Journal of Nutrition and Food Security
Shahid Sadoughi University of Medical Sciences
School of Public Health
Department of Nutrition
Nutrition & Food Security Research Center

eISSN: 2476-7425 pISSN: 2476-7417 JNFS 2020; 5(2): 109-117 Website: jnfs.ssu.ac.ir

The Association between Dietary Intakes and Differentiated Thyroid Cancer: A Cross-Sectional Study among Patients and Healthy People in Iran

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ARTICLE INFO

ORIGINAL ARTICLE

Article history:
Received: 13 Sep 2018
Revised: 25 Dec 2018
Accepted: 23 Mar 2019

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ABSTRACT

Background: Differentiated thyroid cancer (DTC) is the most prevalent endocrine cancer. Evidence showed a significant association between diet and DTC. Thus, this study aimed to assess the relationship between dietary intakes and DTC. **Methods:** This case-control study was accomplished among 300 adult patients and 300 matched (age and gender) controls in Mashhad city, Iran. Dietary assessment was conducted and the relationship between dietary intakes and DTC were examined by a validated food-frequency questionnaire and logistic regression analysis, respectively. **Results:** After adjusting for the confounders, a protective effect was observed for the highest tertile of low-fat dairy (OR=0.3, 95% CI=0.17-0.53, $P < 0.001$) and fruits' intakes (OR=0.28, 95% CI=0.15-0.52, $P < 0.001$) on DTC. However, the highest tertile of sugar intake was significantly related to greater DTC chance (OR=4.01, 95% CI=2.07-7.79, $P < 0.001$). A protective role was also found for vegetables in the second tertile of consumption (OR=0.3, 95% CI= 0. 0.17-0.54, $P < 0.001$) and for tea in the second and third tertiles (OR=0.2, 95% CI= 0.11-0.53, $P < 0.001$; OR=0.42, 95% CI=0.26-0.69, $P = 0.001$ respectively). However, the second and third tertiles of the roasted or fried meat consumption were significantly associated with higher DTC chance (OR=1.66, 95% CI= 1.007-2.76, $P = 0.04$; OR=1.92, 95% CI=1.07-3.42, $P = 0.02$ respectively). No significant association was detected for other dietary intakes. **Conclusions:** Consumption of low fat dairy, fruits, vegetables, and tea had a protective effect on DTC; whereas, roasted or fried meat and sugar consumption was significantly associated with higher DTC chance. Further studies are needed to confirm these results.

Keywords: *Thyroid neoplasms; Dietary intake; Food*

Introduction

Differentiated thyroid cancer (DTC) is the most common endocrine malignancy with a rapid increasing incidence throughout the world. Papillary and follicular thyroid cancer consists of

This paper should be cited as: Sangsefidi ZS, Norouzy A, Safarian M, Kashanifar R, Pourbaferani R, Ghafouri-Taleghani F, et al. ***The Association between Dietary Intakes and Differentiated Thyroid Cancer: A Cross-Sectional Study among Patients and Healthy People in Iran.*** *Journal of Nutrition and Food Security (JNFS)*, 2020; 5 (2): 109-117.

[Downloaded from jnfs.ssu.ac.ir on 2026-11-10]
[DOR: 20.1001.1.24767417.2020.5.2.1.8]
[DOI: 10.18502/jnfs.v5i2.2797]

more than 95% of the DTCs (Choi and Kim, 2014).

The increasing incidence of DTC may be related to several factors such as developments in diagnostic modalities, history of radiation, diet, body mass index (BMI), and physical activity (Bandurska-Stankiewicz *et al.*, 2011, Bosetti *et al.*, 2001, Bosetti *et al.*, 2002, Dal Maso *et al.*, 2009, Franceschi *et al.*, 1991, Galanti *et al.*, 1997, Glattre *et al.*, 1993, Jung *et al.*, 2013, Kolonel *et al.*, 1990, Leitzmann *et al.*, 2010, Memon *et al.*, 2001, Memon *et al.*, 2002, Paes *et al.*, 2010, Truong *et al.*, 2010, Wingren *et al.*, 1993).

Nutritional factors and diet are important modifiable factors, which can influence on cancer prevention (Choi and Kim, 2014, Dal Maso *et al.*, 2009). Several studies investigated the effect of different dietary items on the risk of thyroid cancer. However, the findings of studies are inconsistent in some aspects. For example, some surveys indicated a protective impact for consumption of fish and other iodine-rich foods (Choi and Kim, 2014, Cléro *et al.*, 2012, Dal Maso *et al.*, 2009, Truong *et al.*, 2010, Xhaard *et al.*, 2013) as well as vegetables and fruits (Bosetti *et al.*, 2002, Choi and Kim, 2014, Dal Maso *et al.*, 2009, Jung *et al.*, 2013) against DTC. However, increased consumption of fish (Horn-Ross *et al.*, 2001) and cruciferous vegetables were related to higher risk of DTC in other surveys (Bandurska-Stankiewicz *et al.*, 2011, Memon *et al.*, 2002, Truong *et al.*, 2010) . In addition, researchers reported that higher intakes of chicken, mutton, lamb (Memon *et al.*, 2002), pork, and poultry (Lampe, 2011, Markaki *et al.*, 2003) were associated with increased risk of DTC.

Nevertheless, most studies about dietary intakes and DTC were done among western populations and their results are inconsistence. Furthermore, we are faced with paucity of information regarding the Middle Eastern populations, especially Iranian population, where dietary habits are different from western countries. Thus, this study was conducted to evaluate the association between dietary intakes and DTC in Mashhad city, Iran.

Materials and Methods

Design and study population: In this case-control survey, 300 patients with diagnosed DTC (based on their medical records) were selected as the case group and 300 healthy individuals as controls (based on their self-reports). Purposive sampling method was used for selecting participants. The participants of two groups were matched in terms of gender and age (±5 years). Patients were recruited from thyroid cancer clinic in Ghaem Hospital in Mashhad, Iran, from April 2012 to March 2013. Inclusion criteria for patients were having diagnosed DTC, quitting drugs, being on iodine depletion diet for the last 3 months, and being under treatment in nuclear medicine department after thyroidectomy. The control group consisted of participants with no history of diseases who accompanied patients referring to Ghaem Hospital for reasons other than thyroid problems. Exclusion criteria comprised of having pregnancy, lactation, a special diet, history of any acute or chronic diseases based on medical records or self-reports.

Measurements: The participants' general information (including demographic data, weight, height, disease information) was recorded by a general questionnaire and the dietary intakes were assessed by a validated Iranian food-frequency questionnaire (FFQ) (Jafarabadi *et al.*, 2014, Nematy *et al.*, 2014). The FFQ included 160 food items designed by the department of nutrition in Mashhad university of medical sciences, which was validated among the local population (Jafarabadi *et al.*, 2014, Nematy *et al.*, 2014). For each dietary item, participants were supposed to report their consumption rate (i.e., the number of frequencies and serving sizes per month, week, or day depending on the item). A graphical display was used for each food portion size in FFQ to guide the participants. Later, the completed FFQs were initially scanned, read, and analyzed via a special software designed for this purpose. Dietary intakes for different food items were estimated based on their frequencies and serving sizes of consumption. Next, the food items were categorized to specified food groups based on

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[DOI: 10.18502/jnfs.v5i2.2797]

similarity of nutritional contents and previous studies (Bandurska-Stankiewicz *et al.*, 2011, Bosetti *et al.*, 2001, Brungger *et al.*, 1997, Choi and Kim, 2014, Coulonval *et al.*, 2000, Dal Maso *et al.*, 2009, Franceschi *et al.*, 1991, Franceschi *et al.*, 1990, Frassetto *et al.*, 1998, Galanti *et al.*, 1997, Glattre *et al.*, 1993, Gonzalez and Riboli, 2010, Greenwald *et al.*, 2001, Kolonel *et al.*, 1990, Langseth and Europe, 1996, Memon *et al.*, 2002, Poulaki *et al.*, 2003, Randi *et al.*, 2008, Truong *et al.*, 2010, Wingren *et al.*, 1993). In this regard, low and high-fat dairy, sugars, fruits, vegetables, tea, roasted or fried meat, starchy foods, fish, fast foods, and sugar-sweetened drinks were considered. In should be noted that FFQ did not include information on dietary supplements.

Ethical considerations: The project was approved by the local Committee of Ethics (approval number: 89177) and written informed consent was obtained from all participants.

Data analysis: The statistical software IBM SPSS version 16·0 was used for analysis of data. Frequency and percentage were applied for description of qualitative variables. However, Mann-Whitney U test and independent-samples T-test were run for comparing quantitative variables between cases and controls according to their normal distribution. Kolmogorov-Smirnov test was applied for checking the normality distribution of variables. Comparison of nominal qualitative variables was also conducted by Chi-square test. Furthermore, Logistic regression was used for evaluating the association between dietary intakes and DTC in various models by adjusting different confounders (including total energy intake (Continuous; kcal/d), education level (Illiterate, Primary school, Secondary school and Diploma, Graduate diploma, Bachelors, Masters, PhD or higher), history of smoking (yes/no), and BMI (≤18.5, 18.5-24.9, ≥25 Kg/m^2). In all analysis, the first tertile of dietary intakes was considered as the reference. The P-value of < 0.05 was also considered statistically significant.

Results

Participants' characteristics: shows the distribution of participants according to general characteristics. Most participants in both patients (84.7%) and control (84.7%) groups were female. The mean ages of the case and control groups were 41.7 ± 13.6 and 41.2 ± 13.1 years (P = 0.72), respectively. The majority of participants in patients (87.7%) and controls (83.7%) groups were married. Moreover, the findings indicated that the prevalence of smoking among patients was significantly higher than the controls (10% versus 3.7%, P = 0.002). We also observed that the frequency of educated people was significantly higher among the control group than cases (P < 0.001). Meanwhile, a significant difference was found between cases and controls in terms of BMI (Median and interquartile range: 25.31 (29.65-22.84) and 25.99 (29.29-23.03) kg/m^2, respectively, P = 0.009). According to **Table 2**, most patients had papillary cancer (89.3%).

Dietary intakes and differentiated thyroid cancer: **Table 3** shows the relationship between dietary intakes and DTC. Before and after adjusting for the confounding factors, a significant inverse association was observed between the third tertile of fruit consumption and DTC in comparison to the first tertile (OR=0.27, 95% CI= 0.15-0.51, P < 0.001; OR=0.28, 95% CI=0.15-0.52, P < 0.001, respectively). However, the third tertile of sugar intake was significantly associated with increased odds of DTC (OR=4.26, 95% CI= 2.17-8.39, P < 0.001; OR=4.01, 95% CI=2.07-7.79, P < 0.001, respectively). The results for consumption of roasted or fried meat indicated that participants in the second and third tertiles had significantly greater odds of DTC in comparison to the individuals in the first tertile (OR=1.66, 95% CI= 1.00-2.77, P = 0.05; OR=1.97, 95% CI=1.1-3.53, P = 0.02, respectively). This finding remained unchanged after adjustment of the confounders (OR=1.66, 95% CI= 1.007-2.76, p=0.04; OR=1.92, 95% CI=1.07-3.42, P = 0.02, respectively). Intake of vegetables in the second tertile was also significantly related to decreased odds of DTC in comparison to the first tertile (OR=0.33, 95% CI= 0. 0.18-0.59, P < 0.001). This association did not change after adjusting for the

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[DOI: 10.18502/jnfs.v5i2.2797]

confounders (OR=0.3, 95% CI= 0. 0.17-0.54, P < 0.001). Before and after adjustment of the confounding variables, we observed that participants in the second and third tertiles of the low-fat dairy consumption had significantly lower chance of DTC compared with those in the first tertile (OR=0.29, 95% CI= 0.16-0.53, P < 0.001; OR=0.3, 95% CI=0.17-0.53, P < 0.001, respectively). For tea intake, a significant inverse association was found between drinking tea and DTC odds in the second and third tertiles in comparison to the first tertile (OR=0.2, 95% CI= 0.11-0.35, P < 0.001; OR=0.42, 95% CI=0.25-0.68, P = 0.001, respectively). This result was significant after adjustment of the confounding variables (OR=0.2, 95% CI= 0.11-0.53, P < 0.001,; OR=0.42, 95% CI=0.26-0.69 P = 0.001, respectively). No significant association was detected between other dietary intakes and DTC.

Table 1. Participants' general characteristics in DTC patients and control group.

Characteristics	Patients (N=300)	Control group (N= 300)	P-value[a]
Gender	N (%)	**N (%)**	
Male	46 (15.3)	46 (15.3)	1
Female	254 (84.7)	254 (84.7)	
Marital status			
Single	32 (10.7)	48 (16)	0.075
Married	263 (87.7)	251 (83.7)	
Divorced	1 (0.3)	0 (0)	
Widowed	4 (1.3)	1 (0.3)	
Education level			
Illiterate	52 (17.3)	44 (14.7)	< 0.001
Primary school	90 (30.0)	48 (16.0)	
Secondary school and Diploma	98 (32.7)	101 (33.6)	
Graduate diploma	21 (7.0)	18 (6.0)	
Bachelors	30 (10.0)	54 (18.0)	
Masters	8 (2.7)	29 (9.7)	
PhD or higher	1 (0.3)	6 (2.0)	
Smoking			
Yes	30 (10.0)	11 (3.7)	0.002
No	270 (90.0)	289 (96.3)	

a: Chi-square

Table 2. The prevalence of DTC among patients

Types of cancer among patients	N (%)
Papillary	268 (89.3)
Follicular	30 (10.0)
Medullar	2 (0.7)

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Table 3. Odds ratios (OR) and 95% confidence interval (CI) for DTC across different tertiles (T) of dietary intakes

Dietary intakes	Unadjusted		Adjusted[a]	
	OR (95%CI)	P-value	OR (95%CI)	P-value
Low-fat dairy (g/d)				
T1	Reference		Reference	
T2	0.8 (0.47-1.35)	0.41	0.81 (0.49-1.36)	0.44
T3	0.29 (0.16-0.53)	<0.001	0.3 (0.17-0.53)	<0.001
High-fat dairy (g/d)				
T1	Reference		Reference	
T2	0.86 (0.5-1.46)	0.58	0.88 (0.52-1.49)	0.64
T3	0.57 (0.32-1.02)	0.06	0.58 (0.33-1.03)	0.06
Starchy foods (g/d)				
T1	Reference		Reference	
T2	0.76 (0.45-1.31)	0.33	0.81 (0.48-1.38)	0.45
T3	0.61 (0.31-1.23)	0.17	0.62 (0.31-1.23)	0.18
Fast foods (g/d)				
T1	Reference		Reference	
T2	0.63 (0.29-1.29)	0.25	0.64 (0.29-1.4)	0.26
T3	0.39 (0.12-1.27)	0.12	0.4 (0.12-1.29)	0.12
Fish (g/d)				
T1	Reference		Reference	
T2	0.82 (1.00-4.7)	0.44	0.80 (0.49-1.32)	0.39
T3	1.64 (0.95-2.82)	0.07	1.64 (0.96-2.81)	0.07
Fruits (g/d)				
T1	Reference		Reference	
T2	0.75 (0.44-1.28)	0.3	0.74 (0.44-1.26)	0.27
T3	0.27 (0.15-0.51)	<0.001	0.28 (0.15-0.52)	<0.001
Roasted or fried meats (g/d)				
T1	Reference		Reference	
T2	1.66 (1.00-2.77)	0.05	1.66 (1.007-2.76)	0.04
T3	1.97 (1.1-3.53)	0.02	1.92 (1.07-3.42)	0.02
Sugars (g/d)				
T1	Reference		Reference	
T2	1.12 (0.7-1.79)	0.62	1.1 (0.69-1.74)	0.62
T3	4.26 (2.17-8.39)	<0.001	4.01(2.07-7.79)	<0.001
Vegetables (g/d)				
T1	Reference		Reference	
T2	0.33 (0.18-0.59)	<0.001	0.3 (0.17-0.54)	<0.001
T3	0.98 (0.67-1.76)	0.95	0.91 (0.54-1.55)	0.75
Tea (g/d)				
T1	Reference		Reference	
T2	0.2 (0.11-0.35)	<0.001	0.2 (0.11-0.53)	<0.001
T3	0.42 (0.25-0.68)	0.001	0.42 (0.26-0.69)	0.001
Sugar-sweetened drinks (g/d)				
T1	Reference		Reference	
T2	1.01 (0.61-1.67)	0.97	0.97 (0.59-1.6)	0.91
T3	0.77 (0.44-1.36)	0.38	0.74 (0.42-1.29)	0.29

[a]: Adjusted for education level, history of smoking, total energy intake, and body mass index.

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Discussion

According to our results, an inverse association was observed between DTC chance and consumption of low fat dairy, fruits, vegetables, and tea, while greater intakes of roasted or fried meat and sugar were associated with higher chance of DTC.

In consistence with our research, many other studies (Choi and Kim, 2014, Dal Maso *et al.*, 2009, Franceschi *et al.*, 1991, Kolonel *et al.*, 1990, Ron *et al.*, 1987, Wingren *et al.*, 1993) reported a protective role for intake of fruits and vegetables against DTC.

Contrary to our results, some surveys reported that higher consumption of cruciferous vegetables was related to increased DTC risk (Bandurska-Stankiewicz *et al.*, 2011, Galanti *et al.*, 1997, Memon *et al.*, 2002, Truong *et al.*, 2010). In the present research, we assessed overall vegetables' intake. Therefore, discrepancy between our finding and some surveys might be attributed to this point. Moreover, some of the mentioned studies (Bandurska-Stankiewicz *et al.*, 2011, Galanti *et al.*, 1997, Truong *et al.*, 2010) were conducted in western contries where dietary habits and dietary pattern are different from Iran.

Fruits and vegetables can generally prevent cancer by mechanisms including inhibition of endogenous carcinogen formation, inhibition of damage from carcinogenic substances, and modulation of immune function due to having many beneficial compounds such as vitamins, minerals, and phytochemicals. However, the action of these substances on the thyroid gland is not clear (Choi and Kim, 2014, Dal Maso *et al.*, 2009).

Scarcity of information is available on the association between roasted or fried meat intake and the risk of DTC. Nevertheless, similar to our results, the researchers found that high consumption of meat was related to a greater risk of DTC in Kuwait (Memon *et al.*, 2002). Evidence indicated that heating meat in high temperatures results in production of some carcinogenic agents like heterocyclic amines, polycyclic aromatic hydrocarbons , hetero-cyclic aromatic amines, N-nitroso compounds, or heme iron (Choi and Kim, 2014, Greenwald *et al.*, 2001). Moreover, high protein consumption particularly animal protein causes metabolic acidosis and decreases thyroid function, which might be considered as a potential risk factor for DTC (Brungger *et al.*, 1997, Frassetto *et al.*, 1998). Therefore, our findings about the relationship between high meat consumption and high chance of DTC might be explained via the mentioned mechanisms.

Contrary to the current research, Galanti eta al. reported that higher consumption of dairy products (cheese and butter) was related to higher risk of DTC in the Sweden and Norway. The researchers of this study suggested that this result might be associated with the fortification of dairy products with vitamin A and vitamin D in such areas (Galanti *et al.*, 1997). It was also found that these vitamins might be related to increased risk of thyroid cancer due to the homology among the cellular receptors for steroid hormones, vitamin D, and retinoic acid (Evans, 1988, Galanti *et al.*, 1997). Furthermore, the survey by Galanti eta al. was conducted among the western populations with different dietary habits from those of Iranian population.

Although evidences are available about the protective role of dairy products against cancer via having compounds such as B vitamins, calcium, magnesium, and live microbes (Lampe, 2011), no particular information exists regarding the thyroid cancer. Therefore, the protective effect of low fat dairy products in our study might be associated with the mentioned beneficial compounds.

No study has ever indicated the relationship between sugar consumption and DTC. However, high intake of carbohydrates with high glycemic index (GI) was associated with DTC. Insulin and insulin-like growth factor-1 (IGF-1) secretion increase following consumption of carbohydrates with high GI. Insulin and IGF-1 are necessary cofactors for TSH action on thyroid cells, which may result in continued auto-stimulation of cell replication in thyroid cells. IGF-1 also inhibits apoptosis and stimulates vascular endothelial growth factor in thyroid carcinoma (Coulonval *et al.*, 2000, Poulaki *et al.*, 2003, Randi *et al.*, 2008).

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[DOI: 10.18502/jnfs.v5i2.2797]

As sugar has a high GI, its high intake may be associated with higher risk of DTC.

Similar to some studies (Linos *et al.*, 1988, Takezaki *et al.*, 1996), we found a significant inverse relationship between tea consumption and DTC. Tea contains caffeine that increases cAMP and plays a role as a cancer inhibitor in cells, which consequently prevents DTC (Linos *et al.*, 1988, Takezaki *et al.*, 1996).

The present survey had several strengths. To the best of our knowledge, it was the first survey over the association between dietary intakes and DTC in Iran. In addition, a wide range of confounding factors (including gender, age, total energy intake, history of smoking, education level, and BMI), which might influence DTC chance, were controlled.

Our study also had several limitations. We studied prevalent patients due to the limited number of new cases. However, patients generally did not receive any particular dietary advice after treatment. Therefore, the possibility of changing the dietary behaviors among prevalent cases was low in comparison to new cases and consequently the possibility of bias was also low. Another limitation was measurement error that is an identified feature of any dietary evaluation method. Moreover, we did not evaluate other confounding factors such as exposure to radiation and physical activity level among the participants. Finally, the present research could not fully explain the causality relationship due to its case-control design. Therefore, our findings should be approved by future studies, especially prospective surveys.

Conclusion

An inverse relationship was found between DTC and consumptions of low fat dairy, fruits, vegetables, and tea; whereas, higher intakes of roasted or fried meats and sugar were related to greater chance of DTC. Further surveys specially cohort studies are needed to confirm these findings.

Acknowledgment

The authors thank University of Medical Sciences, Mashhad, Iran that supported this study.

Authors' contributions

Norouzy A, Zakavi SR, and Safarian M designed the study. Sangsefidi ZS, Kashanifar R, and Pourbaferani R collected the data. Sangsefidi ZS performed the statistical analysis. Sangsefidi ZS, fouri-Taleghani F, Taghizadeh-kermani A and Fallahi S wrote the manuscript. Zakavi SR and Norouzy A critically revised the manuscript and approved to submit final version of the manuscript. All authors read and approved the final version of article.

Conflicts of interest

The authors declare no conflict of interests regarding publication of this paper.

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