Review Article
Clin Nutr Res 2014;3:75-88
http://dx.doi.org/10.7762/cnr.2014.3.2.75
pISSN 2287-3732 · eISSN 2287-3740

CLINICAL NUTRITION RESEARCH

Dietary Factors and the Risk of Thyroid Cancer: A Review

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In the past few decades, the incidence of thyroid cancer has rapidly increased worldwide. Thyroid cancer incidence is relatively high in regions where the population's daily iodine intake is insufficient. While low dietary iodine has been considered as a risk factor for thyroid cancer development, previous studies found controversial results across different food types. Among different ethnic groups, dietary factors are influenced by various dietary patterns, eating habits, life-styles, nutrition, and other environmental factors. This review reports the association between dietary factors and thyroid cancer risk among ethnic groups living in different geologic regions. Iodine-rich food such as fish and shellfish may provide a protective role in populations with insufficient daily iodine intake. The consumption of goitrogenic food, such as cruciferous vegetables, showed a positive association with risk. While considered to be a risk factor for other cancers, alcohol intake showed a protective role against thyroid cancer. High consumption of meat such as chicken, pork, and poultry showed a positive association with the risk, but dairy products showed no significant association. Regular use of multivitamins and dietary nitrate and nitrite also showed a positive association with thyroid cancer risk. However, the study results are inconsistent and investigations into the mechanism for how dietary factors change thyroid hormone levels and influence thyroid function are required.

Key Words: Thyroid cancer, Dietary factor, Iodine, Food, Review

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Funding This work was supported by a grant from National Research Foundation of Korea (NRF-2012R1A1A2044332).

Received June 3, 2014
Revised June 19, 2014
Accepted June 20, 2014

Introduction

Thyroid cancer is the most common endocrine cancer, traditionally classified into two major groups based on morphologic and clinical features: differentiated carcinoma (papillary, follicular, and medullary) and undifferentiated (anaplastic) carcinoma [1]. The worldwide incidence of thyroid cancer has been rapidly increasing over the last three decades [2]. Papillary thyroid cancer accounts for about two-thirds of both male and female cases, while follicular accounts for 10-20%, medullary for 5-10%, and anaplastic for less than 5% [1]. In the U.S., based on the Surveillance, Epidemiology, and End Results (SEER) program between 1992 and 2006, the incidence of papillary thyroid cancer was the highest in Asian females (10.96 per 100,000 woman-years), while papillary and follicular thyroid cancer were the highest among White males (3.58 and 0.58 man-years, respectively) [3]. Since 2004, the incidence of thyroid cancer in the U.S. increased by 5.5% in males and 6.6% in females [4]. Compared to the U.S., the incidence of thyroid cancer in South Korea was significantly increased from 1999 to 2011 in both sexes [5]. According to the Korea Centers for Disease Control and Prevention (KCDC) in 2012, food products such as processed, agricultural, meats, and marine products were monitored for measuring dietary iodine in Korean population [6]. Of these food products, dietary iodine from marine products such as seaweed was the highest in Korean adults. Iodine excess contributes to the changes in thyroid-stimulating hormone (TSH) so that it may increase thyroid cancer risk, particularly in women [7]. Therefore, high intake of iodine from marine products may increase the incidence of thyroid cancer in Korean population.

Environmental carcinogens, such as dietary and nutritional factors, may explain the high incidence of thyroid cancer [8]. Previous studies investigated dietary factors that can possibly affect thyroid cancer risk, but the results were inconsistent due to diverse dietary patterns, eating habits, life-styles, and other environmental risk factors. For instance, multi-ethnic groups living in iodine deficient regions with high intake of seafood showed either no association or lowered thyroid cancer risk [9,10]. Therefore, some ethnic groups exposed to certain food types are at a greater or lower thyroid cancer risk compared with those who are not. The purpose of this study was to review the association between dietary factors and thyroid cancer risk in different ethnic populations in various geologic regions.

Materials and Methods

An article search was conducted in PubMed for studies published between January 1st 1995 and April 30th 2014. The keywords were as follows: '(thyroid cancer) AND (diet OR dietary pattern OR dairy food OR fish OR alcohol OR vegetables)'. The following inclusion criteria were used: 1) epidemiological studies including cases and controls (either hospital or population-based) as well as cohort studies, 2) studies investigating the association between dietary factors and thyroid cancer including papillary and follicular type, and 3) studies estimating the thyroid cancer risk with odds, relative ratio or hazard ratio (OR, RR, HR) according to dietary factors.

A total of 905 articles were identified through PubMed (Figure. 1). By screening the title and abstract, articles on topics other than thyroid cancer were excluded (n = 795); full-text articles (n = 110) were reviewed for study selection. Of the 110 full-text articles, an additional 85 articles were excluded due to the following factors: 1) reviews (n = 9), 2) studies without epidemiological research (n = 40), 3) studies without investigating an association between thyroid cancer risk and dietary factors (n = 29), and 4) no case-control or cohort study design (n = 7). Two additional articles were identified through the references of the original articles and were included in the study. A total of 27 articles (e.g., 17 case-control and 10 cohort studies) were included in this review. Considering geologic regions, there were 12 studies (e.g., 3 case-controls and 9 cohorts) identified from the North America (e.g., U.S and Canada), 10 studies from the Europe (e.g., 9 case-controls and 1 cohort), and 5 studies from Asia (e.g., 5 case-controls).

Results

Fish consumption

Fish and shellfish are the primary source of dietary iodine intake in multiethnic populations [11]. Table 1 describes the association between the consumption of fish and thyroid cancer risk including 6 case-control studies and 1 cohort study. In French Polynesia, a region with high thyroid cancer incidence due to iodine deficiency in the population, a decreased thyroid cancer risk was associated with high level of fish, shellfish, and total seafood consumption [10]. In the same region, low intake of total seafood was also considered a significant risk factor for the development of thyroid cancer [12]. Similar to French Polynesia, Melanesian women with iodine deficiency in New Caledonia showed no significant association with saltwater fish, seafood, or canned fish; the consumption of brackish water fish, which is exclusively consumed by Melanesians, was inversely associated with risk [9]. A study from Kuwait showed a decreased risk associated with the high intake of freshwater fish, but consumption of processed fish products showed a positive association with development of thyroid cancer [13]. The studies (e.g., 1 cohort and 2 case-controls) from the U.S. found no significant association with fish consumption [11,14,15]. However, a positive association was found with the high intake of fish sauce as well as dried or salted fish in Asian females living in the San Francisco Bay Area [11], whereas frequent intake of saltwater fish decreased papillary thyroid cancer risk in adult females [14]. In Sweden and Norway, no significant association was found with saltwater fish, freshwater fish, shellfish, and fish products [16]. In Japan, a region with exceptionally high seaweed consumption, a positive association was found between iodine intake via seaweed and thyroid and papillary carcinoma in postmenopausal females [17]. The

http://dx.doi.org/10.7762/cnr.2014.3.2.75

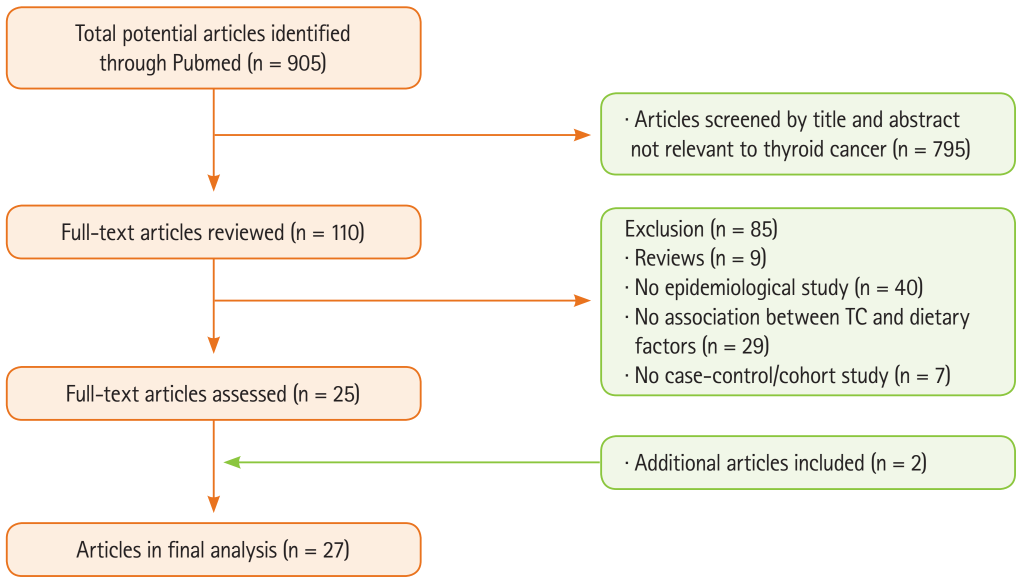

Figure 1. Flow chart for selection of eligible studies.

study explained that the antiestrogenic bioactive compounds in seaweed did not play a protective role among postmenopausal women due to low estrogen and estrogen receptor α (ERα) levels compared with premenopausal women [17].

In previous studies, inconsistent results for the association between fish consumption and thyroid cancer risk were found. In a pooled-analysis [18], fish consumption was not associated with thyroid cancer risk, but a possible protective role in iodine deficient regions was suggested.

Fruits and vegetables

High intake of fruits and vegetables containing active micronutrients (e.g., vitamins and minerals) and phytochemicals provide antioxidant activity that helps to protect against cancers [19]. An individual or combination of bioactive components from fruits and vegetables may provide a protective role in thyroid cancer risk. Table 1 describes the association between the consumption of fruits and vegetables and thyroid cancer risk including 9 case-control studies. In the U.S., the frequent intake of turnips or rutabagas by females was inversely associated with both thyroid and papillary cancer risk [14,20]. The study from Greece examined the association between dietary patterns and thyroid cancer; the dietary pattern of fruits and raw or mixed vegetables showed a non-significant decreased risk, but particularly, fresh tomato and lemon were significantly inversely associated with risk [20]. In South Korea, high levels of raw vegetable and persimmon consumption showed a negative association with both malignant and benign thyroid cancer risk, and tangerine and total vegetable consumption was inversely associated with the risk of malignant and benign thyroid cancer, respectively [21]. This study suggested that a high intake of these fruits and vegetables might help to prevent early thyroid cancer. In Norway, a high intake of citrus fruits was positively associated with thyroid cancer risk, but other fruits such as apples and oranges were not associated with an increased risk [16]. In French Polynesia, traditional and Western dietary patterns were compared across 24 goitrogenic food items, and high cassava intake showed an inverse association with thyroid cancer risk [22].

Cruciferous plants (e.g., brussels sprouts and cabbage) contain a degraded form of thioglucosides, such as thiocyanates (e.g., goitrogen), and may increase thyroid cancer risk by inhibiting iodine transport to the thyroid gland at low concentrations [23]. Four case-control studies found an association between increased thyroid cancer risk and the high cruciferous vegetables intake [9,13,16,24]. The study from New Caledonia among Melanesian women who consume large quantities of cruciferous vegetables and have a low iodine intake (< 96.0 μg/day) showed a positive association [9]. In Sweden, the risk of thyroid cancer associated with a high cruciferous vegetable intake was higher among females who had ever lived in an endemic goiter area [16]. A study from Kuwait showed no clear

Table 1. The association between fish, fruits and vegetables, meat, and dairy food, and thyroid cancer risk

Author, year, country	Study characteristics	N, population	Age, year	Food type	Referent unit, low vs. high	Outcome, OR/HR/RR (95% CI)	Result
Fish & Seafood							
Galanti (1997) Sweden & Norway [16]	Case-control (Population-based)	Sweden (35M/130F;50M/198F) Norway (24M/57F;57M/135F)	18-75	1. Freshwater fish 2. Roe	[portions/mo.] 1. < 1 vs. > 1 2. ≤ 1 vs. > 1	1. OR = 0.6 (0.4-1.1) 2. OR = 0.4 (0.2-0.7)	A monthly intake of freshwater fish and roe inversely assoc with TC risk, but not statistically significant in both Sweden and Norway
Horn-Ross (2001) US [11]	Case-control (Population-based)	608F/558F	20-74	Fish sauce/dried or salted fish	[g/d] 0.0 vs. > 2.0	OR = 2.3 (1.3-4.0)	High intake of fish sauce/dried or salted fish positively assoc TC risk in Asian women
Mack (2002) US [14]	Case-control (Population-based)	292F/292F	15-54	Saltwater fish	[frequency] < few/yr vs. few/wk+	OR = 0.3 (0.1-0.7); p = 0.006	High intake of saltwater fish inversely assoc with PTC in adult female
Memon (2002) Kuwait [13]	Case-control (Population-based)	313/313 (75M/238F)	≤ 70	1. Fish 2. Fish products	[frequency] never/yr vs. 2-4 d or 5-7 d/wk	1. OR = 0.6 (0.3-1.0); p < 0.05 2. OR = 3.0 (1.6-5.3); p < 0.01	High intake of freshwater fish inversely assoc with TC risk High intake of processed/canned/frozen fish products positively assoc with TC risk
Truong (2010) France (New Caledonia) [9]	Case-control (Population-based)	293F/354F	≥ 18	Brackish water fish	[g/d] 0.0 vs. > 10.0	OR = 0.43 (0.20-0.93); p-trend = 0.03	High intake of brackish water fish inversely assoc with TC risk in all ethnic groups (Melanesian, European, and others)
Xhaard (2014) France (French Polynesia) [12]	Case-control (Population-based)	229/373 (26M/203F TC)	≤ 55	Total seafood	[g/d] ≤ 45 vs. ≥ 91	OR = 0.4[0.3-0.8]; p = 0.0002	High intake of total food from sea inversely assoc with TC risk
Cléro (2012) France (French Polynesia) [10]	Case-control (Population-based)	229/371 (26M/203F;47M/324F)	< 56	1. Fish 2. Shellfish 3. Total intake of food from sea	[g/d] 1. ≤ 39 vs. ≥ 80 2. 0 vs. ≥ 8 3. ≤ 45 vs. ≥ 91	1. OR = 0.47[0.27-0.82]; p = 0.008 2. OR = 0.40[0.22-0.72]; p = 0.002 3. OR = 0.44[0.25-0.79]; p = 0.002	High intake of fish, shellfish, and total food from sea inversely assoc with TC risk
Daniel (2011) US [15]	Cohort 1) NIH-AARP (1995-1996) 2) Follow-up (9 yr)	492,186 (250M/333F TC)	50-71	Fish	[g/1000 kcal] 3.6 vs. 21.4	HR = 1.18[0.90-1.55]; p = 0.38	No assoc

Table 1. Continued

Author, year, country	Study characteristics	N, population	Age, year	Food type	Referent unit, low vs. high	Outcome, OR/HR/RR (95% CI)	Result
Michikawa (2012) Japan [17]	Cohort 1) JPHCPS (1993-1994) 2) Follow-up (14.5 yr)	52,679F (134TC)	40-69	Seaweed	[frequency] ≤ 2 d/wk vs. almost daily 1. TC 2. PTC	1. HR = 1.58 (0.91-2.73); p-trend = 0.10 2. HR = 1.86 (1.03-3.34); p-trend = 0.04	High intake of seaweed positively assoc with TC risk, but not statistically significant High intake of seaweed positively assoc with TC and PTC risk in postmenopausal women
Fruits & Vegetables							
Galanti (1997) Sweden & Norway [16]	Case-control (Population-based)	Sweden (35M/130F;50M/198F) Norway (24M/57F;57M/135F)	18-75	Citrus fruits	[portions/mo.] ≤ 5 vs. > 21	OR = 2.8 (1.1-7.5); p = 0.02	High intake of citrus fruits positively assoc with TC risk in Norway
Mack (2002) US [14]	Case-control (Population-based)	292F/292F	15-54	Turnips or Rutabagas	[frequency] < few/yr vs. at least monthly 1. TC 2. PTC	1. OR = 0.5 (0.3-1.1); p = 0.01 2. OR = 0.6 (0.3-1.2); p = 0.03	High intake of turnips/rutabagas inversely assoc with TC/PTC risk
Memon (2002) Kuwait [13]	Case-control (Population-based)	313/313 (75M/238F)	≤ 70	Cabbage	[frequency] never/yr vs. 2-4 d or 5-7 d/wk	OR = 1.9 (1.1-3.3); p-trend = 0.08	High intake of cabbage positively assoc with TC risk, but not statistically significant
Markaki (2003) Greece [20]	Case-control (Population-based)	113/138 (31M/82F;43M/95F)	25-60	1. Tomato, fresh 2. Lemons	[servings/mo.] 1. ≤ 0.5 vs. > 28 2. ≤ 4 vs. > 28	1. OR = 0.32 (0.10-1.01); p-trend = 0.002 2. OR = 0.53 (0.24-1.15); p-trend = 0.001	High intake of fresh tomato and lemon inversely assoc with TC/PTC risk
Truong (2010) France (New Caledonia) [9]	Case-control (Population-based)	293F/354F	≥ 18	Cruciferous vegetables	[g/d] ≤ 27.8 vs. ≥ 65.4	OR = 1.86 (1.01-3.43); p-trend = 0.06	Melanesian women with high intake of cruciferous vegetables with low iodine intake (< 96.0 μg/day) positively assoc with TC risk
Bandurska-S. (2011) Poland [24]	Case-control (Population-based)	297/589 (33M/264F;75M/514F)	-	Cruciferous vegetables	[times/wk] 0-2 vs. 5-7/wk	OR = 1.53 (1.19-1.96)	High intake of cruciferous vegetables positively assoc with TC risk
Cléro (2012) France (French Polynesia) [22]	Case-control (Population-based)	229/371 (26M/203F;47M/324F)	< 56	Cassava	non-consumers vs. consumers	OR = 0.62 (0.39-0.99); p = 0.03	High intake of cassava inversely assoc with TC risk

Table 1. Continued

Author, year, country	Study characteristics	N, population	Age, year	Food type	Referent unit, low vs. high	Outcome, OR/HR/RR (95% CI)	Result
Jung (2013) S. Korea [21]	Case-control (Hospital-based)	Malignant 111F/111F Benign 115F/115F	20-70	1. Malignant 1) Raw vegetables 2) Tangerine 3) Persimmons 2. Benign 1) Raw vegetables 2) Total vegetables 3) Persimmons	[g/d] 1. 1) 4.5 vs. 72.5 2) 4.1 vs.79.3 3) 0.0 vs. 24.8 2. 1) 6.0 vs. 77.3 2) 80.8 vs. 422.2 3) 0.0 vs. 24.8	1. 1) OR = 0.20 (0.07-0.62); p = 0.007 2) OR = 0.34 (0.13-0.86); p = 0.027 3) OR = 0.41 (0.17-0.96); p = 0.061 2. 1) OR = 0.28 (0.10-0.76); p = 0.007 2) OR = 0.11 (0.03-0.47); p = 0.003 3) OR = 0.35 (0.15-0.83) ; p = 0.014	High intake of raw vegetables & persimmons inversely assoc with TC malignant and benign risk High intake of tangerine inversely assoc with TC malignant High intake of total vegetables assoc with TC benign
Meat							
Galanti (1997) Sweden & Norway [16]	Case-control (Population-based)	Sweden (35M/130F;50M/198F) Norway (24M/57F;57M/135F)	18-75	All Meat - sausages/sausage dishes - pork/beef/lamb - wild (reindeer/elk) - chicken/poultry - liver/kidney - blood pudding/ blood bread - smoked meat	[portions/mo.] ≤ 12 vs. > 20	OR = 0.8 (0.5-1.3)	No assoc
Memon (2002) Kuwait [13]	Case-control (Population-Based)	313/313 (75M/238F)	≤ 70	1. Chicken 2. Mutton & Lamb	[frequency] never/yr vs. 2-4 d or 5-7 d/wk	1. OR = 3.0 (1.3-6.8); p < 0.01 2. OR = 1.8 (1.1-2.8); p < 0.01	High intake of chicken or mutton & lamb positively assoc with TC risk
Markaki (2003) Greece [20]	Case-control (Population-based)	113/138 (31M/82F;43M/95F)	25-60	Pork	[servings/mo.] ≤ 0.5 vs. > 3	OR = 2.82 (1.36-5.86); p = 0.001	High intake of pork positively assoc with TC risk in male
Daniel (2011) US [15]	Cohort 1) NIH-AARP (1995-1996) 2) Follow-up (9 yr)	492,186 (250M/333F TC)	50-71	Poultry	[g/1000 kcal] 5.3 vs. 51.2	HR = 1.74 (1.14-2.67); p = 0.005	High intake of poultry positively assoc with TC risk in male
Dairy Food							
Galanti (1997) Sweden & Norway [16]	Case-control (Population-based)	Sweden (35M/130F;50M/198F) Norway (24M/57F;57M/135F)	18-75	1. Cheese (slice) 2. Butter (tpsn)	[portions/mo.] 1. ≤ 40 vs. > 90 2. ≤ 60 vs. > 120	1. OR = 1.5 (1.0-2.4) 2. OR = 1.6 (1.1-2.5)	High intake of cheese & butter positively assoc with TC risk in both Sweden and Norway

http://dx.doi.org/10.7762/cnr.2014.3.2.75

Table 1. Continued

Author, year, country	Study characteristics	N, population	Age, year	Food type	Referent unit, low vs. high	Outcome, OR/HR/RR (95% CI)	Result
Truong (2010) France (New Caledonia) [9]	Case-control (Population-based)	293F/354F	≥ 18	NC	[g/d] 40.6 vs. ≥ 194.9	OR = 1.03 (0.67-1.59); p = 0.85	No assoc
Park (2009) US [27]	Cohort 1) NIH-AARP (1995-2003) 2) Follow-up (7 yr)	36,965M (170TC)/ 16,605F (199TC)	50-71	NC	[servings/1000 kcal/d] 0.2 vs. 1. 1.4 (male) 2. 1.6 (female)	1. RR = 0.78 (0.45-1.37); p = 0.41 2. RR = 1.04 (0.67-1.62); p = 0.74	No assoc

TC/PTC: thyroid/papillary thyroid cancer, NIH-AARP: the national institutes of health-american association of retired persons diet and health study, JPHCPS: the japan public health center-based prospective study, No assoc: no association, Assoc: association, M: male, F: female, NC: not classified.

association with broccoli and Brussels sprout consumption [13]. However, high intake of cabbage showed an increased risk with a borderline significance [13]. No association was found between cruciferous vegetable consumption and thyroid cancer in the French Polynesians [22]. In Poland, frequent cruciferous vegetable consumption was associated with a 1.5-fold increase in the risk of thyroid carcinoma [24]. A pooled analysis suggested that cruciferous vegetables might provide a protective role that was similar to that of other vegetables for moderate (OR = 0.87 [95% CI = 0.75-1.01]) and for high intake levels (OR = 0.94 [95% CI = 0.80-1.10]) [23].

Meat consumption

While cooking red meat at a high temperature, carcinogenic compounds such as heterocyclic amines (HCA), polycyclic aromatic hydrocarbons (PAH), N-nitroso compounds, or heme iron are formed and carcinogenesis is promoted by increasing cell proliferation in the mucosa [25]. Table 1 describes the association between the consumption of meat and thyroid cancer risk including 3 case-control studies and 1 cohort study [13,15,16,20]. The study from Kuwait found a positive association with high intake of chicken or mutton and lamb [13]. Additionally, the studies from Greece and the U.S. found a positive association between thyroid cancer risk and the high intake of pork and poultry [15,20]. No clear association was found between thyroid cancer risk and the consumption of all types of meat in Sweden and Norway [16].

Dairy food consumption

High intake of milk and dairy products was associated with other cancer types such as bladder, prostate, breast, and colon cancer risk in multi-ethnic groups in different geological regions [26]. Table 1 describes the association between the consumption of dairy food and thyroid cancer risk including 2 case-control studies and 1 cohort study [9,16,27]. The study from Sweden and Norway found a positive association with the high intake of cheese and butter; particularly, those who had ever lived in an endemic goiter area and had a high intake of all milk products showed a positive association with thyroid cancer risk [16]. However, the studies from the U.S. and New Caledonia found no significant association [9,27].

Alcohol consumption

There is a hypothesis that alcohol intake may increase the level of TSH, which regulates the growth and function of thyroid gland [28]. Based on this hypothesis, elevation of

Table 2. The association between alcohol consumption and thyroid cancer risk

Author, year, country	Study characteristics	N, population	Age, year	Referent unit, low vs. high	Outcome, OR/HR/RR (95% CI)	Result
Alcohol						
Takezaki (1996) Japan [30]	Case-control (Hospital-based)	94F/22,666F	20-79	[frequency] sometimes/less vs. ≥ 4 times/wk	OR = 0.7 (0.3-1.5)	No assoc
Rossing (2000) US [38]	Case-control (Population-based)	558F/574F (410PTC, 58FTC)	18-64	[drink/yr] never (≤ 12) vs. ≥ 12	OR = 0.7 (0.5-1.0)	High intake of alcohol inversely assoc with PTC risk in female
Mack (2002) US [14]	Case-control (Population-based)	292F/292F	15-54	[drink/wk] none vs. >3	OR = 0.7 (0.3-1.5); p = 0.047	High intake of wine inversely assoc with PTC risk in female
Guignard (2007) France (New Caledonia) [31]	Case-control (Population-based)	332/412 (39M/293F;58M/354F)	≥ 18	[drink/wk] never vs. > 10 1. male 2. female	1. OR = 0.32 (0.05-1.95); p-trend = 0.39 2. OR = 0.92 (0.24-3.45); p-trend = 0.82	No assoc
Nagano (2007) Japan [35]	Case-control (Population-based)	57M/305F	< 75	[frequency] never vs. daily	OR = 0.59 (0.35-1.01); p-trend = 0.032	High intake of alcohol inversely assoc with TC risk in both male and female
Xhaard (2014) France (French Polynesia) [12]	Case-control (Population-based)	229/373 (26M/203F TC)	≤ 55	[frequency] none vs. regular	OR = 1.2 (0.3-4.5); p = 0.8	No assoc
Iribarren (2001) US [32]	Cohort 1) KPMC (1964-1973) 2) Follow-up (20 yr)	204,964 (73M/123F TC)	10-89	[drink/d] 1-2 vs. ≥ 6	RR = 0.95 (0.30-3.02)	No assoc
Navarro Silvera (2005) Canada [33]	Cohort 1) NBSS (1980-1985) 2) Follow up (15.9 yr)	89,835F (169TC)	40-59	[g/d] never vs. > 10 1. TC 2. PTC 3. PTC/FTC	1. HR = 0.80 (0.45-1.42); p = 0.56 2. HR = 0.80 (0.35-1.84); p = 0.49 3. HR = 0.84 (0.44-1.58); p = 0.64	No assoc
Allen (2009) UK [39]	Cohort 1) MWS (1996-2001) 2) Follow-up (7.2 yr)	68,775F (421TC)	-	[drink/wk] ≤ 2 vs. > 15	RR=0.54 (0.31-0.92); p-trend = 0.005	High intake of alcohol inversely assoc with TC risk

http://dx.doi.org/10.7762/cnr.2014.3.2.75

Table 2. Continued

Author, year, country	Study characteristics	N, population	Age, year	Referent unit, low vs. high	Outcome, OR/HR/RR (95% CI)	Result
Meinhold (2009) US [37]	Cohort 1) NIH-AARP (1995-1996) 2) Follow-up (> 7.5 yr)	490,159 (170M/200F TC)	50-71	[drink/d] 1. never vs. ≥ 2 2. none(beer) vs. ≥ 1/wk	1. RR = 0.57 (0.36-0.89); p-trend = 0.01 2. RR = 0.42 (0.21-0.83); p-trend = 0.01	High intake of alcohol inversely assoc with TC risk in both male and female High intake of beer inversely assoc with TC risk in male (p-trend = 0.03), but not in female (p-trend = 0.40)
Kabat (2012) US [34]	Cohort 1) WHI (1993-1998) 2) Follow-up (12.7 yr)	159,340F (331TC, 276PTC)	50-79	[drink/wk] 1. none vs. ≥ 7 [g/d] 2. none vs. ≥ 4	1. TC/PTC HR = 0.66 (0.44-1.01); p = 0.13 HR = 0.79 (0.44-1.11); p = 0.37 2. TC/PTC HR = 0.79 (0.60-1.05); p = 0.17 HR = 0.87 (0.64-1.19); p = 0.57	No assoc in postmenopausal women

TC/PTC/FTC: thyroid, papillary or follicular thyroid cancer, KPMC: kaiser permanente multiphasic cohort, NBSS: the canadian national breast scanning study, NIH-AARP: the national institutes of health-american association of retired persons diet and health study, MWS: the million women study, WHI: the women's health Initiative, No assoc: no association, Assoc: association, M: male, F: female.

TSH levels or changes in thyroid function could be a possible reason for an association between alcohol consumption and an increase in thyroid cancer risk [29]. Table 2 describes the association between the consumption of alcohol and thyroid cancer. Three of the 6 case-control studies [12,30,31] and 3 of the 5 cohort studies [32-34] did not find any significant association between alcohol consumption and thyroid cancer risk. Regarding the frequency of alcohol intake, being male and a daily drinker was inversely associated with risk of thyroid cancer when compared with never drinkers; in those who were exposed to radiation from the atomic bomb in Hiroshima and Nagasaki, alcohol consumption was not associated with a higher risk [35]. The U.S. study found that females who consumed more than 3 glasses of wine had a decreased risk of papillary thyroid cancer when compared with non-drinkers; the consumption of beer and whiskey shots was not associated with thyroid or papillary cancer risk [14]. The results from a previous study may suggest that the anticarcinogenic activity of polyphenolic extracts from grape stems in wine could possibly inhibit the proliferation of thyroid cancer cells [36]. In a cohort study from the U.S., no significant association was found between wine consumption in females and thyroid cancer [37]. In addition, a number of studies demonstrated the protective role of high levels of alcohol intake against thyroid cancer [37-39]. In studies, the number of alcoholic drinks was inversely associated with thyroid cancer risk when compared with non-drinking [37-39]. In a pooled-analysis, frequent weekly wine and beer consumption was inversely associated with thyroid cancer risk without adjustment for smoking ($p = 0.02$) [40]. In a pooled-analysis of 5 prospective studies, alcohol consumption greater than 7 drinks per week also showed an inverse association with thyroid cancer risk without adjustment for smoking (p-trend = 0.002) [41]. The previous studies explained that alcohol intake is highly affected by socioeconomic status, for example, people with high socioeconomic status (e.g., higher education and income) are less likely to drink and more likely to have access to health care compared with those with low socioeconomic status [35,42]. Thus, it is possible that the characteristics of diet and lifestyle associated with alcohol consumption could be important factors that influence thyroid cancer risk. However, the results from previous studies are still inconsistent across different types of alcoholic beverages. Further studies are needed to investigate what changes alcohol intake induces in the thyroid hormone and thyroid function.

Table 3. The association between micronutrients and thyroid cancer risk

Author, year, country	Study characteristics	N, population	Age, year	Dietary factor	Referent unit, low vs. high	Outcome, OR/HR/RR (95% CI)	Result
Iodine							
Horn-Ross (2001) US [11]	Case-control (Population-based)	608F/558F	20-74	Total iodine intake from food sources	[μg/d] < 273 vs. > 537	OR = 0.49 (0.29-0.84)	High intake of dietary iodine inversely assoc with PTC risk in female
Truong (2010) France (New Caledonia) [9]	Case-control (Population-based)	293F/354F	≥ 18	Total iodine intake from food sources	[μg/d] < 75.0 vs. ≥ 112.6	OR = 1.13 (0.68-1.87); p-trend = 0.43	No assoc in all ethnic groups
Cléro (2012) France (French Polynesia) [10]	Case-control (Population-based)	229/371 (26M/203F; 47M/324F)	< 56	Total iodine intake from food sources	[μg/d] ≤ 105 vs. 106-175	OR = 0.39 (0.21-0.72); p-trend = 0.03	Higher intake of dietary iodine inversely assoc with TC risk
Calcium, Vitamin, & Others							
D'Avanzo (1997) Italy [45]	Case-control (Hospital-based)	399/617 (108M/291F; 190M/427F)	16-74	1. Retinol 2. Beta-carotene	[μg/d] 1. < 274 vs. ≥ 1802 2. < 3124 vs. ≥ 5827	TCa: 1. OR = 1.52 (1.0-2.3) 2. OR = 0.58 (0.4-0.9); p < 0.05 PCa: 1. OR = 1.46 (0.9-2.3) 2. OR = 0.59 (0.4-0.9); p < 0.05	High intake of retinol positively assoc with TCa/PCa risk High intake of beta-carotene inversely assoc with TCa/PCa risk
Mack (2002) US [14]	Case-control (Population-based)	292F/292F	15-54	Multivitamin	[frequency] never vs. > 10 yrs 1. TC 2. PTC	1. OR = 1.6 (0.8-3.4); p = 0.07 2. OR = 2.9 (1.2-7.4); p = 0.004	High intake of multivitamin positively assoc with TC/PTC risk
Park (2009) US [27]	Cohort 1) NIH-AARP (1995-2003) 2) Follow-up (7 yr)	36,965M (170TC)/ 16,605F (199TC)	50-71	1. Dietary calcium 2. Supplemental calcium 3. Total calcium	[mg/d] Male/Female 1. 478/409 vs. 1247/1101 2. 0 vs. ≥ 1,000 3. 526/494 vs. 1530/1881	1. Male/Female RR = 1.19 (0.67-2.12) RR = 1.01 (0.64-1.58) p = 0.98 2. Male/Female RR = NA; p = 0.44 RR = NA; p = 0.87 3. Male/Female RR = 0.79 (0.46-1.34); p = 0.43 RR = 1.04 (0.65-1.65); p = 0.98	No assoc

http://dx.doi.org/10.7762/cnr.2014.3.2.75

Table 3. Continued

Author, year, country	Study characteristics	N, population	Age, year	Dietary factor	Referent unit, low vs. high	Outcome, OR/HR/RR (95% CI)	Result
Nitrate & Nitrite							
Ward (2010) US [47]	Cohort 1) Iowa (1955-1988) 2) Follow-up (19 yr)	21,977F	55-69	1. Nitrate from public drinking water supplies 2. Dietary nitrate	[mg/L] 1.0 vs. ≥ 5 [mg/d] 2. ≤ 17.4 vs. > 41.1	1. RR = 2.59 (1.09-6.19); p = 0.04 2. RR = 2.85 (1.00-8.11); p = 0.046	High intake of nitrate from public water supplies and food sources positively assoc with TC risk
A.Kilfoy (2011) US [48]	Cohort 1) NIH-AARP (1995-1996) 2) Follow-up (7 yr)	490,194 (170M/200F;370TC)	50-71	Food sources	[mg/d] 1. 19.4 vs. 94.8 2. 20.8 vs. 87.1 3. 20.8 vs. 87.1 4. 0.5 vs. 0.9	1. TC-Nitrate RR = 2.28 (1.29-4.04); p-trend < 0.01 2. PTC-Nitrate RR = 2.10 (1.09-4.05); p-trend < 0.05 3. FTC-Nitrate RR = 3.42 (1.03-11.4); p-trend < 0.01 4. FTC-Nitrite RR = 2.74 (0.86-8.77); p-trend = 0.04	High intake of nitrate from food sources positively assoc with TC/PTC risk in male High intake of nitrate/nitrite intake from food sources positively assoc with FTC risk in male
A.Kilfoy (2013) US [49]	Cohort 1) SWHS (1996-2000) 2) Follow-up (11 yr)	73,317F (164TC)	40-70	1. Nitrite from animal sources 2. Nitrite from processed meat sources	[mg/1,000 kcal] 1. 0.1 vs. 0.2 2. 0.0 vs. 0.1	1. OR = 1.59 (1.00-2.52); p = 0.02 2. OR = 1.96 (1.28-2.99); p < 0.01	High intake of nitrite from animal sources & processed meat positively assoc with TC risk

TC/PTC/FTC: thyroid cancer, papillary/follicular thyroid cancer, Tca/Pca: thyroid/papillary carcinoma, NIH-AARP: the national institutes of health-american association of retired persons diet and health study, SWHS: the shanghai women's health study, NA: not applicable, No assoc: no association, Assoc: association, M: male, F: female.

Micronutrients

Several micronutrients deficiency interacting with nutritional iodine may affect thyroid function in low income countries, and even occur in well-nourished elderly population [43,44]. Both chronic iodine deficiency and iodine excess may increase thyroid cancer risk [7]. Table 3 describes the association between the consumption of micronutrients and thyroid cancer risk. The multiethnic population of the San Francisco Bay Area with a high intake of iodine, mostly derived from salty foods including rice, pasta, and pizza, had an inverse association between iodine intake and papillary thyroid cancer risk [11]. In French Polynesia, insufficient dietary iodine intake (< 150 μg/day) was found in 60% of both cases and controls [10]; a higher iodine intake was inversely associated with the risk of thyroid cancer, and subjects with severe or moderate iodine intake (< 75 μg/day) had a 2.6-fold risk compared with those with optimal iodine levels (150-299 μg/day) [10]. In New Caledonia, the mean daily iodine intake in Melanesian women in the Northern Province (90.4 μg) and in the Loyalty islands (80.7 μg) was lower than those in the Southern province (102.9 μg) and European women (111.3 μg) [9]; however, no significant association was found in either Melanesian or European women with a high dietary iodine intake. The limitations of the studies from French Polynesia and New Caledonia noted that the food composition table did not include some of the local seafood (e.g., giant clam and coconut crab), which are consumed more frequently in those regions than in Metropolitan France [9,10].

In Italy, other micronutrients, such as the high intake of retinol showed a positive association with both thyroid and papillary carcinoma risk, whereas beta-carotene was inversely associated with that risk [45]. Particularly, beta-carotene is a potential antioxidant that protects protein and lipid membranes, thereby, it reduces cancer risk [19]. In the U.S., subjects taking a multivitamin at least weekly for more than 10 years showed a positive association with both thyroid and papillary cancer when compared to individuals who never took a regular multivitamin [14]. Because the male population was not included in this study, the generalization of results could be limited for all thyroid cancer risk. Another large U.S. cohort study showed no significant association between thyroid cancer risk and dietary, supplemental or total calcium intake [27].

Dietary nitrate and nitrite are considered as carcinogens in both animal and epidemiological studies [46]. There were 3 large U.S. cohort studies that found an increased thyroid cancer risk with dietary nitrate or nitrite consumption. In an Iowa study, high nitrate intake from public water supplies and food sources showed a positive association with thyroid cancer in females [47]. Nitrate contamination is commonly found in drinking water in agricultural areas due to high nitrogen-based fertilizer use [48]. However, this study needs to evaluate other pesticides or perchlorate in drinking water, which can also possibly affect thyroid function [47]. In a large cohort study from the U.S., high nitrate intake from 124 food items was positively associated with thyroid and papillary cancer risk in males, but no significant association was found in females [48]. Additionally, the risk of follicular thyroid cancer showed a positive association with high intake of nitrite from plant sources in males [48]. The Shanghai Women's Health Study (SWHS) investigated the association between the exposure to dietary nitrate and nitrite in Chinese food and thyroid cancer risk. Chinese food is mainly composed of large quantity of plants including cruciferous vegetables, cabbage, and dark green leafy vegetables; nitrate, a natural component of plants, is highly concentrated in leafy vegetables such as lettuce and spinach. High nitrite intake from animal sources in Chinese food showed a positive association with thyroid cancer, with a higher risk associated with processed meat consumption; no significant association was found between thyroid cancer risk and nitrate intake from Chinese food [49]. In this study, dietary intake assessment was evaluated the year prior to baseline; therefore, a limitation of the study could be the possible changes in dietary intake of nitrate and nitrite that occurred over time [49].

Discussion

Previous studies have identified some risk factors relevant to thyroid cancer, but the results are inconsistent due to differences in dietary patterns, life-styles, nutrition, or other environmental risk factors among various ethnic groups. Some studies showed that dietary factors play a significant role in the cause of thyroid cancer, possibly influencing thyroid hormones that affect thyroid function.

Particularly, low iodine intake has been considered as a risk factor for thyroid disease and thyroid cancer. The regions where daily iodine intake is relatively insufficient with a high intake of fish showed a negative association with thyroid cancer risk. In contrast, the region where daily iodine intake is adequate with high intake of seaweed showed a positive association with risk, particularly in postmenopausal women. The goitrogenic food such as cruciferous vegetables including cabbage, broccoli, and cauliflower are considered potential risk factors for thyroid cancer, whereas these vegetables provide some benefits in other types of cancers or diseases. Fruits such as persimmons and tangerines were inversely associated with risk. Surprisingly, some studies found a protective role of alcohol intake against thyroid cancer, particularly in females, but alcohol intake is still a significant risk factor for other cancers. Some meat, such as chicken, pork, and poultry, were positively associated with thyroid cancer risk, but dairy products that contain iodine showed no significant association. Additionally, micronutrients such as multivitamins, nitrates, and nitrites showed a positive association with thyroid, papillary, or follicular cancer. Those who regularly took a multivitamin had an increased risk of both thyroid and papillary cancer compared with those who never used multivitamins, possibly due to a high intake of iodine from multivitamin products that affects thyroid hormone level. Nitrate and nitrite, known as possible carcinogens, showed a positive association with thyroid cancer risk in some animal and epidemiological studies. The populations living in agricultural areas that were exposed to nitrate-contaminated drinking water due to nitrogen-based fertilizer use had an increased thyroid cancer risk. Interestingly, the increased amount of dietary nitrite from animal sources and processed meat in Chinese food showed a positive association with risk, and other dietary factors containing nitrate and nitrite also elevated the risk.

In previous studies, some food types were not significantly associated with thyroid cancer risk. However, foods and drinks consumed for every day contain thousands of constituents, which are known for measures, but some are not [1]. Therefore, further studies need to investigate the role of those constituents in diets associated with hormonal, environmental, and genetic factors affecting thyroid cancer risk. Also, research studies investigating on thyroid cancer risk were conducted for relatively a short time-period compared with other cancer types. Therefore, this review was limited to include studies showing a direct association between thyroid cancer risk and dietary factors.

http://dx.doi.org/10.7762/cnr.2014.3.2.75

Conclusion

Iodine-rich food may provide a protective role against thyroid cancer, but excessive levels of dietary iodine may also negatively affect thyroid function due to the changes in thyroid hormone levels. The results are still controversial because different ethnic groups have various dietary patterns and lifestyles and are exposed to different environmental factors. Further studies need to investigate the changes in thyroid hormone level caused by dietary factors that affect thyroid function.

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http://dx.doi.org/10.7762/cnr.2014.3.2.75