ASSOCIATION OF BASE EXCISION REPAIR PATHWAY GENES OGG1, XRCC1 AND MUTYH POLYMORPHISMS AND THE LEVEL OF 8-OXO-GUANINE WITH INCREASED RISK OF COLORECTAL CANCER OCCURRENCE

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Abstract

Objectives: Reduced efficiency of DNA repair systems has long been a suspected factor in increasing the risk of cancer. In this work authors investigate influence of selected polymorphisms of DNA repair genes (XRCC1, OGG1 and MUTYH) and level of oxidative damage (measured as level of 8-oxo-guanine, 8-oG) on modulation of the risk of colorectal cancer. Material and Methods: In group of 324 patients with colorectal cancer the occurrence of polymorphic variants in Ser326Cys of OGG1, Arg399Gln of XRCC1 and Gln324His of MUTYH were studied with TaqMan technique. In addition level of 8-oG in isolated DNA was determined. Results: Studied polymorphisms of OGG1, XRCC1 and MUTYH genes influence the risk of CRC: OGG1 Ser326Cys (OR = 1.259, 95% CI: 1.058–1.499, p = 0.007), XRCC1 Arg399Gln (OR = 2.481, 95% CI: 1.745–3.529, p < 0.0001) and MUTYH Gln324His (OR = 1.421, 95% CI: 1.017–1.984, p = 0.039) increase the risk. At the same time, studies examined level of 8-oG for each of the genotypes in both the patient and control group, and have shown that OGG1 Ser326Cys and XRCC1 Arg399Gln are associated with elevated 8-oG level, while MUTYH Gln324His is not, suggesting, that in case of OGG1 Ser326Cys and XRCC1 Arg399Gln CRC risk modulation is connected to mechanisms associated with 8-oG levels. Conclusions: This work shows that patients with CRC not only have an increased level of 8-oG and that the studied polymorphisms modulate risk of cancer, but also indicate a relationship between these 2 phenomena, which may contribute to a better understanding of the mechanism of neoplastic process in case of reduced effectiveness of DNA repair mechanisms. Int J Occup Med Environ Health. 2022;35(5):625 – 33

Key words: XRCC1, DNA repair, OGG1, MUTYH, oxidative stress, cancer

INTRODUCTION

Despite ongoing research and progress in both diagnosis and treatment, an rising number of colorectal cancer (CRC) cases can be observed. In 2012 according to Global Cancer Observatory (GLOBOCAN) there were 1 360 000 new CRC cases, which accounted for 9.7% of all newly diagnosed cancers, and CRC was the third most common cancer after breast and lung cancer [1]. Due to the complexity and variety of variants, the exact etiology of the disease remains unknown, however, several factors have been identified.
which may contribute to escalated risk of developing the disease. Genetic factors come to the fore, however, environmental factors should not be underestimated, and in most cases it is expected that the final underlying factor will be the coexistence of the above-mentioned factors. Within the group of genetic predisposition factors, DNA repair systems play a special role. It has been shown that the decrease in the efficacy of DNA repair systems is a key element modulating the occurrence of CRC. The relationship between mutations in the DNA Mismatch Repair (MMR) genes and the increased risk of hereditary nonpolyposis colorectal cancer (HNPCC) in which genetic changes within the MSH2 gene are observed in approx. 60% of patients [2,3], gave rise to search for a similar effect on CRC incidence in other types of DNA repair systems. Particular attention was paid to Base Excision Repair (BER) and Nucleotide Excision Repair (NER) and a number of studies have proved that alterations in those repair systems can increase the risk of CRC [4]. It should be emphasized, however, that often results are ambiguous and sometimes contradictory [5]. This may be due to the differentiation of factors affecting the oncogenesis process. As mentioned above, colorectal cancer is most likely a result of co-interactions of endogenous and exogenous factors. The latter include most of all reactive oxygen species (ROS) [6]. Increased levels of oxidative stress caused by ROS may damage DNA in a way that can lead to oncogenesis [7]. DNA is damaged by ROS in many different ways, but the most common effect is the formation of 8-oxo-guanine (8-oG), modified guanine that can result in a mismatched pairing with adenine resulting in G to T and C to A substitutions. For this reason, the quick and effective removal of 8-oG is extremely important. The effect of 8-oG on the increased risk of cancer has been shown not only for CRC [8], but also for head and neck cancer [9] and lung cancer [10]. In a properly functioning cell, the 8-oG removal from the DNA is provided by BER, mainly by 8-oG glycosylase, also known as OGG1 [11]. The 8-oxo-guanine glycosylase interacts with other BER proteins, therefore, it is responsible for maintaining the genomic stability and defending against potential cancerous transformation.

The aim of this study was to investigate the effect of BER gene polymorphisms OGG1 Ser326Cys, XRCC1 Arg399Gln and MUTYH Gln324His on the modulation of CRC risk. Moreover, these data are supplemented with the levels of 8-oG broken down into each of the tested variants, in order to assess the possible impact of the effectiveness of antioxidant mechanisms on the risk level.

**MATERIAL AND METHODS**

**Population of study**

The source of DNA were lymphocytes from peripheral blood. In this study 324 patients of The Military Medical Academy Memorial Teaching Hospital – Central Veterans’ Hospital in Łódź, Poland, were included. Before sample collection CRC was confirmed histopathologically in case of every patient and any other neoplastic disease was the exclusion criterion. One hundred eighty-nine men and 135 women (with the age of M±SD 67±7 years) were enrolled in the study; 320 cancer free patients admitted to the hospital for other reasons served as control group (age corresponding to the age of the studied group, p < 0.05). History of any neoplastic disease was the exclusion criterion for the control group. Research was approved by the bioethics committee of the Medical University of Lodz.

**DNA isolation and genotyping**

QIAamp DNA Blood Mini Kit from Qiagen was used to isolate DNA in accordance with the manufacturer's instructions; 200 μl of blood was used for each isolation. Polymorphisms Ser326Cys of OGG1 gene (reference SNP cluster ID 1052133 – rs1052133), Arg399Gln of XRCC1 gene (rs25487) and Gln324His of MUTYH gene (rs3219489) were studied with TaqMan technique. The authors used 25 μl of reaction mixture: 1 μl of isolated DNA, 1 μl TaqMan
probes, 13 μl of premix with polymerase and 10 μl of water. Thermocycler Startogene Mx3005P was used to perform the reaction. Reference SNP cluster IDs and thermal conditions are shown in Table 1. Randomly selected 10% samples were subject to repeat genotyping process to confirm copiability. All of the samples were genotyped randomly and case/control status of sample was hidden during genotyping.

8-oxo-guanine levels

To assess 8-oG levels in DNA samples HT 8-oxo-dG ELISA II Kit (R&D Systems) was used. Final DNA concentration of 500 μg/ml, measured with Microliter UV/Vis Spectrophotometer – Picodrop, was used. Reaction is immunobased and allows detection and quantitation of 8-oG in biological samples, including DNA. Reaction was performed according to manufacturer’s instruction. Sensitivity of the kit is at 2 nmol (0.57 ng/ml) 8-OHdG which allows the detection of minimal amounts of the modified base. However, it should be noted that apart from the generally known limitations resulting from the ELISA method, in this particular case the measurement takes place on isolated DNA, which means that the obtained value indicates the level of 8-oG incorporated in the DNA molecule, but there is no information about the amount of 8-oG that was previously removed by repair systems.

Table 1. The refSNP’s and thermal conditions used in the PCR reaction in 324 patients with colorectal cancer, The Military Medical Academy Memorial Teaching Hospital in Łódź, Poland, 2019

| Variable       | Gene          | OGG1          | XRCC1         | MUTYH          |
|----------------|---------------|---------------|---------------|----------------|
| Polymorphism   | OGG1          | Arg399Gln     | Gln324His     |                |
| RefSNP         | rs1052133     | rs25487       | rs3219489     |                |
| Reactions      |               |               |               |                |
|                |               |               |               |
| Alleles        | C>G/C>T       | T>C/T>G       | C>A/C>G       |                |
| Thermal conditions: 1. 95°C – 10 min, 2. 92°C – 15 s, 3. 60°C – 1 min, 4. Step 2 and 3 – 45×. | | | |
| Dyes: ROX, HEX, FAM, ref. dye: ROX. | | | |

Statistical analysis

The genotypes frequency was assessed with Hardy-Weinberg law using the χ² test. Risk modulation of CRC was calculated using means of multivariate regression analysis (odds ratio – OR) with confidence interval (CI) of 95%. The 8-oxo-guanine levels were compared among studied groups by analysis of variance using single factor one-way ANOVA test. In case of unequal means of the 3 populations, a t-test to test each pair of means was performed. In order to determine the equality of 2 population’s variances we performed F-test and depending on the result two-sample assuming unequal variances t-test or two-sample assuming equal variances t-test was used.

RESULTS

Genotyping

The results state that Ser/Cys genotype of Ser326Cys polymorphism of OGG1 gene (as presented in Table 2) increases the risk of colorectal cancer (OR = 1.259, 95% CI: 1.058–1.499, p = 0.007). Similar effect was observed for Arg/Gln genotype of Arg399Gln polymorphism of XRCC1 gene (OR = 2.481, 95% CI: 1.745–3.529, p < 0.0001) and Gln allele (OR = 1.351, 95% CI: 1.076–1.696, p = 0.009) as well as Gln/His genotype of Gln324His polymorphism of MUTYH gene (OR = 1.421, 95% CI: 1.017–1.984, p = 0.039) (Table 2).
Table 2. The distribution of genotypes, allele frequencies and the analysis of the odds ratio (OR) for polymorphism of genes in 324 patients with colorectal cancer and the control group, The Military Medical Academy Memorial Teaching Hospital in Łódź, Poland, 2019

| Variable | Group [n] | OR (95% CI) | p     |
|----------|-----------|-------------|-------|
|          | studied   | control     |       |
| Ser326Cys polymorphism of OGG1 gene |           |             |       |
| Ser/Ser  | 96        | 119         | 1 (ref.) | –     |
| Ser/Cys  | 203       | 158         | 1.259 (1.058–1.499) | 0.007 |
| Cys/Cys  | 21        | 37          | 0.704 (0.386–1.281) | 0.249 |
| Ser      | 395       | 396         | 1 (ref.) | –     |
| Cys      | 245       | 232         | 1.059 (0.844–1.329) | 0.624 |
| Arg399Gln polymorphism of XRCC1 gene |           |             |       |
| Arg/Arg  | 79        | 131         | 1 (ref.) | –     |
| Arg/Gln  | 208       | 139         | 2.481 (1.745–3.529) | <0.0001 |
| Gln/Gln  | 31        | 40          | 1.285 (0.745–2.218) | 0.368 |
| Arg      | 366       | 401         | 1 (ref.) | –     |
| Gln      | 270       | 219         | 1.351 (1.076–1.696) | 0.009 |
| Gln324His polymorphism of MUTYH gene |           |             |       |
| Gln/Gln  | 108       | 125         | 1 (ref.) | –     |
| Gln/His  | 189       | 154         | 1.421 (1.017–1.984) | 0.039 |
| His/His  | 18        | 33          | 0.631 (0.336–1.185) | 0.150 |
| Gln      | 405       | 404         | 1 (ref.) | –     |
| His      | 225       | 220         | 1.020 (0.809–1.286) | 0.862 |

* Genotype distribution in Hardy-Weinberg equilibrium, χ² = 0.156.
* Genotype distribution in Hardy-Weinberg equilibrium, χ² = 0.742.
* Genotype distribution in Hardy-Weinberg equilibrium, χ² = 0.151.

Ser326Cys polymorphism of OGG1 gene: 320 participants in the studied group and 314 in the control group.
Arg399Gln polymorphism of XRCC1 gene: 318 participants in the studied group and 310 in the control group.
Gln324His polymorphism of MUTYH gene: 315 participants in the studied group and 312 in the control group.
Bolded are variables that statistically significantly modulate the risk of CRC.

8-oxo-guanine levels
As initial study 8-oG levels comparison for both the healthy subjects and the patient group was performed, revealing that the mean level for patients was increased (28 615 nmol compared to 58 744 nmol/DNA (μg/μl), p = 0.05). Secondly, measurement of 8-oG levels in relation to specific genotypes showed that group with Ser/Cys genotype of the OGG1 gene had statistically significantly higher level than remaining 2 genotypes. As shown in Figure 1a:

— in case of control group: 42.23 8-oG nmol/DNA (μg/μl) for Ser/Cys vs. 22.92 8-oG nmol/DNA (μg/μl) for Ser/Ser and 20.69 8-oG nmol/DNA (μg/μl) for Cys/Cys,
— in case of patients: 106.00 8-oG nmol/DNA (μg/μl) for Ser/Cys vs. 36.54 8-oG nmol/DNA (μg/μl) for Ser/Ser and 33.69 8-oG nmol/DNA (μg/μl) for Cys/Cys.

This situation is observed both within the patient group and the control group. The same result was observed for the genotype Arg/Gln of XRCC1 gene, and once again
8-oG level was higher for both patients and control groups when compared to other 2 genotypes. As shown in Figure 1b:
- in case of control group: 36,08 8-oG nmol/DNA (μg/μl) for Arg/Gln vs. 23,38 8-oG nmol/DNA (μg/μl) for Arg/Arg and 26,38 8-oG nmol/DNA (μg/μl) for Gln/Gln,
- in case of patients: 92,08 8-oG nmol/DNA (μg/μl) for Arg/Gln vs. 39,85 8-oG nmol/DNA (μg/μl) for Arg/Arg and 44,23 8-oG nmol/DNA (μg/μl) for Gln/Gln.

However, this was not the case with the MUTYH gene, where no statistically significant differences in 8-oG levels between genotypes were observed (Figure 1c).

**DISCUSSION**

The ability of human cells to repair DNA damage is one of the key mechanisms that protect our body against cancer. The firmness of the genome should be a priority since its violation can lead to the accrual of mutations and, consequently, to cancerogenesis. Such a situation can be observed in the case of a decrease in the effectiveness of DNA repair mechanisms. Such a situation can be observed in the case of a decrease in the effectiveness of DNA repair mechanisms, and one of the most common damages resulting from such dysfunction will be those generated by reactive oxygen species. Among DNA lesions resulting from ROS action 8-oG is the most frequent and can lead to discrepancy in base paring [11]. Oxidation of guanine to 8-oG is repaired primarily by DNA glycosylase OGG1, a part of Base Excision Repair mechanism [12]. OGG1 has been shown to interact with XRCC1 [13] and MUTYH [14]. The polymorphisms of all these genes, due to their key function, have been studied in terms of risk modulation in wide spectrum of cancer types, including lung cancer [15], head and neck cancer [16], pancreatic and breast cancer [17] or gallbladder cancer [18]. In case of colorectal cancer OGG1 Ser326Cys has been shown to increase risk [19], not modulate risk at all [20] or decrease risk [21]. XRCC1 Arg399Gln increases the risk of CRC [22] or is considered not to have an influence [23]. Finally MUTYH Gln324His is considered to be risk factor for CRC occurrence [24].
In this study authors have shown that all 3 of those polymorphisms are connected to increased risk of CRC incidence – OGG1 Ser326Cys (OR = 1.259, 95% CI: 1.058–1.499, p = 0.007), XRCC1 Arg399Gln (OR = 2.481, 95% CI: 1.745–3.529, p < 0.0001) as well as MUTYH Gln324His (OR = 1.421, 95% CI: 1.017–1.984, p = 0.039). The causes of inaccuracies, and sometimes even contradictions in the literature data, and thus the comparison of our results to the available results, are to be found in the differences in the studied populations, such as race, abundance, exposure to additional risk factors (smoking, alcohol consumption). The main reason behind the inconsistent reports in this regard is the multifactorial nature of carcinogenesis. For a better understanding of the processes that may underlie at the increased risk of CRC in polymorphisms of studied genes, 8-oG levels were measured. Colorectal cancer patients showed a significantly higher level of oxidative damage measured as the level of 8-oG. This is a result to be expected due to the decreased level of antioxidant mechanisms in cancer patients as well as due to the increased level of oxidative stress during treatment. Previous studies indicate the potential role of BER proteins in regulating the level of 8-oG and the impact of this regulation on the risk of CRC, especially in the case of MUTYH [25]. However, there are no reports on the detailed impact of individual BER protein polymorphisms on the level of 8-oG, so authors compared this levels for patients and control groups broken down into all 3 genotypes of the studied genes. Results indicate that OGG1 Ser326Cys not only, as mentioned above, increases the risk of CRC, but also is connected to increased level of 8-oG in case of patients as well as in healthy individuals. This supports theory, that Ser326Cys polymorphism increases CRC risk due to OGG1 decreased activity – accumulating 8-oG resulting from reduced efficacy of OGG1 leads to increased risk of malignant transformation. Although Janssen et al postulated that there is no connection betweenSer326Cys polymorphism inDNA glycosylase 1 and 8-oG damage repair efficiency in case of lymphocytes [26] authors believe that this may not be the case when it comes to colorectal cancer cells. In the case of a reduction in OGG1 expression, the likely effect will be an increase in the level of mutation and the resulting increase in the intensity of neoplastic transformation, what has been proved by studies that described cancers identified as having reduction in the OGG1 expression, such as head and neck cancer [27] stomach cancer [28] or brain cancer [29]. Moreover activity of DNA repair proteins can be different in lymphocytes and in tissue, as proven by Janik et al [30] in case of lymphocytes compared to lung cells. The same mechanism can be postulated for XRCC1 which has been shown to closely interact with OGG1 [13] and according to obtained results in case of Arg399Gln may escalate CRC risk and is associated with elevated level of 8-oG. Available data seem to support that theory since Arg399Gln XRCC1 patients revealed lower 8-oG incision activity in their lung tissues in non-small-cell lung carcinoma [30]. However, the same phenomenon was not observed with MUTYH Gln324His, which elevates CRC risk but is not associated with increased level of 8-oG. Although all 3 of these proteins (OGG1, XRCC1 and MUTYH) work together for the removal of oxidative damage from DNA, including 8-oG, MUTYH must modulate the risk of CRC occurrence due to other mechanisms than ineffectiveness in repairing oxidized guanine. It is possible that the function of MUTYH in the removal of 8-oG may be taken over by another protein, since different strategies exist to avert the danger of damage caused by ROS [31], therefore, despite the dysfunction of MUTYH, no increase in 8-oG levels will be observed, and the carcinogenic effect will be induced by some other process in which MUTYH is also involved. What may be this process remains unknown, therefore authors postulate that further research in this area is needed.

The results obtained in this study by no means are complete and comprehensive explanation of the mechanism of carcinogenesis resulting from the presence of the polymorphisms studied, however, the potential con-
CONCLUSIONS
Ser/Cys genotype of Ser326Cys polymorphism of OGG1 gene, Arg/Gln genotype of Arg399Gln polymorphism of XRCC1 and Gln/His genotype of Gln324His polymorphism of MUTYH gene increase CRC risk. The 8-oG level in CRC patients is higher than in the control group. At the same time Ser326Cys of OGG1 gene and Arg399Gln of XRCC1 polymorphisms are connected to highly increased 8-oG level. It may suggest that CRC risk modulation is associated with a decrease in activity in the removal of 8-oG, for which responsible may be impaired DNA repair, while underlying cause of elevated CRC risk in case of Gln/His genotype of Gln324His polymorphism of MUTYH gene must be due to some other mechanism, since it is not connected with increased 8-oG level.

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