RESEARCH ARTICLE

Editorial Process: Submission:01/22/2020 Acceptance:12/17/2022

Assessment of *hOGG1* Genetic Polymorphism (rs1052133) and DNA Damage in Radiation-Exposed Workers

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Abstract

Objective: The aim of this study was to assess the effect of radiation exposure, human 8-oxoguanine DNA N-glycosylase-1 (*hOGG1*) exon 7 genetic polymorphism and confounding factors on DNA damage response. **Methods:** Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) and alkaline Comet assay method were applied to determine the *hOGG1* genetic polymorphisms and DNA damage response. A total of 80 participants were enrolled in this study, consisting of 40 radiation-exposed workers as a case group and 40 non-radiation workers as a control group. **Result:** The genotypes frequencies for controls were Ser/Ser (35%), Ser/Cys (32.5%), and Cys/Cys (32.5%), with frequencies of alleles being 326Ser (0.52) and 326Cys (0.48), whereas the genotypes frequencies for radiation-exposed workers (cases group) were Ser/Ser (17.5%), Ser/Cys (57.5%), and Cys/Cys (25%), with frequencies of alleles being 326Ser (0.46) and 326Cys (0.54). The results indicated that DNA damage response were not significantly higher in the exposed workers than in controls (22.55 ± 6.02 versus 21.72 ± 7.14; P=0.58). The time of exposure has a significantly negative correlation with comet tail length value among radiation workers. In addition, it was found that the DNA damage response was strongly associated with age and time of exposure with a decrease of 0.6 percent (P-value: 0.008) and 0.58 percent (P-value: 0.009), respectively. Whereas gender, smoking habit, and equivalent dose were not correlated with DNA damage. **Conclusion:** The single-nucleotide polymorphism of *hOGG1* exon 7 (rs1052133) demonstrated no association with the extent of DNA damage in radiation-exposed workers.

Keywords: DNA damage- radiation-exposed workers- genetic polymorphism- *hOGG1* exon 7- alkaline comet assay

Asian Pac J Cancer Prev, **23 (12)**, 4005-4012

Introduction

Throughout the years, ionizing radiation have been used in medical fields, especially in radiotherapy and radiodiagnostics, industries, and research for more than a century after the discovery of X-rays by Roentgen in 1895 (Donya et al., 2014). The safety side always takes precedence in the use, and application of radiation, especially gamma radiation exposure. The gamma rays can penetrate the nucleus and lead to deoxyribonucleic acid (DNA) found in the nucleus. This will cause ionization of the nucleotide and sugar bases, so generated the DNA damage (Reisz et al., 2014).

Radiotherapy is known to play a role in treating several cancers such as prostate cancer, lung cancer, bone cancer, skin cancer, bladder cancer and breast cancer [Dracham et al., 2018; Berrington de Gonzales et al., 2015; Maciejczyk et al., 2014; Felice et al., 2017; McGregor et al., 2015; Zhang et al., 2015; Grantzau et al., 2015). Furthermore, radiotherapy has a detrimental effect on patients with cancer as well as radiation workers. The levels of responses to radiation-induced DNA damage depend on many factors, such as lifestyle, genetic predisposition, inflammatory responses, age, oxidative stress, and gene variants (Yao et al., 2018; Surniyantoro et al., 2018; Hernandez et al., 2015). Therefore, it is important to analyze the adverse effect of ionizing radiation to DNA damage based on comet assay measurement.

The human 8-oxoguanine DNA N-glycosylase-1 (*hOGG1*) is the most important DNA repair enzyme in repairing DNA damage due to free radicals through base excision repair (BER) pathways (Sebera et al., 2017). This enzyme is encoded by *hOGG1* gene which is located on chromosome 3p25.3. The *hOGG1* is a DNA repair enzyme that secretes 7,8-dihydro-8-oxoguanine (8-oxoG) from DNA (Kang et al., 2017). The single nucleotide

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polymorphism occurs due to the change of cytosine to guanine in base position of 6,802 exon 7 and cause an amino acid substitution from serine into cysteine at codon number of 326. It can be written as Ser326Cys (Zou et al., 2016; Alanazi et al., 2017). The *hOGG1*-326Cys (rs1052133) mutant allele has been reported to have a relationship with the risk of developing various cancers. However, no information is available regarding cancer deaths, other causes of deaths, and modulation by food (Corella et al., 2018). Many studies have described the effect of the Ser326Cys polymorphism of the *hOGG1* gene on cancer susceptibility (Peng et al., 2014; Azevedo et al., 2017; Yuzefovych et al., 2016).

The comet assay is a relatively simple tool, but it is more sensitive than other DNA damage assay, economical in use and well validated to measure strand damage in a single cell. It allows to determine the level of DNA damage and repair in non-dividing nucleated cells (Chernigina et al., 2016). The advantages of the comet assay compared to other tests (PCR, HPLC, Micronuclei assay, FCM, immunological assay, etc.) are that it can detect DNA damage in individual apoptotic cells and distinguish between apoptosis and necrosis in the cells (Fahim et al., 2017).

The study was aimed to assess the effect of radiation exposure on DNA damage response. In the present study, genotype frequencies and confounding factors, i.e. gender, age, smoking status, time of exposure, and an equivalent dose of ionizing radiation were compared for their ability to detect DNA damage in radiation-exposed workers by alkaline comet assay.

Materials and Methods

Study Population

The present study was a case-control study. Research ethics approval was obtained from the National Commission on Ethics of Health Research, Agency for Health Research and Development, Ministry of Health, Indonesia, Number LB.02.01/2/KE.132/2018. A total of 80 participants were enrolled in this study, consisted of 40 radiation-exposed workers as a case group and 40 non-radiation workers as a control group.

All of the participants in the case group are radiation workers (radiographers, radiologists, doctors, nurses, and Cathlab technicians) from several hospitals in Indonesia While the participants in the controls group were obtained from administration staff who had never been occupationally exposed to ionizing radiation. Questionnaires were given to the participants to find out complete information about gender, age, smoking habit, time of exposure, equivalent dose and other information needed in this study. Each of the participants was briefed about the protocol, with specific information about the comet assay, the purpose of the study and signed informed consent. The characteristics of the study population are shown in Table 1.

Blood Sampling and Genomic DNA Extraction

Whole blood samples (10 mL) were obtained from participants (cases and controls) and taken to the Molecular Radiobiology laboratory, Center for Technology of Safety Radiation and Metrology, National Nuclear Energy Agency of Indonesia, Jakarta for extraction process. The genomic DNA was extracted from whole blood using the Genomic DNA Purification kit (Geneaid) according to the kit's instruction. Furthermore, the obtained genomic DNA was stored at -20°C until further analysis.

Detection of hOGG1 exon 7 (rs1052133) Single-Nucleotide Polymorphisms (SNPs)

The detection process of *hOGG1* exon 7 SNPs was carried out using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) as previously described by Nishank et al. (2015) with modification. The forward primer was 5'- TTG CCT TCG GCC CTG TTC CCC AAG GA-3' and the reverse primer was 5'-TTG CTG GTG GCT CCT GAG CAT GGC CG-3'. The PCR reactions were performed with an initial denaturation at 95°C for 2 min, followed by 35 cycles at 94°C (denaturation) for 30 s, 65.5°C (annealing) for 30 s and 72°C (extension) for 45 s, and 72°C (final extension) for 5 min. After the amplification process using GeneAmp® PCR System 9700 (Applied Biosystems), PCR products were restricted using 5 U of MspI restriction enzyme (BioLabs, Inc.) at 37°C for 4 h and electrophoresed on a 2% of agarose gel and stained with ethidium bromide.

The resulting DNA bands can be visualized under UV lights using Gel DocTM XR+ Imaging System (BioRad). The wild-type Ser/Ser genotype for codon 326 was determined by the presence of a single band at 168 bp, the heterozygous mutant Ser/Cys genotype was determined by the presence of two bands at 168 and 142 bp, while the homozygous mutant Cys/Cys genotype was determined by the presence of 142 bp.

Alkaline Comet Assay

DNA damage evaluation was carried out by the alkaline comet assay technique under suitable alkaline conditions by Pu et al., (2015). A total of 10 µl lymphocyte samples were added with 70 µl of low melting point agarose (Sigma Aldrich). A total of 70 µl of the sample mixture dripped on glass preparations that have been coated with normal melting agarose (Sigma Aldrich). The preparations are soaked for 1 hour at 4°C in a lysis solution (2.5 M NaCl, 100 mM Na2EDTA, 10 mM Tris-HCl, adjusted to pH 10 with NaOH (Sigma Aldrich) and added 1% Triton X-100 (Sigma Aldrich) and 10% dimethyl sulfoxide (Sigma Aldrich). Furthermore, object-glass are placed horizontally in an electrophoresis tank, filled by electrophoresis buffer (300 mM NaOH/1 mM EDTA, pH 13.0) and allowed to stand for 20 minutes. Then the electrophoresis process is carried out at 25 V, 300 mA for 20 minutes. After electrophoresis, the samples neutralized in a neutral solution (PBS, pH 7.4, 3 times, 5 minutes). Samples were fixed with absolute methanol and were stained with ethidium bromide. All of the procedures were performed in dark conditions to avoid samples damage caused by light.

Statistical Analysis

The statistical data analysis was calculated with

SPSS version 16.0 for Windows. Data were displayed as mean ± standard deviation (SD). A Kolmogorov-Smirnov test was used to determine data distribution. The data were in the normal distribution if had a P-value > 0.05. An independent sample T-test was used to examine the mean of comet tail length difference between cases and controls group and to test a significant relationship between comet tail length and each of genotypes. Linear regression-correlation analysis was performed to assess the relationship between time of exposure, equivalent dose, and comet tail length in radiation-exposed workers. Poisson regression analysis was applied to evaluate the influence of gender, age, smoking habit, time of exposure, and equivalent dose of ionizing radiation to the DNA damage in the whole population and in both groups separately. The Hardy-Weinberg equilibrium was calculated using the Chi-square test. The significance threshold in the present study was set at P < 0.05.

Results

The strength and novelty of the present study is the assessment of the DNA damage response by using alkaline comet assay to measure comet tail length as a biomarker of DNA damage response. The data were combined and were linked with the genotype distribution of *hOGG1* single nucleotide polymorphism. The confounding factors of the study population, i.e. gender, age, smoking status, time of exposure, and an equivalent dose of ionizing radiation were compared for their ability to influence the DNA damage in radiation-exposed workers, as well as the controls group. Most of the previous studies have examined the role of *hOGG1* in cancer patients but not in healthy people who work with radiation exposure. Thus, this is the first study of *hOGG1* single

Table 1. Characteristics in the Study Population that Can Affect the Increase in DNA Damage.

Parameter	Controls Group	Cases Group	Total
Sample size (n)	40	40	80
Age (years)			
Mean ± SD	40.55 ± 10.59	46.23 ± 8.84	43.39 ± 10.16
Range	23-58	27-63	23-63
Gender			
Male (%)	23 (57.5)	15 (37.5)	38 (47.5)
Female (%)	17 (42.5)	25 (62.5)	42 (52.5)
Smoking habit			
Yes (%)	10 (25)	4 (10)	14 (17.5)
No (%)	30 (75)	36 (90)	66 (82.5)
Time of exposure (years)			
Mean ± SD	-	14.55 ± 7.73	-
Range		Feb-33	
Equivalent dose (mSv)			
Mean ± SD	-	2.20 ± 1.32	-
Range		0.62-6.49	

Table 2. Genotypes and Alleles Frequencies of Ser326Cys (rs1052133) in the Study Population

	N	%	Controls (n=40)	Cases (n=40)	P value
	80				
Genotype					
Ser/Ser	21	26.25	14 (35%)	7 (17.5%)	0.06
Ser/Cys	36	45	13 (32.5%)	23 (57.5%)	
Cys/Cys	23	28.75	13 (32.5%)	10 (25%)	
Allele					0.53
326Ser			0.52	0.46	
326Cys			0.48	0.54	

Note: The Chi-square's P value is 0.06 and 0.53. It means that the genotypes and alleles distribution of study population is in the Hardy-Weinberg Equillibrium (P>0.05).

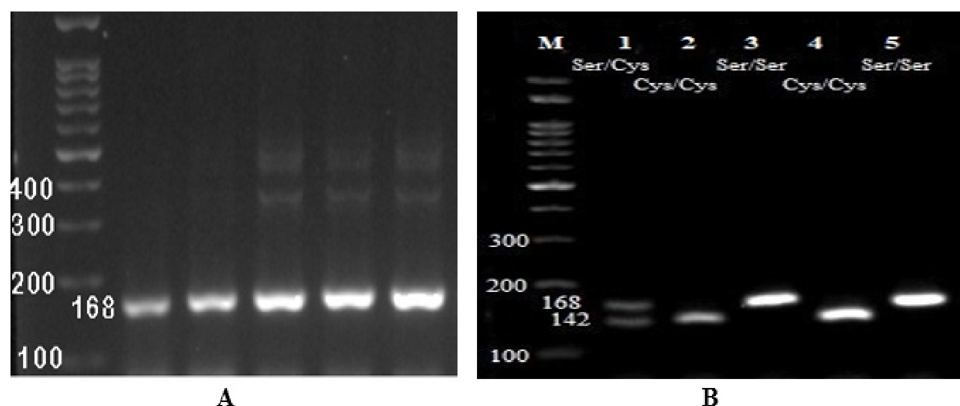

Figure 1. A. The original fragment of PCR product before restriction (168 bp). B. The digestion of PCR product with MspI generates two bands of 168 and 142 bp indicate Ser/Cys (lane 1), single band of 142 indicates Cys/Cys (lane 2 and 4), single band of 168 indicates Ser/Ser (lane 3 and 5), while lane M is DNA ladder/marker.

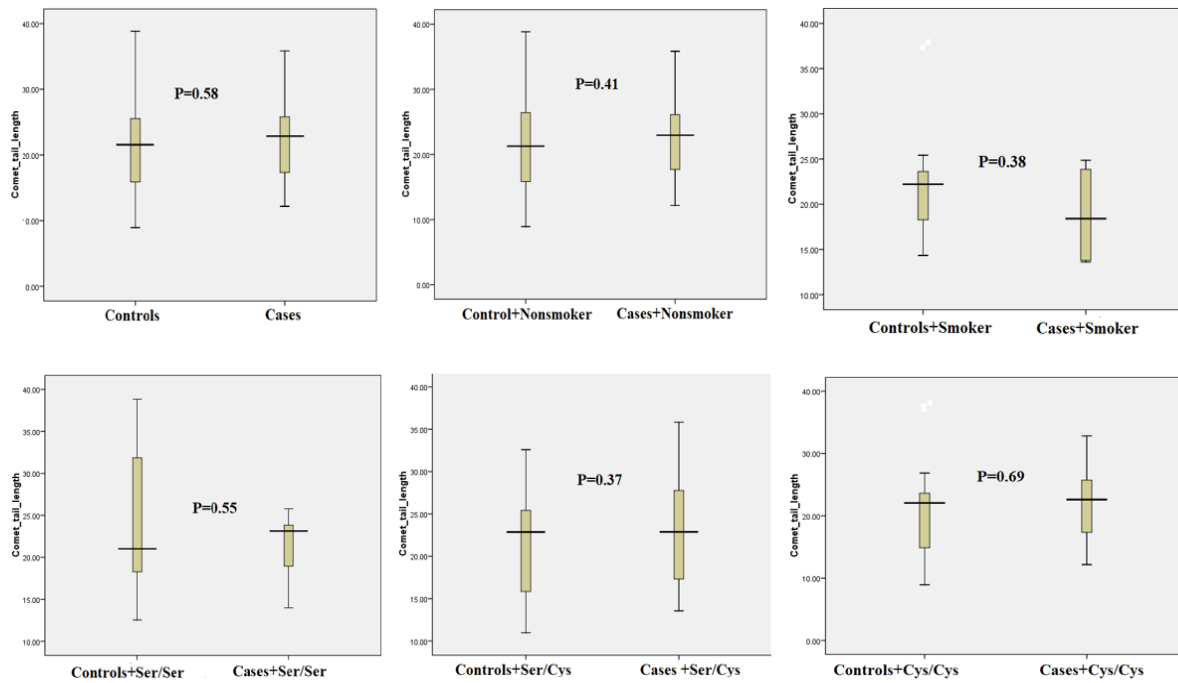

Figure 2. DNA Damage Response (Comet Tail Length) of Controls and Radiation-Exposed Workers According to Smoking Habit, *Ser/Ser, Ser/Cys*, and *Cys/Cys* Genotypes. Box plots of comet tail length were measured in all of participants by alkaline comet assay. The box delimits the 25th and 75th percentiles and the horizontal-thick line inside the box indicate the median. The mean expression values are indicated with squares. The vertical-thick lines indicate the interval between the 5th and 95th percentiles. Significant differences were calculated using an independent sample T-test.

nucleotide polymorphism effects and susceptibility in radiation-exposed workers in Indonesia.

Genotype and Allele Distribution

The genotypes and alleles distribution in the present study are consistent with the Hardy-Weinberg equilibrium for all the SNPs studied, both in controls and cases group, as shown in Table 2 and the genotyping results are shown in Figure 1. The genotypes frequencies for controls were Ser/Ser (35%), Ser/Cys (32.5%), and Cys/Cys (32.5%), with frequencies of alleles being 326Ser (0.52) and 326Cys (0.48), whereas the genotypes frequencies for radiation-exposed workers (cases group) were Ser/Ser (17.5%), Ser/Cys (57.5%), and Cys/Cys (25%), with frequencies of alleles being 326Ser (0.46) and 326Cys (0.54). The result of the Chi-square test showed no significant difference in the same genotype between cases and controls group with P-value for genotype and allele frequencies were 0.06 and 0.53, respectively.

Measurement of DNA Damage Response

The results of the test parameter for the comet tail length of the exposed and control groups are presented in Table 3. Figure 2 shows the difference of comet tail length values more clearly. In the structure of a comet, the damaged DNA will migrate through the electrophoresis gel and is called the comet tail, while the undamaged part of the nucleoid DNA is called the comet head as shown in Figure 3.

The mean of comet tail length (CTL) measured in the exposed group was 22.55 ± 6.02 µm and the control group was 21.72 ± 7.14 µm (P value=0.58). There is no significant difference between cases and controls group. The present study showed that the comet tail length value was higher in the heterozygous mutant of Ser/Cys

Table 3. Comet Tail Length as a Biomarker of the Level of DNA Damage in the Study Population

	Controls Group			Cases Group			P-value
	Participants	CTL±SD	95% CI	Participants	CTL±SD	95 % CI	
`All	40	21.72 ± 7.14	19.51-23.93	40	22.55 ± 6.02	20.68-24.42	0.58
Never smokers	30	21.55 ± 7.21	18.97-24.13	36	22.96 ± 6.47	20.85-25.07	0.41
Current smokers	10	22.20 ± 6.56	18.13-26.26	4	18.82 ± 4.65	14.26-23.38	0.38
hOGG1 exon 7							
Ser/Ser	14	23.17 ± 7.14	19.43-26.91	7	21.21 ± 5.96	16.79-25.63	0.55
Ser/Cys	13	21.21 ± 7.16	17.32-25.10	23	23.28 ± 6.41	20.66-25.89	0.37
Cys/Cys	13	20.66 ± 6.87	16.92-24.39	10	21.79 ± 6.09	18.02-25.56	0.69

Note: CTL, Comet Tail Length (µm); *, The mean difference is significant at the P value < 0.05.

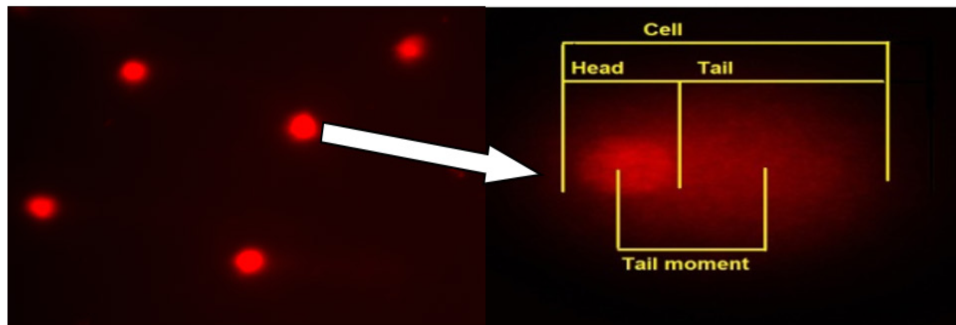

Figure 3. The Epifluorescence Microscopy Visualization of DNA Damage Using Alkaline Comet Assay. The comet head contains undamaged DNA and the comet tail contains damaged DNA fragments. The damage DNA fragments migrate from head to tail during electrophoresis process through the gel matrix.

Table 4. Effect of Confounding Factors on Increasing DNA Damage Tested Using Poisson Regression Analysis.

Confounding factors	IRR	95% CI	P-value
All			
Gender (0,1)	0.992	0.892-1.103	0.82
Age (years)	0.994	0.989-0.998	0.008*
Smoking habit (0,1)	0.956	0.829-1.101	0.53
Time of exposure (years)	0.987	0.977-0.997	0.009*
Equivalent dose (mSv)	0.997	0.946-1.051	0.92
Controls			
Gender (0,1)	1.078	0.923-1.261	0.34
Age (years)	0.993	0.986-0.999	0.02*
Smoking habit (0,1)	0.983	0.825-1.171	0.85
Radiation workers			
Gender (0,1)	0.903	0.773-1.056	0.2
Age (years)	0.997	0.989-1.005	0.46
Smoking habit (0,1)	0.855	0.651-1.123	0.26

genotype compared to the Ser/Ser (wild-type) genotype (23.28 ± 6.41 versus 21.21 ± 5.96) in radiation-exposed workers. On the contrary, a decrease in comet tail length value was observed in controls with a homozygous mutant of Cys/Cys genotype as compared to Ser/Ser (wild-type) genotype (20.66 ± 6.87 versus 23.17 ± 7.14).

The mean value of comet tail length documented in the nonsmokers-cases group was 22.96 ± 6.47 µm, on the contrary, in the nonsmokers-controls group was 21.55 ± 7.21 µm (P=0.41). The mean value of comet tail length documented in the smokers-cases group was 18.82 ± 4.65 µm, on the contrary, in the smokers-controls group was 22.20 ± 6.56 µm (P=0.38).

Influence of Confounding Factors on the DNA Damage Response

Poisson regression analysis was applied to assess the influence of confounding factors, i.e. gender, age, smoking habit, time of exposure, and equivalent dose of ionizing radiation to the DNA damage response. The results showed that significant effects are shown by age (P=0.008) and time of exposure (P=0.009) among participants in the overall population. Whereas in the controls group, age factor influenced significantly to the DNA damage response (P=0.02). In contrast, none of the confounding factors that influenced the DNA damage response in the radiation-exposed workers (P>0.05). The results of Poisson regression analysis are shown comprehensively in Table 4. The results showed that the DNA damage response will be 0.994 times greater for each extra year of age. In other words, there is a 0.6% decrease in the number of DNA damage response for each extra year of

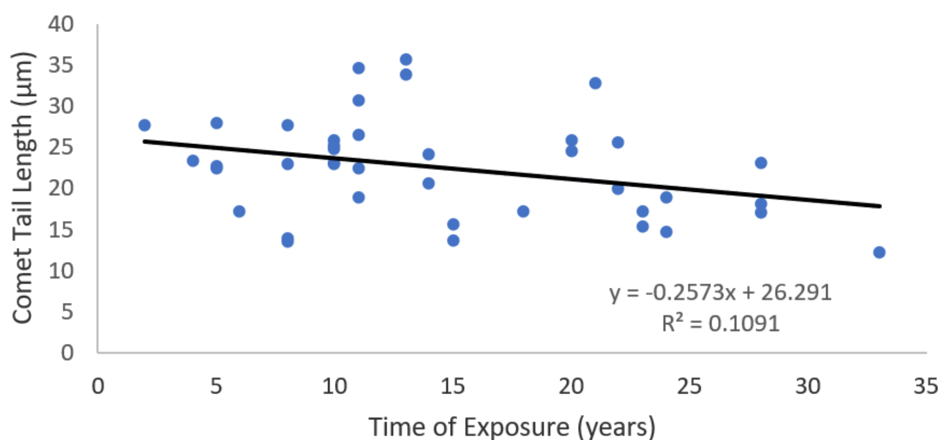

Figure 4. The Relationship between DNA Damage Response, assessed as Comet Tail Length (µm), and Time of Exposure (Years). The thick line is the result of linear regression analysis of the data. β = -0.33, P-value = 0.037.

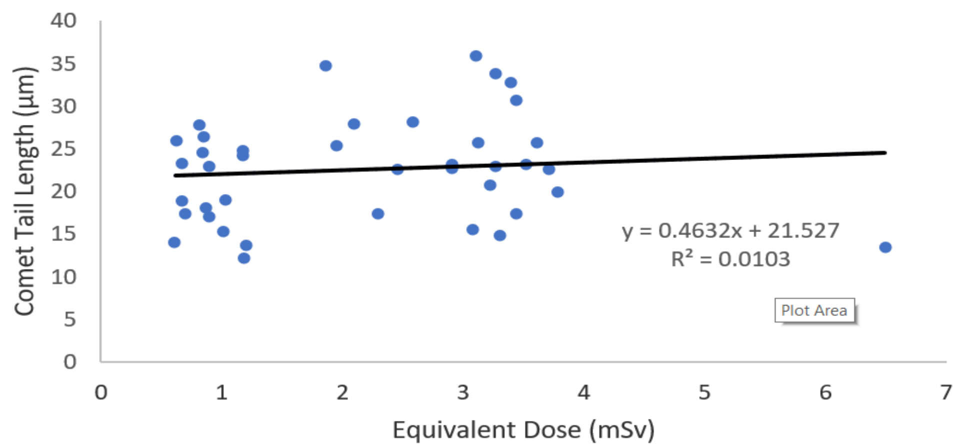

Figure 5. The Relationship between DNA Damage Response, assessed as Comet Tail Length (µm), and Equivalent Dose (mSv). The thick line is the result of linear regression analysis of the data. β = 0.101 , P-value = 0.53.

age. While, the DNA damage response will be 0.987 times greater for each extra year of exposure time, or, there is a 1.3% decrease in the number of DNA damage responses for each extra year of exposure time.

The time of exposure for radiation-exposed workers was 2-33 years with an average working period was 14.55 ± 7.73 years and the equivalent dose for radiation workers was 0.62-6.49 mSv with an average dose was 2.20 ± 1.32 mSv (Table 1). Linear regression analysis was used to examine the relationship between time of exposure and equivalent dose to the DNA damage response. There is a significant relationship between time of exposure and DNA damage response (β= -0.33, P = 0.037; Figure 4). In contrast, no significant relationship between equivalent dose and DNA damage response (β=0.101, P = 0.53; Figure 5).

Discussion

Genotype and allele frequencies can be different in each population. Specific SNPs account (15%) and common SNPs (85%) of all SNPs is different among study population; both types contribute to various characteristics, including drug resistance and skin color (Huang et al., 2015). Apart from the frequency differences between the elderly population and the intense and heterogeneous mixing processes that make up the current Indonesian population, the allele distribution is relatively homogeneous in most countries (Amador et al., 2016).

The results showed that there is no association between Ser326Cys single-nucleotide poymorphism and DNA damage response, assessed by comet tail length value. This fact is in accordance with the previous study which stated that genetic polymorphism of *hOGG1* has no association with DNA damage response or susceptibility of cancer (Mur et al., 2018; Zhang et al., 2018). Wang et al. (2015) stated that there was no significant difference between the *hOGG1* in the pathological type of lung cancer.

In the present study, comet tail length was higher in the current-smoker participants compared with never-smokers in the control group. The cigarette is known to contain a lot of carcinogens, i.e., N-nitrosamines, aromatic polycyclic hydrocarbons (PAHs), radioelement 210Po, aldehydes, aromatic amines, benzene and 1,3-butadiene as the main classes of hazardous substances. Furthermore, DNA damage can be caused by these free radicals substances (Weng et al., 2018; Hecht et al., 2014). We found a lower value of comet tail length in the smokers-cases group compared with the nonsmokers-cases group, perhaps because of the small number of current smokers in the cases group (10%).

The emergence of DNA damage, at least in lymphocytes, is also influenced by endogenous factors (aging, cancer, chronic diseases, reactive oxygen species, genetics, etc.) and exogenous factors (occupational exposure, smoking-drinking habits, UV and X-ray exposure, environmental chemicals, chemotherapeutics, etc.) (Bhattacharyya et al., 2014; Menck and Munford, 2014; Tiwari and Wilson, 2019; Surniyantoro et al., 2019). These parameters need to be considered in biomonitoring studies. Ionizing-radiation exposure to cells is known to be divided into direct and indirect effects. In the first example, the ionizing radiation interacts directly to cell components especially DNA and the damage interferes with normal functioning cell or cause its death. In indirect effect, radiation exposure interacts with H_2O molecules, which is about 80% of the cells that lead to the water radiolysis. This process generates the formation of free radicals especially hydroxyl radicals OH, which have some strong cytotoxic activities. This biological effect is associated with irreparable or incorrect DNA damage in cells exposed to radiation directly (Reisz et al., 2014; Desouky et al., 2015).

Age factor has a significant correlation on the results of this study. A meta-analysis study by Soares et al. (2014) showed an association between age and DNA damage in humans, as well as the smoking habit, sample preparation, and technique that be used. Our previous study also stated that the DNA damage response will be 2.89 times greater for each extra year of age (Surniyantoro et al., 2018). Aging is a consequence of the accumulation of damage to different cellular constituents and where DNA damage is one of the most important. Aging in mammals is accompanied by progressive atrophy of tissues and organs, and accumulation of stochastic damage to macromolecules of DNA, RNA, lipids, and proteins (Maynard et al.,

2015). Normally, the ability of human cells to repair DNA damage declines with age. Different results were obtained in this study. A decrease in the percentage of DNA damage with increasing age and time of exposure (0.6% and 1.3%, respectively) is thought to be caused by the activity of the DNA repair enzymes. The enzymes will maintain genome stability and protect DNA by removing or tolerating damage to ensure overall survival (Chatterjee and Walker, 2017).

There are some limitations to this study. First, the relatively small sample size must be considered a limitation of the study, and thus further research is needed in different populations with larger sample sizes to clarify the role of the *hOGG1* exon 7 (rs1052133) variant in the DNA damage response. Second, the mean of equivalent doses in this study was collected from the medical report of radiation-exposed workers, and these data may be unstable since the data may be influenced by factors such as the population background and radiotherapy treatments.

In conclusion, the present study reported that radiation-exposed workers had higher DNA damage response compared to controls. The single-nucleotide polymorphism of *hOGG1* exon 7 (rs1052133) demonstrated no association with the extent of DNA damage in radiation-exposed workers. The time of exposure has a significantly negative correlation with comet tail length value among radiation workers. In addition, it was found that the DNA damage response was strongly associated with age and time of exposure with a decrease of 0.6% and 0.58%, respectively.

Author Contribution Statement

H.N.E.S. drafted the manuscript, processed the experimental data, performed the statistical analysis, designed the tables and figures, collected the samples, D.Y., T.R., N.R., T.K., S.N., and Y.L. processed the experimental data and collected the samples, M.S and M.P.H. aided in interpreting the results.

Acknowledgements

We would like to thank our co-workers in Radiobiology Laboratory, Center for Technology of Radiation Safety and Metrology, National Nuclear Energy Agency of Indonesia (BATAN) for technical support. None of the authors have any conflict of interests or any financial ties to disclose. Funds to finance this research were fully supported by National Nuclear Energy Agency of Indonesia. Research ethics approval was obtained from the National Commission on Ethics of Health Research, Agency for Health Research and Development, Ministry of Health, Indonesia, Number LB.02.01/2/KE.132/2018.

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