The OGG1 Ser326Cys polymorphism and its association with DNA damage and DNA repair in papillary thyroid cancer

OGG1 Ser326Cys polimorfizmi ve papiller tiroid kanserindeki DNA hasarı ve DNA onarımı ile ilişkisi

Abstract

Aim: Hydrogen peroxide locally produced during thyroid hormone synthesis, leads to oxidative stress in the thyroid gland. Defective repair of oxidative DNA lesions contributes to tumor development. This study aimed to understand the importance of DNA damage and repair on thyroid cancer development through the impact of the DNA repair gene OGG1 Ser326Cys polymorphism that has clinical significance in untreated patients with papillary thyroid cancer.

Methods: The study was performed with 70 patients with papillary thyroid cancer and 73 volunteers as control. In lymphocytes, endogenous DNA damage, H_2O_2-induced DNA damage, and DNA damage after repair were determined by comet assay. The polymerase chain reaction-restriction fragment length polymorphism method was performed for OGG1 genotyping.

Results: Endogenous DNA damage, H_2O_2-induced DNA damage, and DNA damage after repair were higher in patients with thyroid cancer than in the controls (P<0.001). An association was determined between the OGG1 Cys326 allele and increased risk for the development of papillary thyroid cancer. No significant difference was determined between cases carrying different OGG1 genotypes for endogenous DNA damage, H_2O_2-induced DNA damage, and DNA damage after repair in the study groups.

Conclusions: Endogenous DNA damage and cell susceptibility to oxidation increase, and DNA repair is impaired in patients with papillary thyroid cancer. However, the OGG1 Ser326Cys polymorphism is not responsible for the DNA repair defect.

Keywords: DNA damage; DNA repair; polymorphism; thyroid neoplasm

Öz

Amaç: Tiroit hormonu sentezi sırasında lokal olarak üretilen hidrojen peroksit, tiroit bezinde oksidatif strese yol açmaktadır. Oksidatif DNA lezyonlarının kusurlu onarımı tümör gelişimine katkıda bulunur. Bu çalışmada, tedavi edilmemiş papiller tiroit kanserli hastalarda, DNA hasarı ve DNA onarımının tiroit kanseri gelişimindeki rolünün, klinik önemi olan DNA onarım geni OGG1 Ser326Cys polimorfizminin üzerinden belirlenmesi amaçlandı.

Yöntem: Çalışma papiller tiroit kanserli 70 hasta ve kontrol grubu olarak 73 gönüllü ile gerçekleştirildi. Lenfositlerde endojen DNA hasarı, H_2O_2 ile indüklenmiş DNA hasarı ve onarım sonrası DNA hasarı Comet yöntemi ile belirlendi. OGG1 genotiplemesi için polimeraz zincir reaksiyonu-kısıtlama fragman uzunluğu polimorfizmi yöntemi uygulandı.

Bulgular: Tiroit kanserli hastalarda endojen DNA hasarı, H_2O_2 ile indüklenmiş DNA hasarı ve onarım sonrası DNA hasarı kontrollere göre daha yüksekti (P<0.001). OGG1 Cys326 aleli ile papiller tiroit kanseri gelişme riskinin artması arasında bir ilişki belirlendi. Çalışma gruplarında farklı OGG1 genotipi taşıyan olgular arasında endojen DNA hasarı, H_2O_2 ile indüklenmiş DNA hasarı ve onarım sonrası DNA hasarı açısından anlamlı bir fark saptanmadı.

Sonuç: Papiller tiroit kanserli hastalarda endojen DNA hasarı ve hücrenin oksidasyona duyarlılığı artmakta, DNA onarımı bozulmaktadır. Ancak OGG1 Ser326Cys polimorfizmi DNA onarım defektinden sorumlu olmadığı gösterilmiştir.

Anahtar Sözcükler: DNA hasarı; DNA onarımı; polimorfizm; tiroid kanseri

Caglayan Akkaya Engin[1,2], Hakan Yavuzer[3], Serkan Teksoz[4], Selen Soylu[4], Meltem Mete[5], Serap Yavuzer[6], Ali Ata Tuz[7], Mehmet Guven[5], Yildiz Dincer[1]

[1] Department of Medical Biochemistry, Cerrahpasa Medical Faculty, Istanbul University-Cerrahpasa

[2] Program of Medical Laboratory Techniques, Vocational School of Health Services, Istanbul Esenyurt University

[3] Department of Internal Medicine, Faculty of Medicine, Istinye University

[4] Department of General Surgery, Cerrahpasa Medical Faculty, Istanbul University-Cerrahpasa

[5] Department of Medical Biology, Cerrahpasa Medical Faculty, Istanbul University-Cerrahpasa

[6] Department of Internal Medicine, Faculty of Medicine, Istanbul Aydın University

[7] Cerrahpasa Medical Faculty, Istanbul University-Cerrahpasa

Received/*Geliş* : 23.07.2024
Accepted/*Kabul*: 18.10.2024

DOI: 10.21673/anadoluklin.1508336

Corresponding author/*Yazışma yazarı*

Yıldız Dinçer

İstanbul Üniversitesi-Cerrahpaşa, Cerrahpaşa Tıp Fakültesi, Tıbbi Biyokimya Anabilim Dalı, İstanbul, Türkiye.
E-mail: yldz.dincer@gmail.com

ORCID

Çağlayan A. Engin: 0000-0002-1905-0775
Hakan Yavuzer: 0000-0003-2685-6555
Serkan Teksöz: 0000-0002-6733-5644
Selen Soylu: 0000-0002-1459-399X
Meltem Mete: 0000-0002-9297-8254
Serap Yavuzer: 0000-0001-7618-9987
Ali Ata Tuz: 0000-0002-9802-2317
Mehmet Güven: 0000-0002-8749-1708
Yıldız Dinçer: 0000-0002-8393-7901

INTRODUCTION

The most prevalent endocrine system cancer is thyroid cancer. Thyroid tumors develop due to point mutations frequently in Rat sarcoma (RAS) or B-Raf Proto-Oncogene, Serine/Threonine Kinase (BRAF) genes, and translocations in RET/PTC or PAX8/PPARγ genes (1, 2). The most important mutagenic factor for thyrocytes is radiation, which causes tumor development through the excessive production of reactive oxygen species (ROS). The thyroid gland produces large amounts of hydrogen peroxide (H_2O_2) to oxidize iodide for thyroid hormone biosynthesis. This creates a potentially mutagenic environment through ROS production (3, 4). By attacking DNA, ROS causes oxidative DNA damage. Base oxidation and DNA strand breaks occur due to oxidative DNA damage. The most common and harmful oxidative DNA damage is 8-hydroxydeoxyguanosine (8-OHdG). Oxidized guanine can lead to GC-TA transversion mutation (5).

DNA repair plays a pivotal role in the maintenance of genetic integrity. Defective DNA repair is a contributory factor in carcinogenesis. A low DNA repair potential is attributed to an increased risk for many cancers, including thyroid cancer (6,7). There are individual differences in cancer risk. These differences may arise from single nucleotide polymorphisms in DNA repair genes. 8-OHdG is repaired by the base excision repair system. 8-oxo-deoxyguanosine DNA glycosylase 1 (OGG1) excises 8-OHdG adducts. 8-OHdG appears in the bloodstream and is excreted in the urine (8). The Ser326Cys; rs1052133, is the most common OGG1 gene polymorphism. The polymorphic OGG1-Cys326 protein has lower enzymatic activity than the common OGG1-Ser326 protein (9). This means that more mutations may accumulate due to oxidative stress in individuals homozygous for OGG1-Cys326.

There is no study investigating the association between Ser326Cys polymorphism and OGG1 DNA damage in patients with papillary thyroid cancer. In the present study; firstly, the determination of endogenous DNA damage, susceptibility to *in vitro* oxidation by H_2O_2, and repair level after H_2O_2 treatment in patients with papillary thyroid cancer. Secondly, the influence of OGG1 Ser326Cys polymorphism on all these parameters was evaluated.

MATERIAL AND METHODS

This study was approved by Istanbul University Cerrahpasa Medical Faculty Ethics Committee (date: 02.04.2013, decision no:A-33). All individuals signed informed consent.

70 patients with papillary thyroid cancer were recruited from the Department of General Surgery, Cerrahpasa Medical Faculty Hospital. The number of samples was approximately determined with G*Power 3.1.9.7 software. Using a T-test with α error = 0.05 and a power of 1-β = 0.95, we determined that the required sample size for each study group was 71 individuals, and the total sample size was 142. Based on this calculation, we formed a control group of 73 healthy volunteers who matched our exclusion criteria and a patient group of 70 volunteers who were diagnosed with papillary thyroid cancer for the first time. All patients were newly diagnosed, and none of them had undergone anti-cancer therapy previously. The diagnosis of thyroid cancer was based on ultrasound and fine-needle aspiration and confirmed by the pathology reports after resection of the tumors. The control group was composed of 73 patients who were age and gender-matched, had no history of cancer, and had no family history of any cancer. Patient and control features are presented in Table 1. Subjects with acute or chronic inflammatory diseases, infectious diseases, liver and kidney dysfunction were excluded from the study. None of the study cases were smokers and were taking antioxidant supplements.

Lymphocyte isolation

Blood samples were taken into heparinized tubes by venipuncture before the surgical operation. Lymphocyte isolation was performed immediately. For isolation, gradient density centrifugation was performed using histopaque 1077 (Sigma-Aldrich 10771, Germany). The collected lymphocytes were washed with phosphate-buffered saline solution and then suspended in Roswell Park Memorial Institute medium (RPMI 1640) (Sigma-Aldrich 10771, Germany) containing 10% dimethyl sulfoxide (DMSO) (Sigma-Aldrich 10771, Germany) and 60% fetal bovine serum (FBS) (Sigma-Aldrich 10771, Germany). The trypan blue exclusion assay evaluated cell viability (10).

Endogenous DNA damage

Endogenous DNA damage in lymphocytes was evaluated for strand breaks by applying the comet assay as described previously (11). In brief, the cells mixed with low-melting-point agarose were placed on the agarose gel layer on a microscope slide. The lysis was performed with non-ionic detergent and hypertonic lysis solution. After washing steps, the microscope slide was treated with a high alkaline solution (pH > 11) to unwind supercoiled loops.

Strand breaks appear alkali labile sites. Subsequently, electrophoresis was carried out. The breaks migrated towards the anode, giving a comet-tail appearance, whereas undamaged DNA remained within the comet head. Comet images were visualized using the fluorescent staining method. After staining with ethidium bromide, comet images were detected with a camera-equipped fluorescence microscope (Olympus BX51T-32H01). Tail moments were measured with the image analysis software package (Metasystems, Germany). Two slides were studied for each case. A single observer blinded to the subject's diagnosis scrutinized 50 randomly selected cells on each slide (100 cells in total). The tail moment, which is the product of the tail length and the percentage of total DNA in the tail, was used to express the DNA damage.

H_2O_2-induced DNA damage and DNA damage after repair

As is customary in the comet assay, cells were implanted in an agarose layer on two distinct microscope slides to assess H_2O_2-induced DNA damage and DNA damage after repair. The slides were incubated on ice with 50 mM H_2O_2 in phosphate-buffered saline solution for 40 min. The slides were washed to remove H_2O_2 and then put into lysis solution. After washing one of the slides were treated with OGG1 enzyme a damage-specific repair endonuclease for 1 hour at 37°C, whereas latter was not threated. This enzyme generates additional breaks at sites containing 8-OHdG. After the enzyme treatment the slides were washed, electrophoresis was applied as previously mentioned.

Every slide was produced twice for every case. For every slide, the mean values of the tail moment of the cells were computed for every research group.

Genotyping of OGG1 codon 326

A Nucleo-Spin DNA purification kit (Macherey–Nagel GmbH, Duren, Germany) was used to extract genomic DNA from lymphocytes. The OGG1 Ser326Cys polymorphism was determined by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method, as previously described (12). The sequences of the primers were HOGG1F:5'-GGAAGGTGCTTGGGGAAT-3' and HOGG1R:5'-ACTGTCACTAGTCTCACCAG-3'. The amplification process involved a 5-minute denaturation at 95°C, followed by 30 cycles of 95°C for 30 seconds, 58°C for 30 seconds, and 72°C for 1 minute each. After the reaction, a 7-minute incubation step at 72 °C was added. The PCR product is 200 bp long and digested with SatI at 37 °C for 16 hours, yielding a single 200-bp band for the homozygous Ser/Ser hOGG1 variant, a single 100-bp band for the homozygous Cys/Cys hOGG1 variant, and double bands of 200 and 100 bp for the heterozygous Ser/Cys hOGG1 variant. The fragments were separated using a 3% high-resolution metaphor agarose gel. Figure (Figure 1) illustrates the gel showing the genotypes of OGG1 Ser326Cys. Finally, the PCR-RFLP results were validated using the real-time PCR method.

Statistical analysis

IBM Statistical Package for the Social Sciences package program version 22.0 (SPSS Inc., Chicago, IL, USA) for Windows was used for statistical analysis. Because the data were not normally distributed, variables were reported as median (min-max). The measured parameters in the thyroid cancer and control groups were compared with the Mann-Whitney U test. The differences between endogenous DNA damage, H_2O_2-induced DNA damage, and DNA damage after repair in each group were compared with the Kruskal-Wallis test. Then, binary data were compared with the Mann-Whitney U test. The Pearson Chi-Square or Fisher's exact tests (two-sided) were used to determine the relationship between genotypes and alleles in the control and thyroid cancer groups and the deviation of genotype distribution from the Hardy–Weinberg equation. The combined odds ratio (OR) with a 95% confidence interval (95% CI) was calculated to assess the asso-

ciation between the thyroid cancer risk and the Ser-326Cys genotype of the OGG1 gene. Spearman correlation coefficient was used to examine correlations between the variables. The P value less than 0.05 was considered statistically significant.

RESULTS

As shown in Table 2, endogenous DNA damage, H_2O_2-induced DNA damage, and DNA damage after repair in peripheral lymphocytes of patients with thyroid cancer were found to be higher than those in the controls ($p<0.001$). The representative images of patients from the comet assay with their corresponding controls are shown in Figure 2. The Hardy-Weinberg equilibrium was observed in the dispersion of OGG1 Ser326Cys genotypes between thyroid cancer patients and controls ($p>0.05$). Significant differences existed between patients with thyroid cancer and control cases for the genotype distribution and allele frequencies. The distribution of OGG1 Ser326Cys genotypes in the thyroid cancer and control groups is given in the Table 3. OGG1-Cys326 allele and genotypes carrying this allele (Ser326Cys+Cys326Cys) were found to be associated with an increased risk for the development of papillary thyroid cancer. Neither in the patients with thyroid cancer nor the control group, a significant difference was determined between the OGG1 Ser326Cys genotypes for endogenous DNA damage, H_2O_2-induced DNA damage, and DNA damage after repair (Table 4).

No significant correlation exists between thyroids hormones (T3, T4, TSH) and endogenous DNA damage, H_2O_2-induced DNA damage, and DNA damage after repair.

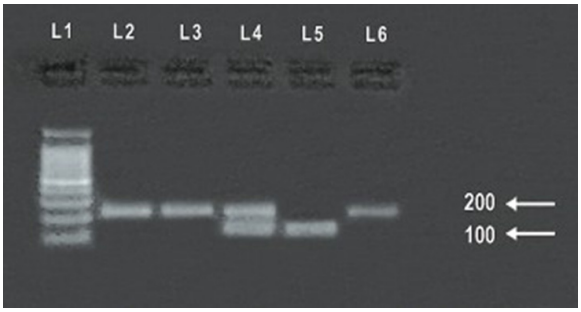

Figure 1. An illustration of the OGG1 Ser326Cys genotypes on the gel. For the 326Cys variation, the 200-bp PCR product is broken down into two 100-bp fragments by Fnu4HI, while the 326Ser allele remains undigested. Lane 1, 100-bp ladder size marker; Lane 2 and Lane 3, a Ser/Ser homozygote; Lane 4, a Ser/Cys heterozygote; Lane 5, a Cys/Cys homozygote; Lane 6, undigested products of PCR.

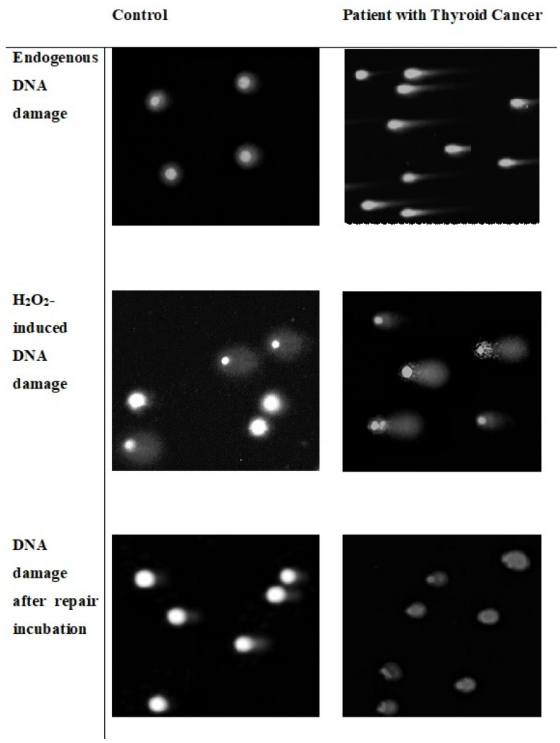

Figure 2. Representative comet assay images show endogenous DNA damage, H_2O_2-induced DNA damage, and DNA damage after repair in the control and patients with thyroid cancer.

DISCUSSION

The thyroid gland may be exposed to more oxidative stress than other tissues. Because a high level of H_2O_2 is produced in the thyroid gland to act as a co-substrate in hormone biosynthesis. H_2O_2 is produced in the thyroid by one or two NADPH oxidases at the apical membrane of thyrocytes to oxidize iodide and then incorporate it into the thyroglobulin (3,13). On the other hand, H_2O_2 acts as an oxidant and induces the formation of ROS that constitute a potentially mutagenic environment in thyrocytes, leading to cancer development (4,14). Therefore, an efficient DNA repair is essential to prevent oxidative damage-induced mutagenesis in the thyroid gland. Unfortunately, compared to other tissues, thyroid tissue detected an 8-10-fold higher spontaneous mutation rate (15). This brings to mind defective DNA repair in thyrocytes. Masha et al.

Table 1. Demographic and clinical data of the study groups.

		Thyroid Cancer Group (n:70)	Control Group (n:73)	p
Age (year)		49 (24-79)	54 (20-69)	0.060
Gender	Men	15	23	
	Women	55	50	
T3 (pg/mL)		3.22 (0.26-4.25)[a]	1.20 (0.86-3.17)	0.000
T4 (ng/dL)		1.21 (0.05-2.54)	1.23 (0.98-1.60)	0,540
TSH (µU/ml)		1.84 (0.01-100.00)	2.13 (0.50-10.46)	0.096

[a] versus control group

T3: Triiodothyronine, T4: Tetraiodothyronine, TSH: Thyroid stimulating hormone, n: Number

Table 2. Endogenous DNA damage, H_2O_2-induced DNA damage, and DNA damage after repair in the study groups.

	Thyroid Cancer Group (n:70)	Control Group (n:73)	p
Endogenous DNA damage (Tail Moment)	0.81 (0.36-1.63)[a]	0.32 (0.19-2.12)	0.000
H_2O_2-induced DNA damage (Tail Moment)	2.36 (0.91-5.70)[b]	1.81 (1.46-4.19)	0.003
DNA damage after repair (Tail Moment)	1.03 (0.43-1.83)[a]	0.52 (0.29-0.76)	0.000

[a] versus control group, [b] versus control group, n: Number

Table 3. Distribution of allele and genotype frequency of OGG1 Ser326Cys polymorphism in the study groups.

	Thyroid Cancer Group n (%)	Control Group (n%)	OR(95% CI)	p
OGG1-326				
Ser/Ser	30(43%)	44(60%)	Reference	
Ser/Cys +Cys/Cys	40(57%)	29(40%)	2.02(1.04-3.94)	0.037
Ser allele frequency	0.43	0.60	Ref	
Cys allele frequency	0.57	0.40	1.99(1.13-3.49)	0.016

Ser: Serine, Cys: Cysteine, OGG1: 8-oxo-deoxyguanosine DNA glycosylase 1, OR: odds ratio, n: Number

Table 4. Endogenous DNA damage, H_2O_2-induced DNA damage, and DNA damage after repair according OGG1 Ser326cys genotypes.

	Endogenous DNA damage	H_2O_2-induced DNA damage	DNA damage after repair
Control Group			
Ser/Ser (n=44)	0.31 (0.19-0.40)	1.79 (1.49-4.19)	0.46 (0.21-0.76)
Ser/Cys+Cys/Cys (n=29)	0.32 (0.19-0.39)	1.82 (1.66-2.08)	0.49 (0.29-0.74)
p*	0.760	0.800	0.960
Thyroid Cancer Group			
Ser/Ser (n=30)	0.72 (0.40-1.56)	2.09 (1.26-4.36)	1.01 (0.55-1.83)
Ser/Cys+ Cys/Cys (n=40)	0.83 (0.360-1.630)	2.50 (0.91-5.70)	1.04 (0.43-1.53)
p*	0.630	0.250	0.640

* p values in each set refer to comparisons between cases with Ser/Ser and Ser/Cys+ Cys/Cys genotypes. Ser: Serine, Cys: Cysteine

(7) reported mismatch repair deficiency in papillary thyroid tumors. Karger et al. (16) determined downregulated DNA repair genes (OGG1, Mut Y homolog (MUTYH), and endonuclease III) and increased 8-OxoG in the nucleus of follicular thyroid carcinoma, compared with follicular adenoma. They suggested that oxidative stress and consequent transcriptional dysregulation in thyrocytes cause mismatch repair deficiency and potentiate papillary thyroid tumorigenesis. Similarly, we discovered in the current study that thyroid cancer patients had reduced *in vitro* repair of DNA damage caused by H_2O_2 treatment in peripheral lymphocytes compared to controls.

DNA repair deficiency may be derived from single nucleotide polymorphisms in DNA repair genes. The OGG1 Ser326Cys polymorphism was reported to modulate repair activity. Aka et al. (17) demonstrated that after challenging with 2 Gy of γ-rays, DNA strand break capacity is slower in peripheral blood lymphocytes of individuals with Ser/Cys or Cys/Cys OGG1 genotypes compared to those with the Ser/Ser OGG1 genotype. These findings agree with other studies. A higher level of DNA strand breaks was detected in the lymphocytes of agricultural workers exposed to pesticides (18) and male workers exposed to cobalt (19) in the presence of the OGG1 326Cys allele. The OGG1 Ser326Cys polymorphism has been widely evaluated in various case-control studies on cancer. Most studies examined the association between OGG1 Ser326Cys polymorphism increases/decreases cancer risk. OGG1 Cys326 allele was found to be associated with an increased risk of nasopharyngeal, esophageal, lung, stomach, prostate, and cervical cancers (20-25). As far as we know, only two groups investigated a potential association between OGG1 Ser326Cys polymorphism and thyroid cancer risk (26,27), and their results did not reveal a significant association. However, their findings were not evidenced by functional studies. None of the previous studies investigated the impact of OGG1 Ser326Cys polymorphism on DNA damage level or DNA repair activity in patients with thyroid cancer. Only García-Quispes et al. (28) examined a functional relationship between OGG1 Ser326Cys polymorphism. They looked into how various DNA repair gene polymorphisms (OGG1, XRCC1, XRCC2, and XRCC3) affected the frequency of micronuclei (MN) in the lymphocytes of a sample of thyroid cancer patients, both spontaneously and through stimulation. They stated that only OGG1 Ser326Cys polymorphism is able to affect MN frequency. It should be noted that this impact was seen only at the spontaneous MN frequency and not at the MN frequency caused by treating lymphocytes with 0.5 Gy of γ-radiation. In our study, although the OGG1 Cys326 allele was found to be associated with an increased risk for the development of papillary thyroid cancer, no significant impact of the OGG1 Cys326 allele were observed on endogenous DNA damage, H_2O_2-induced DNA damage, and DNA damage after repair. The lack of influence of the OGG1 Cys326 allele on DNA damage and repair can be attributed to extensive functional interactions between DNA repair proteins and overlapping specificity within the same repair pathway (29,30). The existing DNA damage may be repaired by an enzyme other than OGG1, and this repair may be deficient, so we observed high DNA damage. Alternatively, DNA repair capacity may be exceeded due to intensive damage. As a limitation of this study, we mainly focused on a DNA repair deficiency, so the requirement of measurement of antioxidant activity in the study groups escaped from our notice. Besides, the small number of study cases is another limitation of this study.

CONCLUSION

In the present study, we demonstrated for the first time that repair of DNA strand breaks is impaired in patients with papillary thyroid cancer, as evidenced by high endogenous DNA damage and high DNA damage after *in vitro* repair. The increased H_2O_2-induced DNA damage in the patients is also a novel finding and reflects an increased susceptibility to oxidation. Increased cell susceptibility to oxidation may occur due to defective antioxidant defense. Finally, this was a functional study to explain the possible role of DNA repair in the development of papillary thyroid cancer. We concluded that oxidative DNA damage and DNA repair deficiency may be critical events in thyroid tumorigenesis, but DNA repair gene OGG1 Ser326Cys polymorphism does not influence this pathogenic event.

Conflict-of-interest and financial disclosure

The authors declare that they have no conflict of interest to disclose. This study was supported and funded by the Istanbul University Scientific Research Projects Unit. (Project No: 31271).

REFERENCES

1. Kroll TG, Sarraf P, Pecciarini L, Mueller E, Spiegelman BM, Fletcher JA. PAX8-PPAR gamma1 fusion oncogene in human thyroid carcinoma (corrected). Science. 2000; 289(5483):1357-60.
2. Fagin JA. Minireview: branded from the start-distinct oncogenic initiating events may determine tumor fate in the thyroid. Mol Endocrinol. 2002; 16(5):903-11
3. De Deken X, Wang D, Dumont JE, Miot F. Characterization of ThOX proteins as components of the thyroid H(2) O(2)-generating system. Exp Cell Res. 2002;273(2):187-96.
4. Krohn K, Maier J, Paschke R. Mechanisms of Disease: hydrogen peroxide, DNA damage and mutagenesis in the development of thyroid tumors. Nat Clin Pract Endocrinol Metab. 2007;3(10):713–20.
5. Cooke MS, Evans MD, Dizdaroglu M, Lunec J. Oxidative DNA damage: mechanisms, mutation, and disease. FASEB J. 2003;17(10):1195-214.
6. Kiwerska K, Szyfter K. DNA repair in cancer initiation, progression, and therapy-a double-edged sword. J Appl Genet. 2019;60(3-4):329-334.
7. Javid M, Sasanakietkul T, Nicolson NG, et al. DNA Mismatch Repair Deficiency Promotes Genomic Instability in a Subset of Papillary Thyroid Cancers World J Surg. 2018;42(2):358-66.
8. Bruner SD, Norman DP, Verdine GL. Structural basis for recognition and repair of the endogenous mutagen 8-oxoguanine in DNA. Nature. 2000;403(6272):859-66.
9. Kershaw RM, Hodges NJ. Repair of oxidative DNA damage is delayed in the Ser326Cys polymorphic variant of the base excision repair protein OGG1. Mutagenesis. 2012;27(4):501-10.
10. Strober W. Trypan blue exclusion test of cell viability. Curr Protoc Immunol. 2001; Appendix 3:Appendix 3B.
11. Dincer Y, Kankaya S. Comet Assay for Determining of DNA Damage: Review. Türkiye Klin J Med Sci. 2010;30:1365-73.
12. Sugimura H, Kohno T, Wakai K, et al. hOGG1 Ser-326Cys polymorphism and lung cancer susceptibility. Cancer Epidemiol Biomark Prev. 1999;8(8):669-74.
13. Janik J, Czarnocka B. Oxidative DNA damage and repair in thyroid gland. Borgis-Postępy Nauk Medycznych 2011;24:950-6.
14. Stone JR, Yang. Hydrogen peroxide: a signaling messenger. Antioxid Redox Signal. 2006;8(3-4):243-70.
15. Maier J, van Steeg H, van Oostrom C, Karger S, Paschke R, Krohn K. Deoxyribonucleic acid damage and spontaneous mutagenesis in the thyroid gland of rats and mice. Endocrinology 2006;147(7): 3391-7.
16. Karger S, Krause K, Engelhardt C, et al. Distinct pattern of oxidative DNA damage and DNA repair in follicular thyroid tumours. J Mol Endocrinol. 2012;48(3):193–02.
17. Aka P, Mateuca R, Buchet JP, Thierens H, Kirsch-Volders M. Are genetic polymorphisms in OGG1, XRCC1 and XRCC3 genes predictive for the DNA strand break repair phenotype and genotoxicity in workers exposed to low dose ionising radiations? Mutat Res. 2004;556(1-2):169-81.
18. Rohr P, da Silva J, Erdtmann B, et al. BER gene polymorphisms (OGG1 Ser326Cys and XRCC1 Arg194Trp) and modulation of DNA damage due to pesticides exposure. Environ Mol Mutagen. 2011;52(1):20-7.
19. Mateuca R, Aka PV, De Boeck M, Hauspie R, Kirsch-Volders M, Lison D. Influence of hOGG1, XRCC1 and XRCC3 genotypes on biomarkers of genotoxicity in workers exposed to cobalt or hard metal dusts. Toxicol Lett. 2005;156(2): 277-88.
20. Janik J, Swoboda M, Janowska B, et al. 8-Oxoguanine incision activity is impaired in lung tissues of NSCLC patients with the polymorphism of OGG1 and XRCC1 genes. Mutat Res. 2011;709-710: 21-31.
21. Takezaki T, Gao CM, Wu JZ, et al. hOGG1 Ser(326) Cys polymorphism and modification by environmental factors of stomach cancer risk in Chinese. Int J Cancer. 2002;99(4):624-7.
22. Chen L, Elahi A, Pow-Sang J, Lazarus P, Park J. Association between polymorphism of human oxoguanine glycosylase 1 and risk of prostate cancer. J Urol. 2003;170(6 Pt 1):2471-4.
23. Cho EY, Hildesheim A, Chen CJ, et al. Nasopharyngeal carcinoma and genetic polymorphisms of DNA repair enzymes XRCC1 and hOGG1. Cancer Epidemiol Biomarkers Prev. 2003;12(10):1100-4.
24. Xing DY, Tan W, Song N. Ser326Cys polymorphism in hOGG1 gene and risk of esophageal cancer in a Chinese population. Int J Cancer. 2001;95(3):140-3.
25. Niwa Y, Matsuo K, Ito H, Hirose K, Tajima K, Nakanishi T, et al. Association of XRCC1 Arg399Gln and OGG1 Ser326Cys polymorphisms with the risk of cervical can-

cer in Japanese subjects. Gynecol Oncol. 2005;99(1):43-9.
26. García-Quispesa WA, Pérez-Machadoa G, Akdia A, et al. Association studies of OGG1, XRCC1, XRCC2 and XRCC3 polymorphisms with differentiated thyroid cancer. Mutat Res. 2011;709-710:67-72.
27. Santos LS, Branco SC, Silva SN, et al. Polymorphisms in base excision repair genes and thyroid cancer risk. Oncol Rep. 2012;28(5):1859-68.
28. García-Quispes WA, Pastor S, Galofré P, et al. Influence of DNA-repair gene variants on the micronucleus frequency in thyroid cancer patient. Mutat Res. 2013;750(1-2):34-9.
29. Altieri F, Grillo C, Maceroni M, Chichiarelli S. DNA damage and repair: from molecular mechanisms to health implications. Antiox Redox Signal. 2008;10(5):891-937.
30. Iarmarcovai G, Bonassi S, Botta A, Baan RA, Orsière T. Genetic polymorphisms and micronucleus formation: a review of the literature. Mutat Res. 2008;658(3):215-33.