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, lifestyle, 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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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 epide-miological 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
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 micro-nutrients (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

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**Figure 1.** Flow chart for selection of eligible studies.
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)        | Case-control          | Sweden (35M/130F, 50M/198F) | 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 |
| Sweden & Norway [16]  | Case-control          | Norway (24M/57F, 57M/135F) |           |           |                             |                            |        |
| Horn-Ross (2001)      | Case-control          | 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)           | Case-control          | 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)          | Case-control          | 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 |
| Kuwait [13]           | Case-control          |               |           |           |                             |                            |        |
| Truong (2010)         | Case-control          | 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) |
| France (New Caledonia) | Case-control          |               |           |           |                             |                            |        |
| Xhaard (2014)         | Case-control          | 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 |
| France (French Polynesia) [12] |               |               |           |           |                             |                            |        |
| Cléro (2012)          | Case-control          | 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)         | Cohort                | 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 |
| US [15]               |                       |               |           |           |                             |                            |        |
## 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 |
| 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 1. Raw vegetables 2. Tangerine 3. Persimmons 20-70 Benign 115F/115F 2. Benign 1. Raw vegetables 2. Total vegetables 3. Persimmons | g/d | 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 | High intake of raw vegetables & persimmons inversely assoc with TC malignant and benign risk |
| Galanti (1997) Sweden & Norway [16] | Case-control (Population-based) | Sweden (35M/130F,50M/198F) All Meat - sausages/sausage dishes - pork/beef/lamb - wild (reindeer/elk) - chicken/poultry - liver/kidney - blood pudding/blood bread - smoked meat 18-75 Norway (24M/57F,57M/135F) | [portions/mo.] ≤ 12 vs. > 20 | OR = 0.8 (0.5-1.3); p < 0.01 | 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 |
| Galanti (1997) Sweden & Norway [16] | Case-control (Population-based) | Sweden (35M/130F,50M/198F) All Meat - sausages/sausage dishes - pork/beef/lamb - wild (reindeer/elk) - chicken/poultry - liver/kidney - blood pudding/blood bread - smoked meat 18-75 Norway (24M/57F,57M/135F) | [portions/mo.] | 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 |
Diet and Thyroid Cancer Risk

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]. The study from Kuwait and poultry found a positive association with thyroid cancer risk [13]. Additionally, the studies from Greece and the US found a positive association with high intake of meat and thyroid cancer risk including 3 case-control studies and 1 cohort study [15-16,20]. The study from Kuwait found a positive association with 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 thyroid cancer risk [16]. However, the studies from the US and New Caledonia found no significant association [27].

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] | 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. 1.14 (male) 2.1.6 (female) | RR = 0.78 (0.45-1.37); p = 0.41 | No assoc |

TCP/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.
### 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/y]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 |
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 risk [38]. Regarding the frequency of alcohol intake, frequent weekly alcohol consumption was inversely associated with thyroid cancer risk without adjustment for smoking (p-trend = 0.02) [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 [38,42]. 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.

| 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 (≥ 75 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 |
| Kabat (2012) US [34] | Cohort 1) WHI (1993-1998) 2) Follow-up (12.7 yr) | 159,340F [33TC, 276PTC] | 50-79 | [drink/wk] 1. none vs. ≥ 7 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: 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.
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)      | 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)         | 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)          | 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)       | Case-control (Hospital-based) | 399/617 (108M/291F; 190M/427F) | 16-74     | 1. Retinol [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 | High intake of retinol positively assoc with TCa/PCa risk |
|                       |                       |               |           |               |                            |                             |        |
| Mack (2002)           | Case-control (Population-based) | 292F/292F     | 15-54     | 1. TC [frequency] never vs. > 10 yrs 1. TC 2. PTC | RR = 1.6 (0.8-3.4); p = 0.07 | High intake of multivitamin positively assoc with TC/PTC risk |
| Park (2009)           | Cohort 1) NIH-AARP (1995-2003)/2) Follow-up (7 yr) | 36,965M (170TC)/16,605F (199TC) | 50-71     | 1. Dietary 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 | No assoc |
|                       |                       |               |           |               |                            |                             |        |
Micronutrients interaction with nutritional iodine may affect thyroid function, and several micronutrient deficiencies interacting with low iodine intake have been linked to increased thyroid cancer risk [7]. Table 3 describes the association between consumption of micronutrients and thyroid cancer risk.

### 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 |
|-----------------------|----------------------|---------------|-----------|---------------|-----------------------------|-----------------------------|--------|
| Ward (2010) US [47]   | Cohort               | 21,977F       | 55-69     | 1. Nitrate from public drinking water supplies 2. Dietary nitrate | [mg/L] 1. 0 vs. ≥ 5 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               | 490,194 (170M/200F;370TC) | 50-71     | Food sources 1. Nitrate from animal sources 2. Nitrate from processed meat 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. FTC-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 |
| A.Kilfoy (2013) US [49] | Cohort               | 73,317F (164TC) | 40-70     | 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 (1.28-2.98); 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.
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 nitrate intake from animal sources in Chinese food showed a positive association 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 nitrate from plant sources in males [48]. The 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 nitrate intake from animal sources in Chinese food showed a positive association 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 nitrate from plant sources in males [48]. The 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 nitrate intake from animal sources in Chinese food showed a positive association 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 nitrate from plant sources in males [48]. The 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 nitrate intake from animal sources in Chinese food showed a positive association 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 nitrate from plant sources in males [48].

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.
Diet and Thyroid Cancer Risk

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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