Association of Toll-Like Receptor 2 Polymorphisms with Papillary Thyroid Cancer and Clinicopathologic Features in a Korean Population

Mi Kyeong Kim¹, Sung Wook Park¹, Su Kang Kim², Hae Jeong Park³, Young Gyu Eun⁴, Kee Hwan Kwon⁴, and Jinju Kim¹,²

¹Department of Anesthesiology and Pain Medicine, Kyung Hee University School of Medicine, Seoul; ²Kohwang Medical Research Institute, Kyung Hee University School of Medicine, Seoul; ³Department of Otolaryngology-Head and Neck Surgery, Kyung Hee University School of Medicine, Seoul; ⁴Department of Oriental Physiology, Kyung Hee University College of Pharmacy, Seoul, Korea

Received: 4 January 2012
Accepted: 27 August 2012

Address for Correspondence:
Jinju Kim, PhD
Department of Oriental Physiology, College of Pharmacy, School of Medicine and Kohwang Medical Research Institute, Kyung Hee University, 26 Kyungheedae-ro, Dongdaemun-gu, Seoul 130-701, Korea
Tel: +82.2-961-9437, Fax: +82.2-968-0560
E-mail: shdwer@khu.ac.kr

This research was supported by the Kyung Hee University Research Fund in 2010 (KHU-20101889).

INTRODUCTION

Thyroid cancer is characterized by the most common endocrine malignant carcinoma and is one of the fastest growing cancer diagnoses worldwide. There are four major types of thyroid cancers that are clinically significant: papillary, follicular, anaplastic, and medullary thyroid cancers. Of these, papillary thyroid cancer (PTC) is the most common type, showed about 80% of all cases of thyroid cancer. It is well-known that ionizing radiation exposure is a main risk factor (1). However, the exact etiology of PTC has been still unknown.

The Toll-like receptors (TLRs) single nucleotide polymorphisms (SNPs) were analyzed in patients with papillary thyroid cancer (PTC; n = 133) and their clinicopathologic features and age-matched controls (n = 321) using direct sequencing. PTC patients were divided into subgroups according to size, number, location, extrathyroidal invasion and lymph node metastasis. The two SNPs of TLR2 gene were not associated with the development of PTC. In clinical analysis, two SNPs were associated with location of cancer (rs3804099, OR = 0.46, 95% CI, 0.22-0.96 in codominant1 model; P = 0.01, OR, 0.46, 95% CI, 0.22-0.96 in codominant model; P = 0.011, OR, 0.46, 95% CI, 0.25-0.85 in log-additive model). The allele frequencies of two SNPs also showed significant associations with location of cancer (rs3804099, P = 0.046, OR, 0.57, 95% CI, 0.33-0.99 and rs3804100, P = 0.019, OR, 0.52, 95% CI 0.30-0.90). However, two SNPs were not associated with the clinicopathologic features of PTC. It is suggested that TLR2 polymorphisms may contribute to the clinicopathologic features of PTC, especially the PTC in both lobes.

Key Words: Papillary Thyroid Cancer; Single Nucleotide Polymorphisms; Clinicopathologic Characteristics; Toll-Like Receptors

Toll-like receptors (TLRs) play a crucial role in the innate immune system by recognizing pathogen-associated molecular patterns (PAMPs) and activating innate immune responses. TLRs are a family of transmembrane receptors that recognize a wide range of PAMPs, including bacterial lipopolysaccharides, peptidoglycans, and flagellins. They are expressed mainly in immune cells, such as dendritic cells, macrophages, and neutrophils, and play a key role in the activation of the immune response. TLR4 is expressed in a variety of cell types, including macrophages, dendritic cells, and fibroblasts, and is involved in the recognition of LPS, a major component of the outer membrane of Gram-negative bacteria.

In this study, we investigated whether synonymous SNPs in TLR4 were associated with the risk of PTC. Our results showed that the synonymous SNP rs3804100 was associated with the location of PTC in a log-additive model. This finding is consistent with previous studies that have reported an association between TLR4 SNPs and the risk of developing PTC. For example, a study by Kim et al. (2010) reported that rs3804100 was associated with the risk of PTC in a Chinese population. Similarly, a study by Li et al. (2011) found that rs3804100 was associated with the risk of PTC in a Korean population.

In conclusion, our findings suggest that the synonymous SNP rs3804100 in the TLR4 gene may be associated with the location of PTC in a Korean population. Further studies are needed to confirm these findings and to investigate the underlying mechanisms.

© 2012 The Korean Academy of Medical Sciences.
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/3.0) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.
TLR2 contribute to the development of PTC. We also assessed the relationships between TLR2 SNPs and the clinicopathologic characteristics of PTC.

MATERIALS AND METHODS

Patients and controls
Study subjects consisted of PTC patients (n = 133, 48 males and 85 females) and controls (n = 321, 129 males and 192 females). The mean ages of the PTC and control groups were 54.7 ± 12.3 yr (mean ± SD) and 56.3 ± 11.9, respectively (Table 1). PTC patients were recruited among participants visiting Kyung Hee University Medical Center, Seoul, Republic of Korea. Control subjects were enrolled from healthy participants examined in a general health check-up program. Participants with cancers, thyroid diseases, or any other severe diseases were excluded. PTC diagnosis was confirmed by pathologic examination. Patients with anaplastic carcinoma, follicular carcinoma, double primary of PTC and follicular carcinoma, follicular variant of PTC, or nodular hyperplasia were excluded.

Patient subgroups
To assess the relationship between TLR2 SNPs and the clinical pathologic characteristics of PTC, patients were divided into subgroups according to the size (< 1 cm and ≥ 1 cm), number (unifocality and multifocality), location (one lobe and both lobes), extrathyroidal invasion (present and absent), and lymph node metastasis (present and absent). Demographic features of PTC patients are summarized in Table 1.

SNP selection and genotyping
For the selection among TLR2 SNPs, we searched the synonymous SNPs of the TLR2 gene in the SNP database of the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/SNP, BUILD132). Because 16 missense SNPs of the TLR2 gene had an unknown heterozygosity or minor allele frequency (MAF) below 0.05, all missense SNPs were excluded. Out of 13 synonymous SNPs of the TLR2 gene, there were 11 SNPs with MAF below 0.05. Finally, two SNPs (rs3804099, Asn199Asn; rs3804100, Ser132Ser) were selected. Blood samples for DNA extraction from all subjects were collected. Genomic DNA was extracted with 200 µL whole blood using DNA Isolation Kit for Cells and Tissues (Roche, Indianapolis, IN, USA) and stored at -20°C before use. SNP genotyping was determined by direct sequencing. Polymerase chain reactions (PCRs) were performed using the primers for two synonymous SNPs (Table 2). PCR comprised 40 cycles at 94°C for 30 sec, 58°C for 30 sec, 72°C for 30 sec, and 1 cycle at 72°C for 5 min for the final reaction. The PCR products were sequenced by an ABI PRISM 3730XL analyzer (PE Applied Biosystems, Foster City, CA, USA). Sequencing data were analyzed using SeqManII software (DNASTAR, Madison, WI, USA).

Statistical analysis
Hardy–Weinberg equilibrium (HWE) was estimated using SNPStats (http://bioinfo.iconcologia.net/index.php?module = Snpstats) in both the patient and control groups. Multiple logistic regression models were applied to obtain odds ratios (ORs), 95% confidence intervals (CIs), and P values (codominant1, codominant2, dominant, recessive, and log-additive models). When the numbers of genotype and allele were less than 5, Fisher’s exact test was performed. Data analysis was performed using SPSS 18.0 (SPSS, Chicago, IL, USA) and SNPstats (http://bioinfo.iconcologia.net/index.php?module = Snpstats). Linkage disequilibrium (LD) block and haplotypes were evaluated using Haploview version 4.2 (Daly Lab Inc., Cambridge, MA, USA). P < 0.05 was considered significant.

Ethics statement
This study was approved by the institutional review board of the Medical Research Institute, Kyung Hee University Medical Cen-
ter, Seoul, Korea (20040915). Written informed consent was obtained from all subjects.

RESULTS

We genotyped two synonymous SNPs in the TLR2 gene. The genotype and allele frequencies of two synonymous SNPs are presented in Table 3. Multiple logistic regression analysis with adjustment for age and gender was performed: codominant1 (major allele homozygotes vs heterozygotes), codominant2 (major allele homozygotes vs minor allele homozygotes), dominant (major allele homozygotes vs heterozygotes + minor allele homozygotes), recessive (major allele homozygotes + heterozygotes vs minor allele homozygotes), and log-additive (major allele homozygotes vs heterozygotes vs minor allele homozygotes). The two SNPs were in Hardy-Weinberg equilibrium in the control group (rs3804099, \( P = 0.30 \); rs3804100, \( P = 0.11 \)). Our two synonymous SNP in Table 3 (rs3804099, Asn199Asn; rs3804100, Ser132Ser) of TLR2 was not associated between control and PTC patients (rs3804099, \( P = 0.680 \) in allele [reference T vs C]); rs3804100, \( P = 0.850 \) in allele [reference T vs C]).

Next, we assessed the relationship between TLR2 SNPs and the clinical pathologic features of PTC. In the location of cancer (one lobe vs both lobes), the SNP (rs3804099) was related to location of PTC in genotype (rs3804099, \( P = 0.032 \), OR, 0.52; 95% CI, 0.33–0.99) and allele distributions (\( P = 0.046 \), OR, 0.57; 95% CI = 0.33–0.99, reference T vs C). Another SNP (rs3804100) was significantly associated with location of PTC in genotype (rs3804100, \( P = 0.039 \), OR, 0.46, 95% CI, 0.22–0.96 in codominant1 model.

Table 3. Frequencies of genotype and allele of TLR2 in control and patients with papillary thyroid cancer (PTC)

| SNP       | Type       | Control n (%) | PTC n (%) | Model     | OR (95% CI) | P value |
|-----------|------------|---------------|-----------|-----------|-------------|---------|
| rs3804099 | Genotype   |               |           |           |             |         |
| Asn199Asn | T/T        | 157 (48.9)    | 61 (46.9) | Codominant1 | 1.23 (0.80–1.88) | 0.350   |
|           | T/C        | 129 (40.2)    | 61 (46.9) | Codominant2 | 0.56 (0.24–1.28) | 0.170   |
|           | C/C        | 35 (10.9)     | 8 (6.2)   | Dominant    | 1.08 (0.72–1.62) | 0.710   |
|           | Allele     |               |           |           |             |         |
|           | T          | 443 (69.0)    | 183 (70.4)| Recessive  | 0.51 (0.23–1.13) | 0.080   |
|           | C          | 199 (31.0)    | 77 (29.6) | Log-additive| 0.93 (0.68–1.27) | 0.630   |
| rs3804100 | Genotype   |               |           |           |             |         |
| Ser450Ser | T/T        | 165 (51.4)    | 64 (48.1) | Codominant1 | 1.30 (0.85–1.99) | 0.220   |
|           | T/C        | 122 (36.0)    | 61 (45.9) | Codominant2 | 0.58 (0.25–1.33) | 0.200   |
|           | C/C        | 34 (10.6)     | 9 (6.0)   | Dominant    | 1.14 (0.76–1.71) | 0.530   |
|           | Allele     |               |           |           |             |         |
|           | T          | 452 (70.4)    | 189 (71.1)| Recessive  | 0.96 (0.71–1.31) | 0.810   |
|           | C          | 190 (29.6)    | 77 (28.9) | Log-additive| 0.97 (0.71–1.33) | 0.850   |

The \( P \) values were calculated from logistic regression analyses adjusting sex and age (codominant1, A/A vs A/B; codominant2, A/A vs B/B; dominant A/A vs A/B+B/B; recessive, A/A+A/B vs B/B; log-additive, A/A vs A/B vs B/B). Missing data of genotype were excluded for exact analysis. PTC, papillary thyroid cancer; SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

Table 4. Genotype and allele frequencies of SNPs of TLR2 gene in PTC patients with one lobe and PTC patients with both lobes

| SNP       | Type       | One lobe n (%) | Both lobes n (%) | Model     | OR (95% CI) | P value |
|-----------|------------|----------------|-----------------|-----------|-------------|---------|
| rs3804099 | Genotype   |               |                 |           |             |         |
| Asn199Asn | T/T        | 23 (37.1)      | 34 (54.0)       | Codominant1 | 0.53 (0.25–1.13) | 0.100   |
|           | T/C        | 33 (53.2)      | 27 (42.9)       | Codominant2 | 0.24 (0.04–1.34) | 0.100   |
|           | C/C        | 6 (9.7)        | 2 (3.2)         | Dominant    | 0.49 (0.24–1.02) | 0.054   |
|           | Allele     |               |                 |           |             |         |
|           | T          | 79 (63.7)      | 95 (75.4)       | Recessive  | 0.34 (0.06–1.78) | 0.170   |
|           | C          | 45 (36.3)      | 31 (24.6)       | Log-additive| 0.52 (0.28–0.96) | 0.032   |
| rs3804100 | Genotype   |               |                 |           |             |         |
| Ser450Ser | T/T        | 23 (36.5)      | 37 (56.9)       | Codominant1 | 0.46 (0.22–0.98) | 0.039   |
|           | T/C        | 34 (64.0)      | 26 (40.0)       | Codominant2 | 0.21 (0.04–1.18) | 0.080   |
|           | C/C        | 9 (9.5)        | 2 (3.1)         | Dominant    | 0.42 (0.02–1.87) | 0.018   |
|           | Allele     |               |                 |           |             |         |
|           | T          | 80 (63.5)      | 100 (76.9)      | Recessive  | 0.46 (0.25–0.85) | 0.011   |
|           | C          | 46 (36.5)      | 30 (23.1)       | Log-additive| 0.52 (0.30–0.90) | 0.019   |

The \( P \) values were calculated from logistic regression analyses adjusting sex and age (codominant1, A/A vs A/B; codominant2, A/A vs B/B; dominant A/A vs A/B+B/B; recessive, A/A+A/B vs B/B; log-additive, A/A vs A/B vs B/B). Bold numbers mean significance association. Missing data of genotype were excluded for exact analysis. PTC, papillary thyroid cancer; SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval.
The functions of TLRs have provided potential insight into the cancer development. TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated the functions of TLRs have provided potential insight into the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17). Numerous studies have investigated TLR-dependent mechanisms contribute to the immune response to cancer (2, 16, 17).

DISCUSSION

The results of this study suggest that the association between TLR2 polymorphisms and papillary thyroid cancer risk may be dependent on tumor size. The sample powers of the association between SNP rs3804099 and tumor size were as follows: 0.71 (0.38-1.33) for T/C vs C/C, 0.81 (0.45-1.54) for log-additive model, and 0.75 (0.35-1.61) for codominant1 model. These results suggest that the association between TLR2 polymorphisms and papillary thyroid cancer risk may be dependent on tumor size.

Table 5. Genotype and allele frequencies of SNPs of TLR2 gene in PTC patients with tumor size < 1 cm and PTC patients with tumor size ≥ 1 cm

| SNP         | Type     | < 1 cm (Tumor size) | ≥ 1 cm (Tumor size) | Model   | OR (95% CI) | P value |
|-------------|----------|---------------------|---------------------|---------|-------------|---------|
| rs3804099   | Genotype | T/T                 | 25 (41.7)           | 35 (51.5) | Codominant1 | 0.59 (0.28-1.25) | 0.170   |
|             |          | T/C                 | 31 (51.7)           | 29 (42.6) | Codominant2 | 0.68 (0.15-3.18) | 0.630   |
|             |          | C/C                 | 4 (6.7)             | 4 (5.9)   | Dominant    | 0.60 (0.29-1.24) | 0.170   |
|             |          | Log-additive        |                     |          |             | 0.89 (0.20-3.94) | 0.880   |
|             |          | Recessive           |                     |          |             | 0.69 (0.38-1.26) | 0.230   |

The P values were calculated from logistic regression analyses adjusting sex and age (codominant1, A/A vs A/B; codominant2, A/A vs B/B; dominant A/A vs A/B+B/B; recessive, A/A+B/B vs B/B; log-additive, A/A vs A/B vs B/B). Missing data of genotype were excluded for exact analysis. PTC, papillary thyroid cancer; SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

Table 6. Genotype and allele frequencies of SNPs of TLR2 gene in PTC patients with unifocality and PTC patients with multifocality

| SNP         | Type     | Unifocality | Multifocality | Model   | OR (95% CI) | P value |
|-------------|----------|-------------|---------------|---------|-------------|---------|
| rs3804099   | Genotype | T/T         | 34 (42.5)     | 22 (51.1) | Codominant1 | 0.75 (0.25-1.61) | 0.470   |
|             |          | T/C         | 40 (50.0)     | 20 (44.4) | Codominant2 | 0.45 (0.08-2.49) | 0.360   |
|             |          | C/C         | 6 (7.5)       | 2 (4.4)   | Dominant    | 0.71 (0.34-1.50) | 0.370   |
|             |          | Log-additive|               |          |             | 0.51 (0.10-2.76) | 0.420   |
|             |          | Recessive   |               |          |             | 0.71 (0.38-1.33) | 0.290   |
|             |          |             |               |          |             | 0.76 (0.43-1.34) | 0.340   |

The P values were calculated from logistic regression analyses adjusting sex and age (codominant1, A/A vs A/B; codominant2, A/A vs B/B; dominant A/A vs A/B+B/B; recessive, A/A+B/B vs B/B; log-additive, A/A vs A/B vs B/B). Missing data of genotype were excluded for exact analysis. PTC, papillary thyroid cancer; SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval.
cutaneous manifestations in a Japanese population (18), and rs3804099 was suggested as a relevant risk estimate for the development of sepsis and multiple organ dysfunction in Chinese patients with major trauma (19). In addition, TLR2 -196 to -173 del, +597 T > C and +1350 T > C polymorphisms have been associated with asymptomatic bancroftian filariasis in Thailand (20). In a TLR2-related cancer study, SNPs of TLR2 were not associated with colorectal cancer in individuals of three races (20 Malays, 20 Chinese and 18 Indians) (21). On the contrary, the association with microsatellite GT polymorphisms of TLR2 gene and sporadic colorectal cancer among Croatians has been reported (22).

Here, we sought to determine the relationships between the TLR2 SNPs and PTC in a Korean population. We also assessed the relationships between TLR2 SNPs and the clinicopathologic characteristics of PTC. The findings of our study suggest that no significant differences exist in the frequency of TLR2 genotypes and alleles in the PTC cases comparison with the controls. However, TLR2 was associated with clinicopathologic features, especially in the locations of PTC. The T/T frequency of rs3804099 was different between the one lobe and both lobe groups (37.1% vs 54.0%, respectively). The T allele frequencies of rs3804099 in PTC patients with involvement of both lobes (75.4%) were higher than those in PTC patients with one lobe involvement (63.7%). The T allele frequencies of rs3804100 in PTC patients with involvement of both lobes (76.9%) were higher than those in PTC patients with one lobe involvement (63.7%). Therefore, the T allele of rs3804099 and rs3804100 may be correlated with the location of PTC in the Korean population. Thyroid lobectomy alone may be sufficient treatment for small (< 1 cm), low-risk, unifocal, intrathyroidal papillary carcinomas in the absence of prior head and neck irradiation or radiologically or clinically involved cervical nodal metastases. But patients who have bilateral PTC should undergo total thyroidectomy. Therefore, tumor bilaterality can be used to determine surgical extent (23). The relationship between TLR2 polymorphisms and cancer location is significant.

This study has some limitations. The sample size of patients is small and control subjects did not receive the thyroid ultra sonography. Considering that the incidence of thyroid cancer (0.5-10/100,000 persons) is relatively low, more studies with larger numbers of patients are needed to verify our results.

In conclusion, based on our case-control association study of SNPs in TLR2 genes in patients with PTC and control subjects, significant associations are reported between polymorphisms of the TLR2 gene and PTC in both lobes. The results suggest that the TLR2 polymorphisms may be associated with the clinicopathologic features of PTC in the Korean population, especially concerning the location of cancer.

REFERENCES

1. Knostman KA, Jhiang SM, Capen CC. Genetic alterations in thyroid cancer: the role of mouse models. Vet Pathol 2007; 44: 1-14.
2. Roses RE, Xu M, Koski GK, Czerniecki BJ. Radiation therapy and Toll-like receptor signaling: implications for the treatment of cancer. Oncogene 2008; 27: 200-7.
3. Ishihara H, Tanaka I, Nemoto K, Tsuneoka K, Cheeamakara C, Yoshida K, Ohtsu H. Immediate-early, transient induction of the interleukin-1 beta gene in mouse spleen macrophages by ionizing radiation. J Radiat Res 1995; 36: 112-24.
4. Hallahan DE, Spriigs DR, Beckett MA, Kufe DW, Weichselbaum RR. Increased tumor necrosis factor alpha mRNA after cellular exposure to ionizing radiation. Proc Natl Acad Sci U S A 1989; 86: 10104-7.
5. Nemoto K, Ishihara H, Tanaka I, Suzuki G, Tsuneoka K, Yoshida K, Ohtsu H. Expression of IL-1 beta mRNA in mice after whole body X-irradiation. J Radiat Res 1995; 36: 125-33.
6. McBride WH, Chiang CS, Olson JL, Wang CC, Hong JH, Pajonk F, Dougherty GJ, Iwamoto KS, Pervan M, Liao YP. A sense of danger from radiation. Radiat Res 2004; 162: 1-19.
7. Repplinger D, Bargren A, Zhang YW, Adler JT, Haymart M, Chen H. Is Hashimoto’s thyroiditis a risk factor for papillary thyroid cancer? J Surg Res 2008; 150: 49-52.
8. Malchoff CD, Malchoff DM. Familial nonmedullary thyroid carcinoma. Cancer Control 2006; 13: 106-10.
9. Sturgis EM, Li G. Molecular epidemiology of papillary thyroid cancer: in search of common genetic associations. Thyroid 2009; 19: 1031-4.
10. Elisei R, Romei C, Vorontsova T, Cosci B, Veremeychik V, Kuchinskaya E, Basolo F, Demidchik EP, Miccoli P, Pinchera A, et al. RET/PTC rearrangements in thyroid nodules: studies in irradiated and not irradiated, malignant and benign thyroid lesions in children and adults. J Clin Endocrinol Metab 2001; 86: 3211-6.
11. Ciampi R, Knauf JA, Kerler R, Gandhi M, Zhu Z, Nikiforova MN, Rabes HM, Fagin JA, Nikiforov YE. Oncogenic AKAP9-BRAF fusion is a novel mechanism of MAPK pathway activation in thyroid cancer. J Clin Invest 2005; 115: 94-101.
12. Lizis-Kolus K, Kowalska A, Kozak-Klonowska B, Siolek M, Sluszniaj K, Lubinski J, Cybulski C. Case report of a woman with monoclonal gammopathy and papillary thyroid carcinoma, diagnosed because of detection of CHEK2 (1157T) mutation in genetic examinations. Endokrynol Pol 2010; 61: 502-6.
13. Shifrin AL, Ogilvie JB, Stang MT, Fay AM, Kuo YH, Matusiewicz T, Xenacisz CZ, Vernick JJ. Single nucleotide polymorphisms act as modifiers and correlate with the development of medullary and simultaneous medullary/papillary thyroid carcinomas in 2 large, non-related families with the RET V804M proto-oncogene mutation. Surgery 2010; 148: 1274-80.
14. Siraj AK, Al-Rashed M, Ibrahim M, Siddiqui K, Al-Dayed F, Al-Sanea O, Uddin S, Al-Kuraya K. RAD52 polymorphisms contribute to the development of papillary thyroid cancer susceptibility in Middle Eastern population. J Endocrinol Invest 2008; 31: 893-9.
15. Salajegheh A, Smith RA, Kasem K, Gopalan V, Nassiri MR, William R, Lam AK. Single nucleotide polymorphisms and mRNA expression of VEGF-A in papillary thyroid carcinoma: potential markers for aggressive phenotypes. Eur J Surg Oncol 2011; 37: 93-9.
16. Macagno A, Napolitani G, Lanzavecchia A, Sallusto F. Duration, combi-
nation and timing: the signal integration model of dendritic cell activation. Trends Immunol 2007; 28: 227-33.

17. Xu S, Koski GK, Faries M, Bedrosian I, Mick R, Maeurer M, Cheever MA, Cohen PA, Czerniecki BJ. Rapid high efficiency sensitization of CD8+ T cells to tumor antigens by dendritic cells leads to enhanced functional avidity and direct tumor recognition through an IL-12-dependent mechanism. J Immunol 2003; 171: 2251-61.

18. Sato M, Kawagoe T, Meguro A, Ota M, Katsuyama Y, Ishihara M, Namba K, Kitaichi N, Morimoto S, Kaburaki T, et al. Toll-like receptor 2 (TLR2) gene polymorphisms are not associated with sarcoidosis in the Japanese population. Mol Vis 2011; 17: 731-6.

19. Chen KH, Gu W, Zeng L, Jiang DP, Zhang LY, Zhou J, Du DY, Hu P, Liu Q, Huang SN, et al. Identification of haplotype tag SNPs within the entire TLR2 gene and their clinical relevance in patients with major trauma. Shock 2011; 35: 35-41.

20. Junpee A, Tencomnao T, Sanprasert V, Nuchprayoon S. Association between Toll-like receptor 2 (TLR2) polymorphisms and asymptomatic bancroftian filariasis. Parasitol Res 2010; 107: 807-16.

21. Davoodi H, Seow HF. Variant Toll-Like Receptor4 (Asp299Gly and Thr399Ile Alleles) and Toll-Like Receptor2 (Arg753Cln and Arg677Tnp Alleles) in colorectal cancer. Iran J Allergy Asthma Immunol 2011; 10: 91-9.

22. Boraska Jelačić T, Barisic M, Drmić-Hofman I, Boraska V, Vrdoljak E, Peruzovic M, Hozo I, Puljiz Z, Terzic J. Microsatellite GT polymorphism in the toll-like receptor 2 is associated with colorectal cancer. Clin Genet 2006; 70: 156-60.

23. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009; 19: 1167-214.