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Association between nutrient intake and thyroid cancer risk in Korean women

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BACKGROUND/OBJECTIVES: The incidence of thyroid cancer has increased in many countries, including Korea. International differences in the incidence of thyroid cancer may indicate a role of diet, but findings from previous studies are inconclusive. Therefore, we aimed to investigate the roles of nutrients in thyroid cancer risk in Korean women.

SUBJECTS/METHODS: We conducted a case-control study comprising 113 cases and 226 age-matched controls. Nutrient intake was assessed using a validated food frequency questionnaire, and the association between nutrient intake and thyroid cancer risk was estimated using a logistic regression model.

RESULTS: We found that high calcium intake was associated with a reduced risk of thyroid cancer (OR [95% CI] = 0.55 [0.35-0.89]). Significant associations were observed among subjects who were older than 50 years, had low BMI, and had low calorie intake. However, other nutrients included in this study did not show any significant associations with thyroid cancer risk.

CONCLUSION: This study suggested a possible protective effect of calcium on thyroid cancer risk. Well-designed prospective studies are required to confirm these findings.

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INTRODUCTION

The incidence of thyroid cancer is increasing worldwide, and thyroid cancer represents the most common type of endocrine tumor [1]. The incidence of thyroid cancer in Korea has increased rapidly in women and has become one of the highest in the world [2]. The increased incidence rate of thyroid cancer may be partially attributed to the increased detection of subclinical cancer due to advanced diagnostic technologies and frequent medical examinations [3]. Although the risk of thyroid cancer has increased, relatively little is known about the etiology of this disease. Established risk factors include ionizing radiation and a history of benign proliferative thyroid diseases, including goiter and thyroid nodules. However, international differences in the incidence of thyroid cancer suggest that lifestyle or environmental factors (including diet) may play a role in thyroid carcinogenesis [4].

Several epidemiologic studies have indicated that dietary habits may play a relevant role in the development of thyroid cancer. Iodine is the most commonly investigated factor because of its role in the formation of thyroid hormones in the thyroid gland and in benign thyroid disorders [5-7]. Some dietary factors may be related to thyroid cancer risk, including the consumption of fish [4,8,9], fruits and vegetables, particularly cruciferous vegetables [10-12]. It is assumed that specific nutrients and components in these foods (e.g., iodine, vitamin C, vitamin E, and β-carotene) may contribute to thyroid carcinogenesis. A few studies have investigated the roles of specific nutrients, but the findings from these studies are still inconclusive [13,14].

The present study investigated the roles of nutrients in thyroid cancer risk in Korean women. We also examined whether these associations differed with respect to other possible risk factors of thyroid cancer.

SUBJECTS AND METHODS

Study population

We conducted a case-control study on participants in the Cancer Screening Program at the National Cancer Center in South Korea [15] between October 2007 and July 2014. Participants were aged 30 years or older and underwent screening examinations for overall health and for selected cancers. All of the participants were asked to complete a self-administered questionnaire during the baseline evaluation. The data collected in the baseline evaluation included

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socio-demographic characteristics, personal and family medical history, lifestyle factors, and reproductive factors. Among 13,646 participants, 9,146 provided FFQ and were used as potential cases and controls.

Potential cases of thyroid cancer (ICD10 code C73) were ascertained by linkage to the Korea Central Cancer Registry (KCCR) database, which was used to determine the incidence of cancer in Korea. One hundred thirteen women thyroid cancer patients were identified as thyroid cancer after a baseline examination. Controls were selected from participants who were free from all cancers. Two controls for each case were matched by age. A total of 113 thyroid cancer cases and 226 controls were used for the final analysis. The study protocol was approved by the Institutional Review Board of the National Cancer Center (NCCNCS13698), and written informed consent was obtained from each participant.

Data collection and dietary assessment

All of the participants were asked to complete a self-administered questionnaire, which included socio-demographic characteristics, personal and family medical history, and lifestyle and reproductive factors. Participants were also asked about their average frequency of intake and portion size of specific foods eaten during the previous year using the validated food frequency questionnaire (FFQ), which covers 106 food items [16]. The detailed procedure used to design the FFQ is described by Ahn *et al*. [17] and the validity and reproducibility of the FFQ used in the current study have been tested using the three-day dietary record as a gold standard [16]. Nine frequency categories (i.e., never or rarely, once a month, two or three times a month, once or twice a week, three or four times a week, five or six times a week, once a day, twice a day, and three times a day) and three portion sizes (i.e., small, medium, and large) were included in the FFQ.

Nutrient intake (e.g., macronutrients, vitamins, and minerals) was computed by multiplying the frequency of consumption of each unit of food with the nutrient content of the specified portions. Dietary protein, fat, calcium, and iron intake were each calculated separately by their sources (animal vs. plant).

Statistical analysis

All statistical analyses were performed using the SAS 9.3 software (SAS Institute Inc., Cary, NC). A two-sided *P*-value less than 0.05 was considered statistically significant.

The chi-square (χ^2) test (for categorical variables) and t-test (for continuous variables) were used to compare general characteristics between cases and controls. Energy-adjusted nutrient intakes were computed as the residuals from the regression model, with total caloric intake as the independent variable and absolute nutrient intake as the dependent variable [18]. We categorized participants into two groups (high/low) based on median nutrient intake levels in the control groups. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using a logistic regression model. Multivariate models were adjusted for body mass index (BMI; calculated as weight in kilograms divided by the square of the height in meters; < 23, 23-25, and ≥ 25) and smoking status (nonsmoker, former smoker, and current smoker) based on a literature search [19, 20]. Protein, fat, calcium, and iron intake were analyzed according to their sources (animal or plant). We also conducted subgroup analyses of the association between dietary calcium intake and thyroid cancer risk by age, BMI, and the level of total caloric intake.

RESULTS

The general characteristics of the study participants are shown in Table 1. The mean age of the study participants was 53.7 years, and only women were included. No differences in age, BMI, education level, income, marital status, smoking

Table 1. General characteristics of the study subjects[1)]

	Cases (n = 113)	Controls (n = 226)	*P*-value
Age (yrs), Mean ± SD	53.7 ± 8.2	53.7 ± 8.2	> 0.999
BMI (kg/m^2)			
< 23	60 (54.1)	113 (51.1)	0.805
23-< 25	26 (23.4)	59 (26.7)	
≥ 25	25 (22.5)	49 (22.2)	
Educational level			
Elementary school or less	11 (10.1)	18 (8.4)	0.736
Middle school	10 (9.2)	14 (6.5)	
High school	55 (50.5)	119 (55.6)	
College or more	33 (30.3)	63 (29.4)	
Monthly household income[2)]			
< 200	30 (31.9)	47 (25.3)	0.408
200-< 400	34 (36.2)	67 (36.0)	
≥ 400	30 (31.9)	72 (38.7)	
Marital status			
Married	93 (83.0)	183 (35.6)	0.834
Unmarried	5 (4.5)	7 (3.2)	
Divorced / Widowed	14 (12.5)	29 (13.2)	
Smoking status			
Nonsmoker	107 (94.7)	208 (92.9)	0.205
Former smoker	6 (5.3)	10 (4.5)	
Current smoker	0 (0.0)	6 (2.7)	
Alcohol consumption			
Nondrinker	77 (68.1)	144 (63.7)	0.028
Former drinker	11 (9.7)	9 (4.0)	
Current drinker	25 (22.1)	73 (32.3)	
Age at menarche (yrs)			
≤ 13	27 (25.2)	51 (24.3)	0.318
14	28 (26.2)	44 (21.0)	
15	30 (28.0)	52 (24.8)	
≥ 16	22 (20.6)	63 (30.0)	
Menopause (yes)	74 (65.5)	142 (62.8)	0.632
Age at menopause (yrs)			
< 46	15 (20.6)	24 (17.1)	0.753
46-< 49	10 (13.7)	24 (17.1)	
49-< 52	24 (32.9)	40 (28.6)	
≥ 52	24 (32.9)	52 (37.1)	

1) Data were analyzed using chi-square test (for categorical variables) and t-test (for continuous variables).
Data are presented as n (%) unless otherwise indicated.
2) Unit is 10,000 Korean won.

Table 2. Comparison of nutrient intake among study participants[1)]

	Cases (n = 113)	Controls (n = 226)	*P*-value
Energy (kcal)	1,654.1 ± 514.8	1,678.4 ± 574.3	0.886
Protein (g)	59.3 ± 10.6	59.6 ± 10.4	0.728
Fat (g)	29.0 ± 9.1	30.2 ± 10.6	0.483
Carbohydrate (g)	292.2 ± 26.8	289.9 ± 28.9	0.453
Fiber (g)	20.4 ± 6.4	19.8 ± 6.8	0.278
Calcium (mg)	507.8 ± 202.5	518.6 ± 193.4	0.521
Phosphorus (mg)	917.8 ± 181.0	918.7 ± 168.9	0.895
Iron (mg)	11.9 ± 3.7	11.7 ± 3.9	0.556
Zinc (mg)	7.6 ± 1.3	7.7 ± 2.0	0.808
Vitamin A (μg RE)	557.4 ± 316.6	524.2 ± 296.2	0.381
Retinol (μg)	82.3 ± 47.5	85.8 ± 52.4	0.671
β-carotene (μg)	2,856.3 ± 1,890.5	2,643.9 ± 1,710.8	0.359
Vitamin B_1 (mg)	1.0 ± 0.2	1.0 ± 0.2	0.742
Vitamin B_2 (mg)	0.9 ± 0.3	1.0 ± 0.3	0.489
Vitamin B_6 (mg)	1.8 ± 0.5	1.8 ± 0.6	0.982
Niacin (mg)	14.8 ± 3.2	14.7 ± 3.4	0.692
Vitamin C (mg)	136.2 ± 68.7	132.5 ± 71.6	0.574
Folate (μg)	253.2 ± 100.0	249.0 ± 102.9	0.626
Vitamin E (mg)	9.1 ± 2.7	9.3 ± 3.1	0.755
Cholesterol (mg)	186.7 ± 106.9	185.8 ± 95.2	0.586

[1)] Data were analyzed using t-test and are presented as mean ± SD.

Table 3. Association between the level of calcium intake and thyroid cancer risk[1)]

	Median	No. of controls/cases		OR (95% CI) High vs. Low	*P*-value
		Low	High		
Energy (kcal)	1,569.5	113/56	113/57	1.03 (0.65-1.62)	0.914
Protein (g)	58.2	113/58	113/55	0.94 (0.59-1.48)	0.778
Fat (g)	29.1	113/58	113/55	0.95 (0.60-1.51)	0.834
Carbohydrate (g)	290.3	113/51	113/62	1.22 (0.77-1.94)	0.388
Fiber (g)	18.8	113/52	113/61	1.18 (0.75-1.87)	0.470
Calcium (mg)	502.3	113/72	113/41	0.55 (0.35-0.89)	0.014
Phosphorus (mg)	895.7	113/61	113/52	0.83 (0.53-1.32)	0.437
Iron (mg)	11.2	113/56	113/57	1.00 (0.63-1.57)	0.989
Zinc (mg)	7.4	113/58	113/55	0.95 (0.61-1.50)	0.833
Vitamin A (μg RE)	451.4	113/49	113/64	1.32 (0.83-2.09)	0.238
Retinol (μg)	74.3	113/58	113/55	0.95 (0.60-1.52)	0.840
β-carotene (μg)	2,185.8	113/51	113/62	1.22 (0.77-1.93)	0.389
Vitamin B_1 (mg)	0.97	113/61	113/52	0.83 (0.53-1.32)	0.432
Vitamin B_2 (mg)	0.93	113/56	113/57	1.03 (0.65-1.63)	0.903
Vitamin B_6 (mg)	1.69	113/59	113/54	0.92 (0.58-1.45)	0.716
Niacin (mg)	14.1	113/54	113/59	1.09 (0.69-1.72)	0.716
Vitamin C (mg)	123.2	113/52	113/61	1.17 (0.74-1.85)	0.491
Folate (μg)	233.2	113/55	113/58	1.07 (0.68-1.68)	0.784
Vitamin E (mg)	8.7	113/55	113/58	1.06 (0.67-1.67)	0.814
Cholesterol (mg)	174.9	113/62	113/51	0.82 (0.52-1.31)	0.409

[1)] Data were categorized into two groups (high/low) based on median nutrient intake levels in the control group and were analyzed using a logistic regression model.

status, or reproductive factors were observed between the cases and the controls. Cases were less likely to drink alcohol than controls.

Table 2 shows the nutrient intakes of the subjects. The estimated mean intake of energy in this study was 1,670 kcal/day. We also compared the intake of macronutrients (protein, fat, and carbohydrates), vitamins (vitamin A, retinol, β-carotene, vitamin B_1, vitamin B_2, vitamin B_6, niacin, and vitamin C) and minerals (calcium, phosphorus, iron, zinc) between cases and controls. However, we did not find any differences between cases and controls with respect to these dietary factors.

Table 3 shows the ORs and 95% CIs of thyroid cancer risk for selected nutrients in women. We found that a high

Table 4. Participant characteristics by calcium intake[1)]

	Low calcium[2)] (n = 185)	High calcium (n = 154)	*P*-value
Age (yrs), Mean ± SD	52.7 ± 8.4	55.0 ± 7.7	0.011
BMI (kg/m^2)			
< 23	83 (45.9)	90 (59.6)	0.044
23-< 25	53 (29.3)	32 (21.2)	
≥ 25	45 (24.9)	29 (19.2)	
Educational level			
Elementary school or less	19 (11.0)	10 (6.7)	0.205
Middle school	16 (9.3)	8 (5.3)	
High school	92 (53.2)	82 (54.7)	
College or more	46 (26.6)	50 (33.3)	
Monthly household income[3)]			
< 200	43 (28.9)	34 (26.0)	0.810
200-< 400	54 (36.2)	47 (35.9)	
≥ 400	52 (34.9)	50 (38.2)	
Marital status			
Married	156 (86.7)	120 (79.5)	0.042
Unmarried	8 (4.4)	4 (2.7)	
Divorced / Widowed	16 (8.9)	27 (17.9)	
Smoking status			
Nonsmoker	167 (91.3)	148 (96.1)	0.085
Former smoker	13 (7.1)	3 (2.0)	
Current smoker	3 (1.6)	3 (2.0)	
Alcohol consumption			
Nondrinker	116 (62.7)	105 (68.2)	0.567
Former drinker	12 (6.5)	8 (5.2)	
Current drinker	57 (30.8)	41 (26.6)	
Age at menarche (yrs)			
≤ 13	39 (22.9)	39 (26.5)	0.064
14	47 (27.7)	25 (17.0)	
15	46 (27.1)	36 (24.5)	
≥ 16	38 (22.4)	47 (32.0)	
Menopause (yes)	111 (60.0)	105 (68.2)	0.119
Age at menopause (yrs)			
< 46	19 (17.3)	20 (19.4)	0.809
46-< 49	18 (16.4)	16 (15.5)	
49-< 52	36 (32.7)	28 (27.2)	
≥ 52	37 (33.6)	39 (37.9)	

[1)] Data were analyzed using chi-square test (for categorical variables) and t-test (for continuous variables).
Data are presented as n (%) unless otherwise indicated.
[2)] Data were categorized into two groups (high/low) based on median nutrient intake levels in the control group.
[3)] Unit is 10,000 Korean won.

Table 5. Association between calcium intake and thyroid cancer risk

		No. of controls/cases		OR (95% CI)
		Low[1)]	High	High vs. Low
Total calcium				
Age	< 50	40/23	30/12	0.70 (0.30-1.62)
	≥ 50	73/49	83/29	0.52 (0.30-0.91)
BMI (kg/m^2)	< 23	45/38	68/22	0.38 (0.20-0.73)
	≥ 23	66/32	42/19	0.93 (0.47-1.86)
Calorie intake	Low	52/37	61/19	0.44 (0.23-0.85)
	High	61/35	52/22	0.74 (0.39-1.41)
Plant calcium				
Age	< 50	38/19	32/16	1.00 (0.44-2.26)
	≥ 50	75/43	81/35	0.75 (0.44-1.30)
BMI (kg/m^2)	< 23	54/36	59/24	0.61 (0.32-1.51)
	≥ 23	54/24	54/27	1.13 (0.58-2.19)
Calorie intake	Low	49/33	64/23	0.53 (0.28-1.02)
	High	64/29	49/28	1.26 (0.67-2.39)
Animal calcium				
Age	< 50	38/19	32/16	1.00 (0.44-2.26)
	≥ 50	75/37	81/41	1.03 (0.60-1.77)
BMI (kg/m^2)	< 23	46/29	67/31	0.73 (0.39-1.38)
	≥ 23	65/26	43/25	1.45 (0.74-2.84)
Calorie intake	Low	49/28	64/28	0.77 (0.40-1.46)
	High	64/28	49/29	1.35 (0.71-2.56)

1) Data were categorized into two groups (high/low) based on median nutrient intake levels in the control group.

consumption of calcium was associated with a reduced risk of thyroid cancer (OR [95% CI] = 0.55 [0.35-0.89]; $P = 0.014$). We did not observe any significant associations between thyroid cancer risk and the other nutrients.

We therefore categorized the participants into two groups according to their levels of calcium intake and examined whether the general characteristics of the participants differed by calcium intake levels. The general characteristics of the participants were not significantly different in the high calcium and low calcium intake groups (Table 4).

To examine the effects of other risk factors on the association between calcium intake and thyroid cancer risk, we conducted subgroup analyses by age, BMI, smoking status, and the level of total caloric intake (Table 5). Significant associations were observed in subjects who were older than 50 (OR [95% CI] = 0.52 [0.30-0.91]), had low BMI (OR [95% CI] = 0.38 [0.20-0.73]), and had low calorie intake (OR [95% CI] = 0.44 [0.23-0.85]). However, these significant associations were not observed in a subgroup analysis differentiating the source of calcium (plant vs. animal). Multivariate logistic regressions adjusted by BMI and smoking status showed similar associations. Therefore, we only report the results from crude analyses.

DISCUSSION

This case-control study found that total calcium intake was inversely associated with the incidence of thyroid cancer. This association differed by age, BMI, and total calorie intake. However, other nutrients included in this study were not associated with the incidence of thyroid cancer.

Several epidemiological studies have investigated the role of specific nutrients, including calcium, with respect to cancer risk. One case-control study in the United States investigated the association between thyroid cancer and calcium, zinc, magnesium, and iron supplements but reported no significant associations [21]. Two cohort studies in the United States assessed the risk of thyroid cancer by levels of calcium and other nutrients, but these studies found no significant differences in risk [14,22]. However, the chemo-preventive effect of calcium on other types of cancer was reported in previous experimental and epidemiological studies. Evidence from animal studies suggested that a high calcium intake reduces colonic carcinogenesis [23]. Calcium supplements also reduce colonic epithelial cell proliferation in humans [24]. In a randomized clinical trial, Lappe *et al.* [25] found that improving calcium nutritional status substantially decreased the risk of cancer in postmenopausal women. A pooled analysis of 10 cohort studies [26] also reported that calcium intake is associated with a 15% to 20% reduced risk of colorectal cancer. A significant inverse association of calcium intake was also observed with breast cancer risk [27]. The present study did not identify associations between thyroid cancer risk and other nutrients, including antioxidants. Previous studies reported a potential inverse association of β-carotene, vitamins C and E, and selenium with thyroid cancer risk [28,29]. The role of these nutrients in cancer prevention stems from their antioxidant properties. The role of antioxidants in thyroid carcinogenesis requires further investigation.

The mechanism by which calcium affects thyroid carcinogenesis is not clear. Calcium is an important micronutrient that controls numerous intracellular and extracellular processes [30]. Calcium reduces proliferation, stimulates differentiation, and induces apoptosis [31,32], which may play a role in carcinogenesis [33, 34]. Evidence suggests that calcium has direct effects in both normal and tumor cells [31], and may improve signaling within cells, thereby causing cancer cells to differentiate or die [31,35]. An experimental study demonstrated that elevated calcium concentrations decrease cell proliferation and induce the differentiation of mammary cells [36]. However, the role of calcium in carcinogenesis may differ by cancer site [22]. In the gastrointestinal tract, calcium binds to bile and fatty acids to form insoluble complexes, which may reduce the proliferative stimuli of these compounds [31]. Calcium is hypothesized to reduce fat-induced cell proliferation in breast cancer by maintaining intracellular calcium concentrations [32]. However, the exact mechanisms by which calcium helps reduce the risk of thyroid cancer are unclear due to a lack of evidence, and these mechanisms should be investigated further.

Several factors may affect the role of calcium in thyroid carcinogenesis. We conducted subgroup analyses of known risk factors of thyroid cancer, such as age, sex, BMI, and high caloric intake [37]. The incidence of thyroid cancer is higher in women than in men, and smoking is inversely associated with thyroid cancer risk [20]. Previous studies indicated that obesity was weakly associated with an elevated risk of thyroid cancer [37], and data from the Korea National Health and Nutrition Examination Survey reported that a higher calcium intake was associated with a decreased prevalence of obesity in Koreans [38]. We found a significant inverse association only in subjects with lower BMIs. Other nutrients, such as vitamin D, may also affect the role of calcium in carcinogenesis [26]. The mean age of the study population was 53.7 years, and the study participants consumed more calcium from non-dairy sources than from dairy products, which is in contrast to Western populations. The population characteristics in this study may also affect the associations found. Calcium intake in Korean populations is lower than in Western populations [38]. An understanding of how these factors modify the association between calcium and thyroid cancer risk may help elucidate the etiology of thyroid cancer.

However, the findings from this study should be interpreted with caution because of several limitations. First, this was a case-control study and had its own limitations (e.g., recall bias, selection bias). Recall of diet may be influenced by disease status. Second, the sample size of the study was relatively small, and some significant associations may have been missed. In addition, due to the large number of nutrients included in this analysis, the association between calcium and thyroid cancer risk could be a chance finding. Third, the data from the FFQ may limit our estimations of nutritional effects on thyroid cancer risk because self-reporting is subject to measurement error. The FFQ surveyed information from the previous year, but dietary intake varies from day to day and over the course of a lifetime. Further errors may also have been introduced by the conversion of food data into nutrient data using tables detailing the chemical compositions of foods. Finally, we did not examine whether associations with calcium intake differed by tumor subtype or tumor aggressiveness. Therefore, we may have missed some associations that exist only for certain tumor subtypes or for more or less aggressive tumors.

In conclusion, this study suggested a possible protective effect of calcium on thyroid cancer risk in Korean women. However, further large prospective studies are required to confirm this finding.

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