Foods and Desserts Pattern has the highest positive loading factors with fruit crisp, pasta, lasagna, macaroni and cheese. The second most prominent pattern represented a high intake of vegetables and fruits (eigenvalue: 6.8, total variance explained: 4.7%). The Fruits and Vegetables Pattern included the highest positive loading factors observed with broccoli, lettuce, tomato, onion, sweet pepper, apple, and raw greens. The third dietary pattern (eigenvalue: 4.9, total variance explained:

3.3%), which is labeled as High Protein and Fat Pattern, featured by beef/cheese burger, ground beef, hot dog, bacon, spare ribs, cold cuts. The three dietary patterns accounted for 19.1% of the variability of the original dietary variables.

A protective effect for overall TC was observed among individuals in the highest quartile of Fruits and Vegetables Pattern with very significant dose-response relationship (OR=0.59, 95%CI: 0.40-0.86, P_{trend}=0.006, Table 3) comparing to those who are in the lowest quartile, before adjusting for confounders. After adjusting for confounding factors, the protective effect against overall TC still existed (OR=0.59, 95%CI: 0.39-0.90, P_{trend}=0.023), among those in the highest quartile of the Fruits and Vegetables Pattern. Associations between other food pattern and TC were not statistically significant. Since the majority of the cases were diagnosed as papillary TC, we further investigated the association between food pattern and papillary TC (Table 4). The previously observed protective effect still existed among those consumed the highest amount of fruits and vegetables with a borderline significance (OR=0.62, 95%CI: 0.40-0.98, P_{trend}=0.07). We did not analyze the data for follicular thyroid cancer and other subtypes due to small numbers.

When stratified by sex, the negative association between Fruits and Vegetables Pattern and overall TC risk (OR=0.54, 95%CI: 0.34-0.88, P_{trend}=0.03, Table 5), as well as between Fruits and Vegetables Pattern and papillary TC risk (OR=0.58, 95%CI: 0.35, 0.96, P_{trend}=0.06) existed among females. Moreover, comparing to the first quartile, women who were in the second (OR=0.60, 95%CI: 0.38-0.96) and third quartile

(OR=0.55, 95%CI: 0.34-0.88) of Starchy Foods and Desserts Pattern also had a significantly decreased risk of overall TC, and a borderline significant protective association was observed with the third quartile of the same pattern in papillary TC (OR=0. 61, 95%CI: 0.38-1.00), while no dose-response relationship was observed. However, a positive association between a diet rich in starchy foods and desserts and risk of overall TC was observed in males, comparing the third (OR=3.34, 95%CI: 1.25-8.91, P_{trend}=0.007) and forth quartiles (OR=3.00, 95%CI: 1.11-8.13, P_{trend}=0.007) to the first quartile, with a significant dose-response relationship. No significant associations between food patterns and well-differentiated TC (papillary and follicular) or papillary TC alone were observed, after stratified by tumor size (Table 7, Table 8).

We also conducted age-stratified analyses in women. After adjusting for confounders, consuming a diet high in fruits and vegetables was associated with a reduced risks of both overall TC (OR=0.45, 95%CI: 0.24-0.86, P_{trend}=0.036, Table 6) and papillary TC (OR=0.42, 95%CI: 0.21-0.84, P_{trend}=0.031) among women aged 50 years or older, with a clear dose-response relationship. No such associations were observed among women less than 50 years of age.

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, and an even stronger protective effect was observed among women who aged 50 years and older. We also observed a negative association between a diet high in starchy foods and desserts and overall TC risk among women in the second and third quartiles of the food pattern, and a borderline significant protective effect with papillary TC risk among women who ate a normal amount (second quartile) of starchy food and desserts. A positive association between high starchy foods and desserts intake and overall TC risk was observed 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 variance in the data (Moeller and others 2007). All together, the three dietary patterns we selected accounted for 19.1% of the total variability in the original food variables, which is consistent with other epidemiologic studies that explained 18.6% and 20.7% of their total variability (Epstein and others 2015; Link and others 2013).

Our study found a significant protective effect against overall TC and papillary TC with a diet rich in fruits and vegetables. The health beneficial effect of fruits and vegetables is well established. Fruits and vegetables may help 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 (Jung and others 2013). Previous studies indicated a high intake of fruits and vegetables containing active micronutrients, such as vitamins, folate, and minerals, and phytochemicals could also help to protect against cancers, either by an individual or combination of bioactive components from fruits and vegetables (Choi and Kim 2014). The two studies investigated food patterns have examined the association between high intake of fruits and vegetables and TC. Although not significant, the study from Greece suggested intake of fruits and raw vegetables has a decreased risk of TC. While in the French Polynesian study, a high cassava intake showed an inverse association with TC risk. Results drawn from our study were consistent with these studies.

We further observed that the protective effect of diet rich in fruits and vegetables is stronger among women after 50 years of age. The reason for the choice of cut point of 50 years old was because it is the average age at onset of menopause, and the cut-point for worsen prognosis with TC (Haymart 2009). It is plausible that changes before and after menopause in either estrogen or luteinizing hormone/follicle-stimulating hormone affect the growth and extension of tumor size of thyroid cancer (Haymart 2009). Although not reported in other thyroid cancer studies, a stronger invert association was observed between high fruits and vegetables intake and breast cancer among postmenopausal women (Potentas and others 2015). Fruits and vegetable intake may be more influential with the change of female endogenous hormonal status. More studies are warranted to explain the precise mechanism of how diet rich in fruits and vegetables has a stronger effect on TC among post-menopausal women.

Few studies have looked into the relationship between high carbohydrate intake, such as consumption of starchy foods and desserts, and TC. Previous studies have observed positive associations between high carbohydrate intake and risk of TC and breast cancer (Marcello and others 2012; Romieu and others 2004). However, the underlying mechanisms of the association were not fully understood. One hypothesis suggested from a breast cancer study is that the increase risk of cancer is related to the insulin pathway. 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 increase the availability of IGF-I. Insulin and IGF-I can both enhance the development of breast tumors (Kaaks 2001). The results from our suggested diet rich in carbohydrate increased TC risks among men, with contrary results among women (*P* for interaction <0.001). We could hypothesize that the mechanism for increased risk of TC should be the same as the hypothesis made for breast cancer. Future studies are needed to confirm our findings of both positive and negative associations between carbohydrates intake and risk of TC, among women and men.

One of the strengths of our study is that all cases were histologically confirmed, which minimized the likelihood for disease misclassification. Another strength is the relatively large sample size, which allowed us to collect information on, and adjust for important confounders. We also stratified our analyses by sex and age, which may help the understanding of the associations between dietary patterns and TC within different population subgroups. Although our study had the largest sample size comparing to other two dietary pattern and TC studies, the sample size was limited for us to examine other histologic subtypes, such as follicular, medullary, and anaplastic thyroid cancers, which is one concern of the study. Another potential limitation could be that the dietary information used in the study was collected through DHQ, thus cases may have recalled their diet information differently from controls, and leading to recall bias.

Conclusion

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

References

American Cancer Society. Thyroid Cancer Detailed Guide. 2016

Caini, S.; Gibelli, B.; Palli, D.; Saieva, C.; Ruscica, M.; Gandini, S. Menstrual and reproductive history and use of exogenous sex hormones and risk of thyroid cancer among women: a meta-analysis of prospective studies. Cancer Causes Control. 26:511-518; 2015

Choi, W.J.; Kim, J. Dietary factors and the risk of thyroid cancer: a review. Clin Nutr Res. 3:75-88; 2014

Clero, E.; Doyon, F.; Chungue, V.; Rachedi, F.; Boissin, J.L.; Sebbag, J.; Shan, L.; Rubino, C.; de Vathaire, F. Dietary patterns, goitrogenic food, and thyroid cancer: a case-control study in French Polynesia. Nutrition and cancer. 64:929-936; 2012

Cramer, J.D.; Fu, P.; Harth, K.C.; Margevicius, S.; Wilhelm, S.M. Analysis of the rising incidence of thyroid cancer using the Surveillance, Epidemiology and End Results national cancer data registry. Surgery. 148:1147-1152; discussion 1152-1143; 2010

Dal Maso, L.; Bosetti, C.; La Vecchia, C.; Franceschi, S. Risk factors for thyroid cancer: an epidemiological review focused on nutritional factors. Cancer Causes Control. 20:75-86; 2009

DeLellis, R.A. Pathology and genetics of tumours of endocrine organs. Lyon: IARC Press; 2004

Epstein, M.M.; Chang, E.T.; Zhang, Y.; Fung, T.T.; Batista, J.L.; Ambinder, R.F.; Zheng, T.; Mueller, N.E.; Birmann, B.M. Dietary pattern and risk of hodgkin lymphoma in a population-based case-control study. American journal of epidemiology. 182:405-416; 2015

Franceschi, S.; Levi, F.; Negri, E.; Fassina, A.; La Vecchia, C. Diet and thyroid cancer: a pooled analysis of four European case-control studies. Int J Cancer. 48:395-398; 1991

Hansson, L.M.; Galanti, M.R. Diet-associated risks of disease and self-reported food consumption: how shall we treat partial nonresponse in a food frequency questionnaire? Nutrition and cancer. 36:1-6; 2000

Harris, H.R.; Bergkvist, L.; Wolk, A. An estrogen-associated dietary pattern and breast cancer risk in the Swedish Mammography Cohort. Int J Cancer. 137:2149-2154; 2015

Haymart, M.R. Understanding the relationship between age and thyroid cancer. Oncologist. 14:216-221; 2009

Hu, F.B. Dietary pattern analysis: a new direction in nutritional epidemiology. Curr Opin Lipidol. 13:3-9; 2002

Jung, S.K.; Kim, K.; Tae, K.; Kong, G.; Kim, M.K. The effect of raw vegetable and fruit intake on thyroid cancer risk among women: a case-control study in South Korea. The British journal of nutrition. 109:118-128; 2013

Kaaks, R. [Plasma insulin, IGF-I and breast cancer]. Gynecol Obstet Fertil. 29:185-191; 2001

Knudsen, N.; Brix, T.H. Genetic and non-iodine-related factors in the aetiology of nodular goitre. Best Pract Res Clin Endocrinol Metab. 28:495-506; 2014

Kocak, M.; Erem, C.; Deger, O.; Topbas, M.; Ersoz, H.O.; Can, E. Current prevalence of goiter determined by ultrasonography and associated risk factors in a formerly iodine-deficient area of Turkey. Endocrine. 47:290-298; 2014

Lin, Y.; Yngve, A.; Lagergren, J.; Lu, Y. A dietary pattern rich in lignans, quercetin and resveratrol decreases the risk of oesophageal cancer. The British journal of nutrition. 112:2002-2009; 2014

Link, L.B.; Canchola, A.J.; Bernstein, L.; Clarke, C.A.; Stram, D.O.; Ursin, G.; Horn-Ross, P.L. Dietary patterns and breast cancer risk in the California Teachers Study cohort. The American journal of clinical nutrition. 98:1524-1532; 2013

Marcello, M.A.; Sampaio, A.C.; Geloneze, B.; Vasques, A.C.; Assumpcao, L.V.; Ward, L.S. Obesity and excess protein and carbohydrate consumption are risk factors for thyroid cancer. Nutrition and cancer. 64:1190-1195; 2012

Markaki, I.; Linos, D.; Linos, A. The influence of dietary patterns on the development of thyroid cancer. Eur J Cancer. 39:1912-1919; 2003

Moeller, S.M.; Reedy, J.; Millen, A.E.; Dixon, L.B.; Newby, P.K.; Tucker, K.L.; Krebs-Smith, S.M.; Guenther, P.M. Dietary patterns: challenges and opportunities in dietary patterns research an Experimental Biology workshop, April 1, 2006. J Am Diet Assoc. 107:1233-1239; 2007

Potentas, E.; Witkowska, A.M.; Zujko, M.E. Mediterranean diet for breast cancer prevention and treatment in postmenopausal women. Prz Menopauzalny. 14:247-253; 2015

Romieu, I.; Lazcano-Ponce, E.; Sanchez-Zamorano, L.M.; Willett, W.; Hernandez-Avila, M. Carbohydrates and the risk of breast cancer among Mexican women. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 13:1283-1289; 2004

SAS Institute. Principal Component Analysis - SAS. http://support.sas.com/publishing/pubcat/chaps/55129.pdf.

Tavani, A.; La Vecchia, C.; Gallus, S.; Lagiou, P.; Trichopoulos, D.; Levi, F.; Negri, E. Red meat intake and cancer risk: a study in Italy. Int J Cancer. 86:425-428; 2000

Zhang, Y.; Chen, Y.; Huang, H.; Sandler, J.; Dai, M.; Ma, S.; Udelsman, R. Diagnostic radiography exposure increases the risk for thyroid microcarcinoma: a population-based case-control study. Eur J Cancer Prev. 24:439-446; 2015