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미국갑상선학회 risk stratification system 따른 갑상선 유두암 재발 위험도와 식이섭취와의 관련성

Association Between Diet and Risk of Recurrence of Papillary Thyroid Cancer According to the Risk Stratification System of the American Thyroid Association

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국문요약

본 연구는 갑상선암종 중 재발위험이 가장 높은 갑상선 유두암 환자를 대상으로 하였으며, 식이요인이 갑상선암의 재발 위험과 관련성이 있을 것이라는 가설을 검증하고자 수행되었다. 갑상선암 환자들은 미국갑상선학회 진료권고안인 갑상선암 재발 위험도 (American Thyroid Association risk stratification) 기준에 의해 재발 중간위험군(intermediated risk group, n=228)과 재발 저위험군 (low risk goup, n=136)으로 분류하였다. 식이와 영양소 섭취를 비교한 결과 중간 위험군의 곡류, 육류, 유제품, 열량, 지질, 동물성 지질, 단백질, 동물성 단백질의 섭취량이 저 위험군 보다 유의하게 많았다. 다변량 분석에서는 혼란인자 연령, 성별, 열량, 음주, 허리둘레 보정한 후에도 동물성 지질, 육류, 유제품의 섭취가 갑상선암의 재발 위험도를 유의하게 상승시키는 것으로 나타났다. 특히 육류 섭취가 증가할수록 1cm 이상의 원발종양 크기와, 림프절 전이의 위험도는 유의하게 상승하는 것으로 나타났다. 또한, 비만한 환자에서는 육류 섭취와 원발종양 병기 (T3 or T4)와 양의 상관성을 나타내었다.

Key words : diet, obesity, recurrence of papillary thyroid cancer
주제어 : 식이, 비만, 갑상선암 유두암 재발

Ⅰ. INTRODUCTION

Thyroid cancer is the most common endocrine malignancy, and its incidence is increasing in worldwide (Ito et al. 2013). Most thyroid malignancies are papillary thyroid cancer (PTC), accounting for approximately 85% of cases (Sipos & Mazzaferri, 2010). Local lymphatic recurrence in PTC is associated with poor prognosis, morbidity, and mortality (Lee et al. 2007). A meta-analysis of studies suggested that risk factors of recurrence of PTC included being male, extrathyroid extension, lymph node metastasis, tumor size greater than 2 cm, distant metastasis, and subtotal thyroidectomy (Guo & Wang, 2014).

Diet has been also suggested as a modifiable risk factor of recurrence of breast cancer (Chlebowski et al. 2006), but there has been no study of the association of diet and risk of recurrence of thyroid cancer in humans. Studies suggest that the initial occurrence of thyroid cancer is associated with starchy foods, meat and dairy products (Franceschi et al. 1991). In addition, body mass index (BMI) has been associated with tumor size, lymph node metastasis, extrathyroidal invasion, and advanced stage of tumor-node-metastasis (TNM) in patients with PTC (Kim et al. 2013).

The TNM system is recognized as an accurate staging system for the prediction of life expectancy in thyroid cancer (Tanase et al. 2015). The American Thyroid Association (ATA) risk stratification system for assessment of risk of recurrence after initial treatment is also a good predictor of recurrent/persistent disease in thyroid cancer (Tuttle et al. 2010). The purpose of the present study was to investigate the hypothesis that diet is associated with risk of recurrence of PTC based on the ATA risk stratification system.

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Ⅱ. METHODS

1. Patients

Patients undergoing thyroid surgery were recruited consecutively at the cancer clinic of Hanyang University Seoul Hospital from March 2011 to June 2015. Patients (n=364) with confirmed PTC were included for analysis. The study protocol was conducted according to the guidelines laid out in the Declaration of Helsinki and was approved by the Institutional Review Boards of Hanyang University Hospital (HYU 2010-02-001-031) and Hanyang University (HYI-15-069). Written informed consent was obtained from all patients. Patients were classified according to the AJCC/UICC TNM staging system and ATA risk stratification (Cooper et al. 2009). ATA risk stratification for assessment of recurrence risk was divided into three levels with following characteristics: low risk patients had no local or distant metastases, complete resection of all microscopic tumor, no tumor invasion of locoregional tissues or structures (N0, M0) no aggressive histology or vascular invasion, and no RAI avid metastatic foci outside the thyroid bed on the first post-treatmetn whole-body RAI scan, if131I was given. Intermediate risk patients had microscopic invasion of tumor into the perithyroidal soft tissues at initial surgery(T3), cervical lymph node metastases(N1) tumor with aggressive histology or vascular invasion and RAI avid metastatic foci in the neck on the first post-treatment whole-body RAI scan. High risk patients had macroscopic tumor invasion, incomplete tumor resection, distant metastases and post-operative serum thyroglobulin suggestive of distant metastases. On the basis of ATA risk stratification, 136 patients were classified as low risk group, 228 patients as intermediate risk group and no one as high risk group.

2. Data collection

Information on age at diagnosis, sex, height and weight for calculating BMI, tumor size, presence of thyroiditis, TNM stage, and medical history was obtained from medical records and pathology reports. Information on waist circumference, dietary supplement use, cigarette smoking, and alcohol drinking were collected through face-to-face interviews. Diet was assessed by 24 hour recall and analyzed using Can-pro 4.0 (Computer Aided Nutritional analysis program, Korean Nutrition Society, Seoul, Korea).

3. Statistical analyses

All analyses were performed using SPSS, version 21.0 (SPSS Inc., Chicago, IL, USA), and P-values < 0.05 were considered statistically significant. Continuous variables expressed as mean ± standard deviation (SD) were used to compare the low- and intermediate-risk groups using independent t tests. Proportions of nominal variables were compared using the χ^2test. Odds ratio (OR) and 95% confidence intervals (CI) were obtained using multivariable logistic regression analysis after adjusting for total energy, sex, age, waist circumference, and drinking in order to determine the associations of daily nutrients and foods intake according to risk of recurrence. Dietary and food intake were categorized into quartiles based on the low risk group. Binary logistic regression analysis was used to determine risk of aggressive clinicopathological features according to meat intake group. The following clinicopathological features were used as binary variables: tumor size, advanced tumor stage, lymph node metastasis, advanced TNM stage, and thyroiditis. Trend tests were conducted by treating the median values of each quartile of daily food intake as continuous values.

Ⅲ. RESULTS

1. Characteristics of patients with PTC according to low and intermediate risk of recurrence of PTC

The intermediate-risk group was significantly younger and had more males, obese patients, and advanced tumors as determined by tumor size, tumor stage, lymph node metastasis, and TNM stage compared to the low-risk group (Table 1).

Table1. Characteristics of patients with papillary thyroid cancer (PTC) according to low and intermediate risk of recurrence.

	LRG[1)] (n=136)	IRG (n=228)	P-value[3)]
Age (years)	50.81 ± 9.53[2)]	47.31 ± 12.73	0.003
Male, n (%)	11 (8.1)	55 (24.1)	<0.001
Body mass index (kg/m^2)	24.22 ± 3.14	24.48 ± 3.43	0.478
≥25 kg/m^2,n(%)	55 (40.4)	91 (39.9)	0.788

Waist circumference (cm)	78.94 ± .59	80.64 ± 8.34	0.033
Abdominal obesity[4]	33 (24.3)	81 (35.7)	0.029
Thyroiditis, n (%)	41 (31.2)	73 (32.1)	0.710
Tumor size (cm)[5]	0.71 ± .47	1.09 ± 0.82	<0.001
>1 cm, n (%)	27 (20.0)	102 (44.9)	<0.001
Tumor stage[6], n (%)			
T1a/T1b/T2	136 (100.0)	53 (28.0)	<0.001
T3/T4a/T4b	0 (0.0)	175 (76.8)	
Lymph node metastasis[7], n (%)			
N0/Nx	136 (100.0)	76 (33.3)	<0.001
N1a/N1b	0 (0.0)	152 (66.7)	
TNM[8] stage, n (%)			
Stages 1 & 2	136 (100.0)	84 (36.8)	<0.001
Stages 3 & 4	0 (0.0)	144 (63.2)	

[1]LRG = Low-risk group, IRG = Intermediate-risk group; [2]Values are mean ± standard deviation or number of participants (percentage distribution), as appropriate; [3]P values were determined by independent t-test for continuous variables and the χ2 test for categorical variables between the low-risk and intermediate-risk groups; [4]Cut off point for abdominal obesity was 90 cm in men 85 cm in women; [5]Largest tumor diameter; [6]T1a = primary tumor ≤1 cm, confined to the thyroid gland; T1b = primary tumor >1 and ≤2 cm, confined to the thyroid gland; T2 = primary tumor >2 cm and ≤4 cm, confined to the thyroid gland; T3 = primary tumor >4 cm, confined to the thyroid gland or any tumor with minimal extrathyroid extension; T4a = primary tumor with invasion of subcutaneous soft tissues, larynx, trachea, esophagus and recurrent laryngeal nerve; T4b = primary tumor with invasion of prevertebral fascia, mediastinal vessels and encasing of carotid artery; [7]N0 = No lymph node metastases; N1a = metastasis in level VI (pre- and paratracheal); N1b = metastasis in lymph nodes outside of level VI including mediastinal lymph nodes; [8]TNM = primary tumor (T), regional nodes (N), and metastasis (M).

2. Association between risk of recurrence of PTC and dietary intake

Intake of energy, lipids, animal lipids, protein, and animal protein was significantly higher in the intermediate- than low-risk group (Table 2). The intermediate-risk group consumed significantly more grains, meat, and dairy products than the low-risk group. Multivariable-adjusted regression analysis showed that the risk of recurrence of PTC was positively associated with intake of animal lipids, meat, and dairy products after adjusting for energy, sex, age, waist circumference, and drinking (Table 3). The risk of recurrence of PTC was significantly higher in patients in the third and fourth quartiles of animal lipid intake compared with those in the first quartile. In addition, risk of recurrence of PTC was significantly higher in patients in the fourth quartile of meat and dairy product intake compared with those in the first quartile.

Table 2. Daily intake of nutrients and foods in patients with papillary thyroid cancer (PTC) according to low and intermediate risk of recurrence.

	LRG[1](n=136)	IRG (n=228)	P-value[3]
Energy (KJ)	6175.39 ± 1403.66[2]	6711.66 ± 1950.98	0.003
Carbohydrate (g)	242.91 ± 58.26	251.80 ± 76.52	0.212
Lipid (g)	33.22 ± 17.77	39.54 ± 20.78	0.003
Vegetable lipid (g)	19.68 ± 12.22	22.14 ± 14.63	0.100
Animal lipid (g)	13.52 ± 12.41	17.40 ± 13.07	0.006
Protein (g)	59.22 ± 21.18	65.16 ± 24.33	0.019
Vegetable protein (g)	34.18 ± 13.55	34.60 ± 12.99	0.768
Animal protein (g)	25.04 ± 16.22	30.56 ± 19.30	0.004
Fiber (g)	23.11 ± 9.66	22.77 ± 10.58	0.754
Grains (g)	225.71 ± 105.46	257.95 ± 119.87	0.008
Meat (g)	54.05 ± 68.49	70.80 ± 83.27	0.048
Dairy products (g)	52.87 ± 84.69	84.00 ± 128.05	0.006

[1]LRG = Low-risk group, IRG = Intermediate-risk group; [2]Values are mean ± standard deviation; [3]P values were determined by independent t-test for continuous variables

3. Associations between meat intake and clinicopathological characteristics

Intake of meat was positively associated with aggressive clinicopathological features of PTCs such as tumor size > 1 cm and lymph node metastasis before and after adjusting for confounders (Table 4). On the other hand, meat intake was negatively associated with presence of thyroiditis before and after adjusting for confounders. Other clinicopathological characteristics such as advanced tumor and TNM stage were

Table 3. Association between risk of recurrence of papillary thyroid cancer and daily dietary intake by multivariable logistic regression analysis.

	Quartile of dietary intake				*P* for trend[1]
	Q1	Q2	Q3	Q4	
Animal lipid					
No. of IRG/LRG[2]	30/34	38/34	73/34	87/34	
Cut off (g)	≤4.97	4.97 < to ≤10.20	10.20 < to ≤18.03	> 18.03	0.025
OR[3] (95% CI)	1	1.204 (0.60-2.43)	2.041 (1.04-4.03)*	2.193 (1.04-4.62)*	
Meat					
No. of IRG/LRG	55/49	40/23	60/31	73/33	
Cut off (g)	≤0.00	0.00 < to ≤30.00	30.00 < to ≤80.00	> 80.00	0.056
OR (95% CI)	1	1.440 (0.75-2.77)	1.675 (0.92-3.04)	1.866 (1.05-3.31)*	
Dairy products					
No. of IRG/LRG	103/70	48/29	16/16	61/21	

Cut off (g)	≤0.00	0.00 < to ≤ 90.00	90.00 < to ≤180.00	> 180.00	0.048
OR (95% CI)	1	1.108 (0.62 – 1.99)	0.668 (0.30 –1.48)	2.027 (1.11 – 3.71)*	

*P <0.05, **P<0.01 compared to the first quartile by logistic regression analysis
1)Estimates of P values for a linear trend were based on linear scores derived from the medians of quartiles for intake of nutrients and foods in the low-risk group; 2)LRG = Low-risk group, IRG = Intermediate-risk group; 3)OR was adjusted for total energy, sex, age, waist circumference, and drinking

Table 4. The risk of aggressive clinicopathological features in patients with papillary thyroid cancer (PTC) according to quartile of meat intake by logistic regression analysis.

	Quartile of daily meat intake (g)				*P* for trend1)
	≤0.00 (n=104)	0.00<to≤40.00 (n=81)	40.00<to≤91.88 (n=88)	>91.88 (n=91)	
Tumor size > 1 cm2)					
Adjusted OR (95% CI)3)	1	0.906 (0.47–.1.73)	0.894 (0.47–1.69)	2.083 (1.10–3.96)*	0.010
Advanced tumor stage					
Adjusted OR (95% CI)	1	0.990 (0.54–1.81)	0.936 (0.52–1.70)	1.337 (0.72–2.49)	0.280
Lymph node metastasis					
Adjusted OR (95% CI)	1	1.291 (0.68–2.45)	2.029 (1.10–3.75)*	1.954 (1.04–3.68)*	0.044
Advanced TNM stage4)					
Adjusted OR (95% CI)	1	1.085 (0.56–2.10)	1.443 (0.76–2.76)	1.072 (0.54–2.14)	0.819
Thyroiditis5)					
Adjusted OR (95% CI)	1	0.546 (0.28–1.08)	1.807 (0.97–3.37)	0.318 (0.15–0.68)**	0.030

** P <0.01 *P <0.05 compared to the first quartile by logistic regression analysis
1)Estimates of P values for a linear trend were based on linear scores derived from the medians of quartiles for intake of meat; 2)N=359 for tumor size; 3)OR was adjusted for total energy, sex, age, drinking, and waist circumference; 4)TNM = primary tumor (T), regional nodes (N), and metastasis (M); 5)Presence of lymphocytic thyroiditis or Hashimoto's thyroiditis not associated with meat intake.

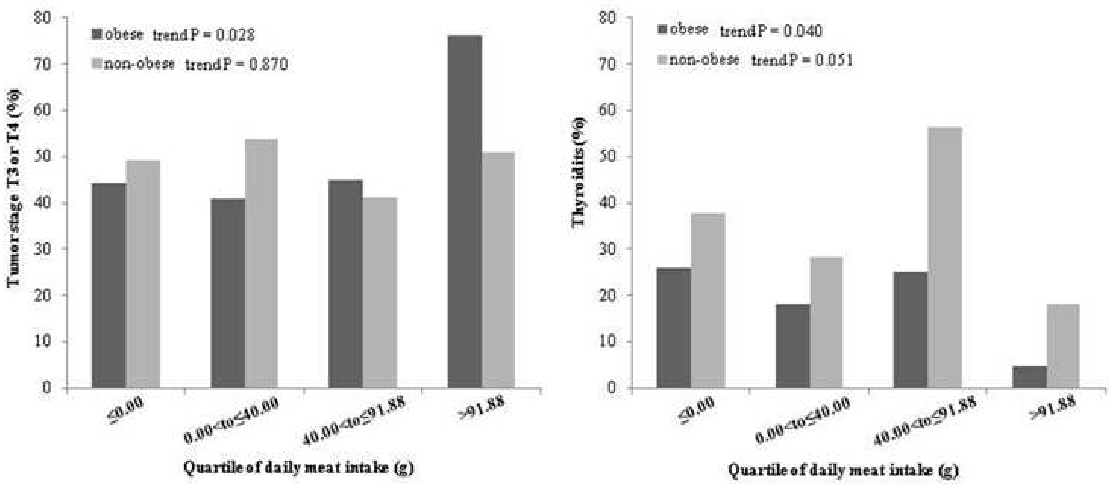

Figure 1. The percentage of T3 or T4 in obese (n=90) and non-obese (n=193) patients with papillary thyroid cancer according to quartile of daily meat intake by multivariable logistic regression; P-trends were adjusted for energy, age, gender and drinking; Obesity was defined by BMI ≥ 25 kg/m^2 and WC ≥ 85 cm for women or ≥ 90 cm for men; T3 = primary tumor >4 cm, confined to the thyroid gland or any tumor with minimal extrathyroid extension; T4a = primary tumor with invasion of subcutaneous soft tissues, larynx, trachea, esophagus and recurrent laryngeal nerve; T4b = primary tumor with invasion of prevertebral fascia, mediastinal vessels and encasing of carotid artery.

not associated with meat intake.

Meat intake was positively associated with advance tumor stage (T3 or T4) and presence of thyroiditis in obese patients but not in non-obese patients (Figure I). There was no significant association, however, between meat intake and other clinicopathological characteristics such as lymph node metastasis and advanced TNM stage in either obese or non-obese patients (data not shown).

Ⅳ. DISCUSSION

The present study is the first report of a positive association between risk of recurrence of PTC and intake of animal lipids from meat and dairy products in patients with PTC. We consistently observed a positive association between meat intake and aggressive tumor characteristics related to recurrence of PTC, particularly in obese patients.

Although there has been no previous study on diet and recurrence of thyroid cancer, initial occurrence of thyroid cancer is associated with diet, particularly intake of iodine (Peterson et al. 2012). Two major histological types of well differentiated thyroid cancer, papillary and follicular, have been linked to iodine-rich and iodine-deficient diets, respectively, suggesting that thyroid cancer risk differs based on iodine availability (Cho & Kim, 2015). A pooled analysis study showed that iodine from fish consumption was negatively associated with the risk of developing thyroid cancer only in iodine-deficient areas (Bosetti et al 2001). However, iodine intake and urinary excretion are higher in Koreans than in patients from other countries because of higher seaweed consumption in Korea (Kim et al. 1998).

Several epidemiologic studies have reported that intake of high fat, mainly animal fat, is associated with increased risk of developing thyroid cancer (Franceschi et al 1989; Franceschi et al. 1991; Glanti et al. 1997; Markaki et al. 2003). In particular, studies on Western populations have described a positive association between thyroid cancer and intake of meat such as pork, cooked ham, salami, and sausages and dairy products such as cheese and butter (Franceschi et al 1989; Glanti et al. 1997; Markaki et al. 2003). In Asian populations, thyroid cancer has been positively associated with consumption of mutton, lamb, and nitrites from processed meat (Memon et al. 2002; Aschebrook-kilfoy et al. 2013). In addition, a meta-analysis showed that higher nitrite intake from animal sources such as processed meat is accompanied by an increased risk of incurrence of thyroid cancer (Bahadoran et al. 2015).

There are a few possible mechanisms explaining the association between meat intake and thyroid tumor progression. N-nitroso compounds, induced by reaction between nitrite and amines, are known carcinogenic agents in human cancers (Jakszyn & Gonzalez, 2006). A high-fat diet has been also shown to upregulate fatty-acids synthase, which is associated with poor prognosis, higher risk of recurrence, and shorter survival of human cancers, including thyroid cancer (Kuhajda et al. 2000). Mice fed a high-fat diet have larger tumors and lower survival time than those fed a low-fat diet, suggesting that a high-fat diet induces aggressive tumor characteristics related to recurrence of thyroid cancer (Kim et al. 2013).

Among clinicopathologic characteristics, tumor size and lymph node metastasis were positively associated with meat intake in the present study. However, presence of thyroiditis was negatively associated with meat intake. A previous meta-analysis reported that PTC with Hashimoto's thyroiditis had favorable clinicopathologic characteristics such as no lymph node metastasis or extrathyroidal extension compared to PTC without Hashimoto's thyroiditis (Lee et al. 2013).

Epidemiologic studies have reported that obesity is positively related to occurrence of thyroid cancer (Kitahara et al. 2012; Schmid et al. 2015). In agreement, Schmid et al. reported that BMI and waist and hip circumference are positively associated with risk of development of thyroid cancer. In addition, BMI is strongly associated with larger tumor size, extrathyroidal invasion, lymph node metastasis and advanced TNM stage of PTCs (Kim et al. 2013). The National Health and Nutrition Examination Survey (NHANES) demonstrated positive associations between meat intake and risk of obesity and abdominal obesity, suggesting that persons who consume meat have a higher energy intake (Wang & Beydoun, 2009). The present study consistently showed that the association between meat intake and advanced tumor stage was greater in PTC patients with BMI $\geq$ 25 and waist circumference $\geq$ 85 for women or $\geq$ 90 for men, suggesting synergic interaction between meat intake and obesity.

There were a few limitations of this study. First, because of the cross-sectional study design, we could not establish a cause-and-effect relationship between dietary intake and risk of recurrence in papillary thyroid cancer. Second, although this study adjusted for some confounders, there was a possibility that unmeasured factors affected the results. Lastly, only low- to intermediate-risk patients were included in the study. However, this was the first study investigating the association between dietary intake and risk of recurrence of PTC.

In conclusion, high fat intake from meat and dairy products was positively associated with risk of recurrence in patients with PTC, particularly obese patients. However, prospective and experimental studies are needed to confirm the cause-effect relationship between high-fat diet and risk of recurrence in PTC.

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