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GA GENOTYPE OF THE ARG280HIS POLYMORPHISM ON THE *XRCC1* GENE: GENETIC SUSCEPTIBILITY GENOTYPE IN DIFFERENTIATED THYROID CARCINOMAS?

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ABSTRACT

Differentiated thyroid carcinomas (DTC) are the most common form of endocrine malignancies. The role of genetic variations in the development of papillary thyroid carcinoma (PTC) is approximately 60.0-70.0%. The X-ray repair cross-complementing group 1 (*XRCC1*) protein has an important role in DNA repair mechanisms and genomic polymorphisms of *XRCC1* gene affect the function of the protein. In the present case-control study, we aimed to compare the genotype frequency distributions of *XRCC1* single nucleotide polymorphisms (SNPs) in terms of the presence of other risk factors (Hashimoto's thyroiditis, smoking, obesity, radiation exposure) in patients with thyroid nodules who had fine-needle aspiration biopsy (FNAB) and/or thyroid surgery due to thyroid cancer. The genotype frequency distributions of three common *XRCC1* SNPs (Arg194Trp, Arg399Gln, Arg280His) were compared to those with DTC (n = 228), benign thyroid nodules (BTN, n = 100) and healthy controls (n = 93) in terms of certain pre defined risk factors such as the presence of Hashimoto's thyroiditis, smoking, obesity, a family history of thyroid cancer and radiation exposure. The frequency of the GA genotype of Arg280His in DTC cases was found to be higher than in those with BTN and the healthy control group (p <0.001). The DTC group had the lowest frequency of AA genotype of Arg280His (35.5%, p <0.001). Among those with a family history of thyroid cancer, 78.9% had a GA genotype and 21.1% had the AA genotype of Arg280His (p = 0.004). The Arg280His GA genotype was more common in DTC than in cancer-free controls. The GA genotype frequency was also high in DTC cases with a family history of thyroid cancer.

Keywords: Arg280His; Differentiated thyroid carcinomas (DTC); Environmental factors; Thyroid cancer genetics; *XRCC1* gene.

INTRODUCTION

More than 90.0% of thyroid carcinoma, the most common endocrine malignancy, is constituted by differentiated thyroid carcinomas (DTC) [1]. Exact mechanisms leading to DTC have not yet been clarified. Exposure to ionizing radiation at a young age seems to be the most prominent risk factor [2]. Currently, numerous studies are trying to define other environmental risk factors for thyroid cancer, including obesity, smoking and other chemicals [3,4].

Our knowledge of the molecular mechanism behind DTC has increased rapidly. The role of genetic variations in the development of papillary thyroid carcinoma (PTC) is about 60.0-70.0%. Among these variations are point mutations in the B-type rapidly growing fibrosarcoma kinase (*BRAF*) and rat sarcoma (*RAS*) genes, and rearranged during transfection(RET)/PTC thyrosine kinase rearrangements. All these genetic variations lead to the development of cancer by activating a mitogen-activated protein kinase (MAPK) pathway [2,3,5]. As a result of its continuous exposure to DNA damaging agents, there is a constant generation of abasic sites, different base damage and single-stranded breaks in the human genome. To repair these lesions, base excision repair, nucleotide excision repair, and single-strand break repair (SSBR) pathways are used. To repair delaminated bases and oxidatively damaged bases due to reactive oxygen species, base excision repair is considered the major pathway. A skeleton protein encoded by X-ray repair cross-complementing

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group 1 (*XRCC1*) is involved in the repair mechanism of a SSBR, whereas to repair DNA damage due to ionizing radiation, alkylating agents and oxidation, base excision repair (BER) is induced. There is evidence indicating that different *XRCC1* mutations disrupt protein function, either by altering substrate binding or by introducing changes in the catalytic domain [6].

In addition to several point mutations, genomic polymorphisms of the *XRCC1* gene were reported as the most common single nucleotide polymorphisms (SNPs) with effects on the relevant function of the protein. The potential biological significance of the three most common *XRCC1* (Arg399Gln, Arg194Trp and Arg280His) poly-morphisms has been investigated in numerous studies. There are only very few studies investigating these genomic variations concerning the clinical findings in thyroid cancer patients [6,7].

The present case-control study aimed to compare the genotype frequency distributions of three common *XRCC1* SNPs in DTC patients and cancer-free controls in terms of various predefined clinical characteristics, such as the presence of Hashimoto's thyroiditis, smoking, obesity, radiation exposure, and family history of thyroid cancer. For this purpose, the association of the *XRCC1* SNP was analyzed, and the presence of other risk factors (presence of Hashimoto's thyroiditis, smoking, obesity, radiation exposure) were investigated in patients with thyroid nodules who underwent fine-needle aspiration biopsy (FNAB) and/or thyroid surgery for thyroid cancer.

MATERIALS AND METHODS

In a case-control setting, all subjects admitted to the outpatient clinic of the Department of Endocrinology and Metabolism in Başkent University, Faculty of Medicine, Ankara, Turkey, between January 2005 and December 2015 were evaluated consecutively for inclusion in the study. The present study protocol was reviewed and approved by the Institutional Review Board of Başkent University College of Medicine [approval No. KA14/223]. This study has been approved by Başkent University's Medical Sciences Ethics Committee, and therefore performed per the ethical standards laid down by the 1964 Declaration of Helsinki and its later amendments.

All subjects were between 18-75 years of age. The exclusion criteria of the study included patient disagreement, having bleeding diathesis (hematological diseases, drug use, *etc.*) precluding performance of FNAB or the coexistence of another cancer. A total of 383 cases had thyroid nodules bearing indication for FNAB. A total of 100 patients with FNAB results constituted the cancer-free goitrous control group with benign thyroid nodules (BTN). Patients in the BTN group were the patients with indication for biopsy due to existing nodules, and underwent biopsy at least once. It comprised patients who required repeat biopsy (*e.g.,* increase in size, change in nodule characteristics) during their follow-up and whose biopsy results were benign. Among these patients, we did not find any whose first biopsy was benign and whose repeat biopsy from the same nodule was malignant. The remaining 228 patients comprised the DTC group. The third group was comprised of 93 healthy participants with normal thyroid function and ultrasonography. Clinical variables such as radiation exposure, family history, smoking status, body fat distribution and the presence of Hashimoto's thyroiditis were determined from patients' medical records. Peripheral blood samples were drawn for *XRCC1* genotyping and polymorphism evaluation.

Genotyping Analysis. Genomic DNA was extracted from peripheral lymphocytes using phenol-chloroform extraction. Using real-time polymerase chain reaction (qPCR), followed by melting curve analysis with fluorescence-labeled hybridization probes in a LightCycler (Roche Diagnostics GmbH, Mannheim, Germany), *XRCC1* Arg194Trp (rs1799782), Arg280His (rs25489) and Arg399Gln (rs25487) genotypes were analyzed [8].

The PCR primers and probes were designed using TIB MolBiol tool (TIB MolBiol Syntheselabor GmbH, Berlin, Germany). The annealing temperature of the primers was 60 °C. For all polymorphisms, PCR was performed with LC fast start DNA master HybProbere agents (Roche Diagnostics GmbH) in a volume of 10 μL using 10 ng of DNA. Reaction conditions were as follows: initial denaturation at 95 °C for 10 seconds, followed by 40 cycles of denaturation at 95 °C for 15 seconds, annealing at 55 °C for 10 seconds, and elongation at 72 °C for 12 seconds. Melting curve analysis was performed with an initial denaturing step at 95 °C for 5 seconds, 45 °C for 20 seconds, slow heating to 75 °C with a ramp rate of 0.11 °C/second and continuous fluorescence detection.

Statistical Analyses. The χ^2 test was used to compare the *XRCC1* genotype frequencies of the groups. Genotype frequencies in each group were determined by univariate analysis and evaluated for Hardy-Weinberg disequilibrium by the χ^2 test. The Student's t-test was used to compare the means of two independent groups when assumptions for the parametric tests were met. When these assumptions were not met, the Mann-Whitney U test was used to compare the medians of two groups. The results were expressed as *n* for the number of observations, (X ± Sx) for mean ± SD, (M) for median, and minimum-maximum values. Pearson χ^2 test was used to analyze categorical variables, and Fisher's exact test was used to determine the association between the variables. Data were analyzed using the Statistical Package for the Social Sciences, version 17.0 (SSPS Inc., Chicago IL, USA). A *p* value of <0.05 was considered to be statistically significant.

RESULTS

The baseline characteristics [age, sex, body mass index (BMI), family history of thyroid cancer, presence of Hashimoto's thyroiditis, smoking status, thyroid stimulating hormone (TSH) levels of both case and control groups] are shown in Table 1. None of the patients enrolled in our study had radiation exposure to the neck.

There was no significant difference in terms of BMI between DTC and the healthy control group ($p = 0.056$). The genotype frequencies of the three *XRCC1* polymorphisms (Arg194Trp, Arg280His, and Arg399Gln) in all cases are given in Table 2. Genotype frequency of GA in *XRCC1* Arg280His polymorphism in the DTC group was significantly higher than the BTN group ($p <0.001$) and healthy control group ($p <0.0001$). Genotype frequency of AA in *XRCC1* Arg280His polymorphism was significantly higher in the BTN group (65.0%) and highest in the healthy control group (96.8%). The genotype frequency of AA in *XRCC1* Arg280His polymorphism was the lowest in the DTC group (35.5%). The difference was statistically significant ($p <0.001$) (Table 2; Figure 1).

In *XRCC1* Arg194Trp polymorphism, genotype frequency of CC was high in all three groups. However, the genotype frequency of CT in *XRCC1* Arg194Trp polymor-

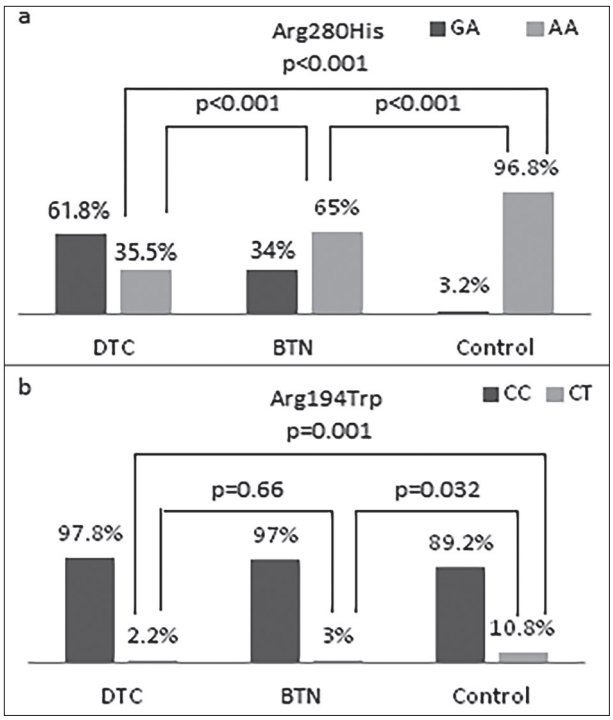

Figure 1. The frequency distribution of Arg280His (a), and Arg194Trp (b) gene polymorphisms among the study groups. DTC: differentiated thyroid carcinoma; BTN: benign thyroid nodule.

Table 1. General characteristics of the differentiated thyroid carcinoma cases, benign thyroid nodule cases and control groups.

Characteristics	DTC Cases *n*=228 (%)	BTN Cases *n*=100 (%)	Controls *n*=93 (%)	*p* Value[a]	*p* Value[b]
Age (years)	45.44±12.89	46.64±13.28	45.06±11.25	0.647	0.960
Gender:				0.025	0.051
females	176 (77.2)	83 (83.0)	62 (66.7)		
males	52 (22.8)	17 (17.0)	31 (33.3)		
Body mass index:				<0.001	0.056
<25	130 (57.0)	43 (43.0)	65 (69.9)		
≤25-<30	47 (20.6)	16 (16.0)	17 (18.3)		
≥30	51 (22.4)	41 (41.0)	11 (11.8)		
Family history of thyroid cancer:				0.001	0.005
yes	18 (7.9)	1 (1.0)	0 (0.0)		
no	210 (92.1)	99 (99.0)	93 (100.0)		
Histological type:					
papillary carcinoma	221 (96.9)				
follicular carcinoma	7 (3.1)				
Hashimoto's thyroiditis:				0.013	0.690
yes	28 (12.3)	25 (25.0)	13 (14.0)		
no	199 (87.7)	75 (75.0)	80 (86.0)		
Smoking status:				0.201	0.817
yes	44 (19.3)	28 (28.0)	19 (20.4)		
no	184 (80.7)	72 (72.0)	74 (78.4)		
Thyroid stimulating hormone level:				<0.001	0.063
<0.35	7 (3.1)	8 (8.0)	0 (0.0)		
0.35-4.50	215 (94.3)	66 (66.0)	93 (100.0)		
>4.50	6 (2.6)	26 (26.0)	0 (0.0)		

DTC: differentiated thyroid carcinomas; BTN: benign thyroid nodule

[a] The comparison of DTC *vs.* BTN *vs.* controls.

[b] The comparison of DTC *vs.* controls.

Table 2. Genotype frequencies for each of the selected XRCC1 polymorphisms in differentiated thyroid carcinoma, benign thyroid nodule and control groups.

Polymorphisms	**DTC Cases** ***n*=228 (%)**	**BTN Cases** ***n*=100 (%)**	**Controls** ***n*=93 (%)**	***p* Value**
Genotype Frequency: Arg280His				
GG	5 (2.6)[a]	1 (1.0)	0 (0.0)	0.04[a]
GA	141 (61.8)[b]	34 (34.0)[b]	3 (3.2)	<0.0001[b]
AA	81 (35.5)[c]	65 (65.0)	90 (96.8)[c]	<0.001[a]
Allele frequency:				
A	305 (67.0)	162 (81.0)	183 (98.0)	
G	151 (33.0)	38 (19.0)	3 (2.0)	
Genotype frequency: Arg194Trp				
CC	223 (97.8)	97 (97.0)	83 (89.2)	0.001[a]
CT	5 (2.2)[a]	3 (3.0)[a]	10 (10.8)	0.032[c]
Allele frequency:				
C	451 (99.0)	197 (98.0)	176 (95.0)	
T	5 (1.0)	3 (2.0)	10 (5.0)	
Genotype frequency: Arg399Gln				
GG	106 (46.5)	52 (52.0)	33 (35.5)	
GA	100 (43.9)	33 (33.0)	48 (51.6)	
AA	22 (9.6)	15 (15.0)	12 (12.9)	
Allele frequency:				
G	311 (68.0)	138 (69.0)	114 (61.0)	
A	145 (32.0)	62 (31.0)	72 (39.0)	

DTC: differentiated thyroid carcinoma; BTN: benign thyroid nodules.

[a] Differentiated thyroid carcinoma and controls.

[b] Differentiated thyroid carcinoma and controls; BTN and controls.

[c] Benign thyroid nodules and controls.

Table 3. Genotype frequencies in patients with a family history of thyroid cancer.

Polymorphisms	**DTC Cases** ***n*=228 (%)**	**BTN Cases** ***n*=100**	**Total** ***n*=328 (%)**	***p* Value**
Arg280His:				0.004
GG	0 (0.0)	0 (0.0)	0 (0.0)	
GA	15 (83.3)	0 (0.0)	15 (78.9)	
AA	3 (16.7)	1 (100.0)	4 (21.1)	
Arg194Trp:				0.346
CC	18 (100.0)	1 (100.0)	19 (100.0)	
CT	0 (0.0)	0 (0.0)	0 (0.0)	
Aarg399Gln:				0.704
GG	7 (38.9)	0 (0.0)	7 (36.8)	
GA	9 (50.0)	0 (0.0)	9 (47.4)	
AA	2 (11.1)	1 (100.0)	3 (15.8)	

DTC: differentiated thyroid canrcinoma; BTN: benign thyroid nodule.

phism was less in all groups (2.2, 3.0 and 10.8%, respectively). Moreover, the CT genotype was significantly more common in the healthy control group when compared to DTC and BTN groups ($p = 0.001$ and $p = 0.032$, respectively) [Table 2; Figure 1(b)]. The distribution of genotype frequencies in the *XRCC1* Arg399Gln polymorphism were similar in all three groups ($p = 0.064$).

Distributions of the three *XRCC1* genotypes were similar among obese, overweight and normal-weight individuals. Furthermore, the coexistence of obesity and any of the three genotypes of *XRCC1* were not correlated with the presence of thyroid cancer.

The highest frequency of Hashimoto's thyroiditis was encountered in the BTN group (25.0%), which was statistically significant ($p = 0.004$). The coexistence of Hashimoto's thyroiditis and any of the *XRCC1* genotypes was not found to be correlated with the presence of thyroid cancer.

The frequency of those with a family history of thyroid cancer was 7.9% ($n = 18$) in the DTC group and 1.0% ($n = 1$) in the BTN group. The difference was statistically

significant ($p = 0.014$). There was no case with a family history of thyroid cancer in the healthy control group, which caused a statistically significant difference among the groups ($p = 0.005$).

Of the cases with *XRCC1* Arg280His polymorphism among those with a family history of thyroid cancer, 78.9% had the GA genotype and 21.1% had the AA genotype, but none had the GG genotype ($p = 0.004$). There was no significant difference in terms of the distribution of Arg399Gln and Arg194Trp polymorphisms of *XRCC1* between those with and without a family history of thyroid cancer ($p = 0.704$, $p = 0.346$, respectively) (Table 3). Among the DTC cases, regarding the histological type of thyroid cancer, there was no difference in the frequency of the three genotypes of *XRCC1* (Arg280His, Arg194Trp, Arg399Gln) in those with papillary and follicular thyroid cancer.

DISCUSSION

Carcinogenesis leading to thyroid cancer has a complex molecular mechanism. The only well-known risk factor is exposure to radiation. Similar to our cases in the present study, most patients with thyroid cancer have no history of radiation exposure. There are many unknown risk factors for patients exposed to environmental insults, as well as unidentified thyroid cancer susceptibility genes [1-3].

Previous studies have reported that *XRCC1* gene poly-morphisms may modify the risk of cancer, including lung, breast and colorectal cancer [9-11]. In recent years, there have been several case-control studies addressing the possible associations between *XRCC1* polymorphisms and DTC. However, most of these studies have yielded inconsistent results due to limited sample size, different races and risk factors [12-16].

A report from the USA has reported that the AA genotype in *XRCC1* Arg399Gln polymorphism decreases the risk of PTC [11], but this association was not demonstrated in other studies [13,14,17]. In Caucasians, it has been reported that the AA genotype in *XRCC1* Arg399Gln polymorphism causes a significant decrease in the risk of DTC [2]. In another study, the AA genotype in *XRCC1* Arg399Gln was found to be preventive against thyroid cancer in mixed races [12], though this was not the case for Caucasians and Asians [13,14,18]. In a study conducted in Korea, any genotype frequency in the *XRCC1* Arg399Gln polymorphism was found to be similar in DTC and control groups, but the AT genotype in *XRCC1* Arg194Trp polymorphism was significantly associated with a decreased risk of PTC compared to the AA genotype [16]. On the other hand, another study from the USA reported that the CT genotype in *XRCC1* Arg194Trp polymorphism was associated with an increased risk of DTC [12]. No association was found between any genotype in the *XRCC1* Arg194Trp polymorphism and DTC by Zhu *et al.* [15]. Wang *et al.* [19] showed an association of this genotype with DTC, especially in smokers and drinkers.

In our case-control study, we found no difference in any genotype frequencies in Arg194Trp and Arg399Gln *XRCC1* with and without cancer, including subgroups with different clinical characteristics (obese, Hashimoto's thyroiditis, smoking and family history of thyroid cancer). Among the *XRCC1* polymorphisms, only the Arg280His polymorphism was significantly different between DTC patients. In the present study, the GA genotype frequency in *XRCC1* Arg280His polymorphism was statistically higher in the DTC group than in the BTN and healthy control groups. The GA genotype of Arg280His was seen in approximately 62.0% of DTC cases, while the AA genotype was most frequently (90.0%) encountered in cancer-free cases. Although the *XRCC1* Arg280His polymorphism is also one of the most frequently encountered genotype revealing an association with DTC in Caucasians [20], there are also conflicting reports that could not demonstrate any association with this genotype and thyroid cancer [2,6,13,21].

Although little is known about the functional effects of the G>A substitution in codon 280 of exon 9 (Arg→His in the non synonymous polymorphism in *XRCC1*), functional changes in the *XRCC1* protein may occur due to the essence of the amino acid substitutions, thus impairing DNA repair efficiency or accuracy, consequently contributing to the risk of cancer. The H280 allele may be dysfunctional, which can lead to haploinsufficiency, or it may exert a dominant-negative effect on the Arg280 allele. The *XRCC1* Arg280His is located in proliferating cell nuclear antigen-binding region [22]. Codon 280 of the *XRCC1* polypeptide lies within the apurinic/apyrimidinic endonuclease (APE)-binding domain. There is a possibility that the Arg280His SNP could alter the *XRCC1* structure, and its ability to interact with APE [23-25]. A functional study demonstrated that when human *XRCC1* variant proteins are introduced to *XRCC1* mutant Chinese hamster ovary (CHO) cells, *XRCC1* carrying 280His could not rescue the SSBR deficiency in mutant cells [26].

Despite functional studies revealing the possible mechanisms through which the *XRCC1* Arg280His polymorphism may lead to cancer development, there are contradicting results from the epidemiological studies [27-32]. This may be explained by the low effect potential of this polymorphism in carcinogenesis about the presence of different molecular and environmental insults to DNA.

Cigarette smoking is associated with the production of free radical intermediates, which are partly corrected

by the involvement of *XRCC1*. Thus, smoke may interact with the *XRCC1* Arg280His polymorphism to initiate and promote tumorigenesis [33]. In a study by Wang *et al.* [19], the Arg194Trp genotype was associated with increased DTC, especially in smokers. However, in our study, smoking was not found to be an additional predisposing risk factor for cancer in any of the *XRCC1* genotypes. This is probably due to the small number of our thyroid cancer cases who were smokers.

Association of Hashimoto's thyroiditis with papillary thyroid cancer was first reported by Dailey *et al.* [34] in 1955. More recent studies on this topic revealed contradictory results [35,36]. There was no association between the presence of Hashimoto's thyroiditis and DTC with the distribution of *XRCC1* genotypes in our study.

In our study, we had 19 cases of DTC with a family history of thyroid cancer. Among those patients, approximately 83.0% revealed a GA genotype of the Arg280His. There was only one case with a family history of thyroid cancer in the BTN group that revealed an AA genotype of *XRCC1* Arg280His. Although the GA genotype frequency of the *XRCC1* Arg280His was highest in thyroid cancer cases, it did not appear specifically in families with thyroid cancer. Instead, it was encountered frequently in benign nodular goiter cases without a family history of known thyroid cancer. This may have been due to low penetrance alleles. However, it may also have been a consequence of low dose environmental risk for carcinogenesis in those carrying the *XRCC1* Arg280His genotype and BTN that end up with benign neoplasms of the thyroid. This issue should be studied with a sufficient number of goiter cases with a family history of thyroid cancer.

Our findings also revealed that the CC genotype of Arg194Trp polymorphism and the GG, GA and AA genotypes of the Arg399Gln polymorphisms of *XRCC1* did not play a role in thyroid carcinogenesis in our study population. This finding may not mean that these decrease the risk of DTC as stated by Akulevich *et al.* [2], but the presence of these polymorphisms may help to define a low-risk group for the development of DTC. Further well-designed studies involving larger sample sizes and considering different variables, such as gender, lifestyle, chronic thyroiditis, smoking, alcohol consumption, and radiation exposure, are needed to fully elucidate the possible roles and associations of *XRCC1* polymorphisms as DTC susceptibility markers in specific subgroups of patients.

CONCLUSIONS

Our study demonstrates that the GA genotype in the *XRCC1* Arg280His polymorphism is more frequently encountered in DTC patients than cancer-free controls. The GA genotype frequency is also rather high in DTC cases with a family history of thyroid cancer. Obesity, presence of Hashimoto's thyroiditis and smoking, which are commonly accepted as environmental risk factors for thyroid cancer, did not appear to affect tumorigenesis in the presence of the GA genotype in the *XRCC1* Arg280His polymorphism.

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Declaration of Interest. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

REFERENCES

1. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States 1973-2002. JAMA. 2006; 295(18): 2164-2167.
2. Akulevich NM, Saenko VA, Rogounovitch TI, Drozd VM, Lushnikov EF, Ivanov VK, *et al.* Polymorphisms of DNA damage response genes in radiation-related and sporadic papillary thyroid carcinoma. Endocr Relat Cancer. 2009; 16(2): 491-503.
3. Lence-Anta JJ, Xhaard C, Ortiz RM, Kassim H, Pereda CM, Turcios S, *et al.* Environmental, lifestyle, and anthropometric riskfactors for differentiated thyroid cancer in cuba: a case-control study. Eur Thyroid J. 2014; 3(3): 189-196.
4. Bashir K, Sarwar R, Fatima S, Saeed S, Mahjabeen I, Akhtar Kayani M. Haplotype analysis of XRCC1 gene polymorphisms and the risk of thyroid carcinoma. J BUON. 2018; 23(1): 234-243.
5. Matsuse M, Mitsutake N, Tanimura S, Ogi T, Nishihara E, Hirokawa M, *et al.* Functional characterization of the novel BRAF complexmutation, BRAF (V600 delinsYM), identified in papillarythyroid carcinoma. Int J Cancer. 2013; 132(3): 738-743.
6. Hu Z, Hu X, Long J, Su L, Wei B. XRCC1 polymorphisms and differentiated thyroid carcinoma risk: A meta-analysis. Gene. 2013; 528(2): 67-73.

7. Du Y, Han LY, Li DD, Liu H, Gao YH, Sun D. Associations between XRCC1 Arg399Gln, Arg194Trp, and Arg280His polymorphisms and risk of differentiated thyroid carcinoma: A meta-analysis. Asian Pac J Cancer Prev. 2013; 14(9): 5483-5487.
8. Chang-Claud J, Popanda O, Tan XL, Kropp S, Helmbold I, von Fournier D, *et al.* Association between polymorphisms in the DNA repair genes, XRCC1, APE1, and XPD and acute side effects of radiotherapy in breast cancer patients. Clin Cancer Res. 2005; 11(13): 4802-4809.
9. Zhai W, Feng R, Wang H, Wang Y. Note of clarification of data in the papertitled X-ray repair cross-complementing group 1 codon 399 polymorphism and lung cancer risk: An updated meta-analysis. Tumour Biol. 2015; 36(5): 3179-3189.
10. Bu T, Liu L, Sun Y, Zhao L, Peng Y, Zhou S, *et al.* XRCC1 Arg399Gln polymorphism confers risk of breast cancer in American population: A meta-analysis of 10846 cases and 11723 controls. PLoS One. 2014; 9(1): e86086.
11. Tian Z, Li YL, Liu JG. XRCC1 Arg399Gln polymorphism contributes to increased risk of colorectal cancer in Chinese population. Mol Biol Rep. 2013; 40(7): 4147-4151.
12. Ho T, Li G, Lu J, Zhao C, Wei Q, Sturgis EM. Association of XRCC1 polymorphisms and risk of differentiated thyroid carcinoma: A case-control analysis. Thyroid. 2009; 19(2): 129-135.
13. Chiang FY, Wu CW, Hsiao PJ, Kuo WR, Lee KW, Lin LC, *et al.* Association between polymorphisms in DNA base excision repair genes XRCC1, APE1, and ADPRT and differentiated thyroid carcinoma. Clin Cancer Res. 2008; 14(18): 5919-5924.
14. Garcia-Quispes WA, Perez-Machado G, Akdi A, Pastor S, Galofre P, Biarnes F, *et al.* Association studies of OGG1, XRCC1, XRCC2 and XRCC3 polymorphisms with differentiated thyroid cancer. Mutat Res. 2011: 709-710: 67-72.
15. Zhu QX, Bian JC, Shen Q, Pastor S, Galofré P, Zhang HW, *et al.* Genetic polymorphisms in X-ray repair cross-complementing gene 1 and susceptibility to papillary thyroid carcinoma. Zhonghua Liu Xing Bing Xue Za Zhi. 2004; 25(8): 702-705.
16. Ryu RA, Tae K, Min HJ, Jeong JH, Cho SH, Lee SH, *et al.* XRCC1 polymorphisms and risk of papillary thyroid carcinoma in a Korean sample. J Korean Med Sci. 2011; 26(8): 991-995.
17. Zhu J, Qi P, Li Z. Interaction between XRCC1 gene polymorphisms and obesity on susceptibility to papillary thyroid cancer in Chinese Han population. Cell Physiol Biochem. 2018; 49(2): 638-644.
18. Sigurdson AJ, Land CE, Bhatti P, Pineda M, Brenner A, Carr Z, *et al.* Thyroid nodules, polymorphic variants in DNA repair and RET-related genes, and interaction with ionizing radiation exposure from nuclear tests in Kazakhstan. Radiat Res. 2009; 171(1): 77-88.
19. Wang X, Zhang K, Liu X, Liu B, Wang Z. Association between XRCC1 and XRCC3 gene polymorphisms and risk of thyroid cancer. Int J Clin Exp Pathol. 2015; 8(3): 3160-3167.
20. Wang C, Ai Z. Association of XRCC1 polymorphisms with thyroid cancer risk. Tumour Biol. 2014;35:4791-7.
21. Yan L, Li Q, Li X, Ji H, Zhang L. Association studies between XRCC1, XRCC2, XRCC3 polymorphisms and differentiated thyroid carcinoma. Cell Physiol Biochem. 2016; 38(3): 1075-1084.
22. Fan J, Otterlei M, Wong HK, Tomkinson AE, Wilson DM 3rd. XRCC1 co-localizes and physically interacts with PCNA. Nucleic Acid Res. 2004; 32(7): 2193-2201.
23. Caldecott KW. XRCC1 and DNA strand repair. DNA Repair (Amst). 2003; 2(9): 955-969.
24. Hung RJ, Hall J, Brennan P, Boffetta P. Genetic polymorphism in the base excision repair pathway and cancer risk. A HuGE review. Am J Epidemiol. 2005; 162(10): 925-942.
25. Yan L, Yanan D, Donglan S, Na W, Rongmiao Z, Zhifeng C. Polymorphisms of XRCC1 gene and risk of gastric cardiac adenocarcinoma. Dis Esophagus. 2009; 22(5): 396-401.
26. Takanami T, Nakamura J, Kubota Y, Horiuchi S. The Arg280His polymorphism in X-ray repair cross-complementing gene 1 impairs DNA repairability. Mutat Res. 2005; 582(1-2): 135-145.
27. Zhang K, Zhou B, Wang Y, Rao L, Zhang L. The XRCC1 Arg280His polymorphism contributes to cancer susceptibility: An update by meta-analysis of 53 individual studies. Gene. 2012; 510(2): 93-101.
28. Qian K, Liu KJ, Xu F, Chen XY, Chen GN, Yi WJ, *et al.* X-ray repair cross-complementing group 1 (XRCC1) genetic polymorphisms and thyroid carcinoma risk: A meta-analysis. Asian Pac J Cancer Prev. 2012; 13(12): 6385-6390.
29. Yang D, Han L-Y, Li D-D, Liu H, Gao YH, Sun DJ. Associations between XRCC1 Arg399Gln, Arg194Trp, and Arg280His polymorphisms and risk of differentiated thyroid carcinoma: A meta-analysis. Asian Pac J Cancer Prev. 2013; 14(9): 5483-5487.

30. Hu Z, Hu X, Long J, Su L, Wei B. XRCC1 poly-morphisms and differentiated thyroid carcinoma risk: A meta-analysis. Gene. 2013; 528(2): 67-73.
31. Bao Y, Jiang L, Zhou JY, Zou JJ, Zheng JY, Chen XF, *et al.* XRCC1 gene polymorphisms and the risk of differentiated thyroid carcinoma (DTC): A meta-analysis of case-control studies. PLos One. 2013; 8(5): e64851.
32. Wang C, Ai Z. Association of XRCC1 polymorphisms with thyroid cancer risk. Tumor Biol. 2014; 35(5): 4791-4797.
33. Zhou W, Liu G, Miller DP, Thurston SW, Xu LL, Wain JC, *et al.* Polymorphisms in the DNA repair genes XRCC1 and ERCC2, smoking and lung cancer risk. Cancer Epidemiol Biomarkers Prev. 2003; 12(4): 359-365.
34. Dailey ME, Lindsay S, Skahen R. Relation of thyroid neoplasms to Hashimoto disease of the thyroid gland. Arch Surg. 1955; 70(2): 291-297.
35. Cheema Y, Olson S, Elson D, Chen H. What is the biology and optimal treatment for papillary microcarcinoma of the thyroid? J Surg Res. 2006; 134(2): 160-162.
36. Jankovic B, Le KT, Hershman JM. Clinical Review: Hashimoto's thyroiditis and papillary thyroid carcinoma: Is there a correlation? J Clin Endocrinol Metab. 2013; 98(2): 474-482.