Functional polymorphisms of oxidative stress and repair genes as biomarkers of the risk of developing breast cancer

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Abstract. Breast cancer has the highest incidence and is the fifth leading cause of death in women worldwide. Cancer formation is a multistep, multistep process involving cellular and molecular events. At all its stages, in an initially healthy single cell, there is a gradual accumulation of genetic changes in DNA caused by endogenous and exogenous factors. Breast cancer-predisposing mutations are not evenly distributed among populations, and each ethnic group is descended from its own pool of ancestors who carried a unique spectrum of alleles associated with the disease, making it imperative that studies of this kind be conducted to identify "population-specific markers."

1 Introduction

Of all cancers, breast cancer (BC) has the highest incidence (2.3 million new cases per year) and is the fifth leading cause of death in women worldwide [1]. Cancer formation is a multistep, multistep process involving cellular and molecular events [2]. At all its stages, in an initially healthy single cell, there is a gradual accumulation of genetic changes in DNA, caused by endogenous and exogenous factors, leading to "disruption of its mitotic activity" [3]. Damage affects the integrity and stability of DNA, but is constantly and efficiently corrected by DNA repair pathways [4]. The cell's susceptibility to DNA damage and its ability to repair DNA are important for the induction, promotion and progression of cancer [5]. Functional polymorphisms of the XPD (Asp312Asn and Lys751Gln), XRCC1 (Arg399Gln and Arg194Trp) genes have been widely studied in many types of cancer [6, 7, 8], and their association with the risk of certain types of cancer has been shown. Reactive oxygen species (ROS) play an important role in the regulation of cellular function, the imbalance of which mechanism leads to the occurrence of oxidative stress. ROS and their ability of free radical oxidation products to damage macromolecules are currently considered an important cause of malignant neoplasms [9].

It is worth noting, however, that mutations predisposing to breast cancer in populations are, by definition, far unevenly distributed. Each ethnic group is descended from its own pool of ancestors who were carriers of a unique spectrum of disease-associated alleles. Therefore, national communities should be characterized by distinct patterns of hereditary diseases and pathogenic variants. Moreover, extensive studies have been conducted in

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different populations to identify such variants, but results from different populations are inconsistent [10], which in turn influences the results of association studies. This makes it imperative that studies of this kind be conducted for each individual population in an attempt to identify "population-specific markers." Knowledge of such genetic markers predisposing to the development of breast cancer and its relationship with reproductive risk factors is of paramount importance for identifying people at high risk. This would allow for early diagnosis and treatment of breast cancer, which would ultimately lead to a reduction in mortality.

The purpose of our study was to determine the significance of any of the SNPs and haplotypes of DNA repair genes (XRCC1, XPD) and oxidative stress (CAT) in the modulation of breast cancer

2 Research Methodology

The study involved women, ethnic Chechens living in the Chechen Republic. Patients were identified through contact with the department of the State Budgetary Institution "Republican Oncology Dispensary" of the Chechen Republic and local clinics. Control groups were women with no personal history of breast cancer. Demographic data revealed no significant differences between patients and controls regarding age (P = 0.104) (Table 1). All data were collected through a self-administered questionnaire. Written informed consent was obtained from all participants.

Table 1. Demographic characteristics of study participants.

	n	Average age	P
happening	206	47,68±11,35	0,104
control	359	45,29±11,73	

Study participants donated a blood sample in a volume of 2-3 ml. Venous blood (2-3 ml) was collected into vacuum tubes with EDTA containing K2 and K3. Stored at -40 C in the freezer.

For genotyping, 6 functional single nucleotide polymorphisms were selected based on literature data on their occurrence in different populations and their effect on the development of breast cancer [1, 11, 12]: two polymorphisms of the oxidative stress genes CAT (rs4756146, rs2284365); DNA repair genes XRCC1 (rs1799782, rs 25487) and XPD (ERCC2)(rs13181, rs1799793). All SNPs were in Hardy-Weinberg equilibrium in cases and controls.

Genomic DNA was isolated from whole blood mononuclear cells using the universal sample preparation method using a ready-made Diatom DNA Prep 200 kit (Galart-Diagnosticum LLC, Moscow). For gentyping by tetraprimer PCR, GenPak® PCR Core (12x8) (Galart-Diagnosticum LLC, Moscow) was used. Primer sequences are listed in Table 2.

Table 2. Characteristics of primers for tetraprimer PCR reactions, annealing temperature and fragment sizes.

SNP	Primer sequence	SNP	Primer sequence
XRCC1 Arg194Trp rs1799782	TGCCAGCAGCCCACCTATAA CCAGCCTCCAGACCTCTCAA GGGGGCTCTCTTCTTCAGCT GGGGATGTCTTGTTGATCCG	XPD (ERCC2) Asp312Asn 1799793	CTGGCCCCTGTCTGACTTGT CTCAGGAAGCCCAGGAAATG AACCCTGTGCTGCCCA ACCCTGCAGCACTTCGTC
XRCC1 Arg399Gln rs25487	TCTGTCTCCCCTGTCTCGTTC/ CCGCTCCTCTCAGTAGTCTGC TCGGCGTCTGTCCTCCCA GCGTGTGAGTCCTTACCTCC	rs4756146 CAT	TTGCTCCACATCCTACCAAC AGCCTACACATGATTCCACAT
XPD (ERCC2) Lys751Gln	CCTGCGATTAAAGGCTGTGG GATGGCCCGCTCTGGATTAT CTGAGCAATCTGCTCTATCCTCTG AGCTAGAATCAGAGGAGACGCTGA	rs1001179	GAGGACTGCCTTCTGATTGG TCCATCCTTTGGTTGCAAAT CCCGGTGTGCTCGGA GCCCTGTGTTCGGCTATC

Nucleotide sequences were analyzed using a Real-time CFX96 thermal cycler (BioRad). Categorical variables were analyzed by the chi-square test ($\chi 2$) or Fisher's exact test for small sample sizes. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated, and the criterion for significance was set at $p < 0.05$.

3 Results and Discussions

Two single nucleotide polymorphisms (SNPs) within CAT were genotyped among BC patients and healthy controls (Table 3). The frequency of minor alleles selected by SNPs was >5%. The genotypes of all SNPs in the controls were consistent with Hardy-Weinberg equilibrium ($p>0.05$), indicating that the subjects were representative of the population.

CAT gene polymorphism rs4756146. The population frequency of SNP rs4756146 was 0.12 and was comparable to data for the European population (0.13) [13]. The genotype distribution observed in the control and case groups did not deviate from Hardy Weinberg equilibrium (HWE).

76.88% of women in the control group were homozygous for the wild-type T allele. In the group of women with breast cancer, the frequency of wild-type homozygotes was 78.15%. There were slightly more heterozygous carriers of the mutant allele C in the control group than in the patient group: 21.44% versus 19.9%. At the same time, among women with breast cancer there is a trend level increase in the frequency of the homozygous genotype for the minor allele, compared with the control group - 1.94% versus 1.67.

The frequency of the minor allele C in the group of patients was lower than in the control group: 11.9% versus 12.4%.

The search for associations did not reveal a significant effect on the risk of breast cancer of the C allele of the CAT rs4756146 polymorphism ($p >0.05$).

Table 3. Odds ratios and 95% confidence intervals for the association between CAT variants (rs4756146 and rs1001179) and breast cancer risk.

Gene (rs)	Genotype	n	%	n	%	OR (95 % CI)	P
CAT		Case (n = 206)		Control group (n =359)			
(rs4756146)	TT	161	78,15	276	76,88	1,00	
	TC	41	19,9	77	21,44	0,91 (0,60 – 1,40)	0,747
	CC	4	1,94	6	1,67	1,14 (0,32 – 4,10)	1,000
	TC и CC	45	21,84	83	23,12	0,93 (0,62 – 1,40)	0,755
Alleles	T		88,11		87,6		
	C		11,89		12,4		
CAT		Case (n = 199)		Control group (n =343)			
rs1001179	CC	128	64,3	229	66,7		
	CT	68	34,2	100	29,1	1,26 (0,87 – 1,83)	0,248
	TT	3	1,5	14	4,1	0,36 (0,10 – 1,26)	0,126
	CT и TT	71	35,7	114	33,2	1,11 (0,77 – 1,61)	0,574
Alleles	C	81,4		81,3			
	T	18,6		18,7			

Polymorphism rs1001179 of the CAT gene. The frequency of the minor allele T of the rs1001179 polymorphism of the CAT gene in the control sample was 0.187. For comparison, the frequency of the T allele in the European population is 0.221731 [14]. The genotypes of the polymorphic variant of the CAT 262C/T gene promoter in two groups were distributed in two samples with a significant predominance of homozygotes for the minor T allele in the control, 4.1% versus 1.5%. The frequency of wild-type homozygotes in the group of patients was 64.3%, which is slightly less than in the control group (66.7%), 34.2% were heterozygous carriers of the T allele, while in the control group 29.1% of women had a heterozygous genotype. Analysis of various genetic models revealed an insignificant effect of the allele on the risk of developing breast cancer (OR=1.11, 95% CI: 0.77 – 1.61, p=0.574). At the same time, a significant protective effect of two TT alleles versus one was revealed (continuity-corrected one-sided p = 0.036): OR = 0.32 [95% CI = 0.09 – 1.13].

XRCC1 rs1799782 polymorphism. The genotypes of the polymorphic variant of the XRCC1 repair gene Arg194Trp in two groups of women were distributed as follows: homozygous genotype for the wild-type allele G: 89.9% in the control group and 88.35% in the group of patients; heterozygotes among patients were 11.16% versus 10.05% in controls. In one case (0.48%), a genotype homozygous for the minor AA allele was found among the patients. Analysis of the association of the Arg194Trp XRCC1 polymorphism with the risk of breast cancer shows an extremely high risk of developing cancer for rs 179978. in the recessive model in women with the AA genotype homozygous for the mutant allele (OR=5.23 (CI: 0.21 – 128.38) and an increased risk for heterozygotes (OR = 1.12, CI: 0.65 – 1.65) However, these effects were not reliably significant (Table 4).

Within XRCC1 and XPD, 8 SNPs were genotyped in a cohort of breast cancer patients and healthy controls. The equilibrium of genotype frequencies in accordance with the Hardy-Weinberg law was confirmed by the $\chi 2$ test.

XRCC1 rs25484 polymorphism. The genotypes of the XRCC1 Arg399Gln (rs25484) polymorphism were distributed in the control group as follows: 15.82% TT homozygotes, 49.43% heterozygotes; and 34.74% CC homozygotes. In the case group, TT homozygotes accounted for 16.13%, TC heterozygotes - 44.35%, and CC homozygotes 39.52%. The frequency of allele C was 64.18. For comparison, the frequency of this allele in the European population is 65.59%. Genotypic and allelic frequencies were not statistically

different between the two groups. There was a trend towards a reduced risk of developing a neoplastic process in individuals with the TC genotype (OR = 0.82 [95% CI: 0.54 – 1.23]). In the case of the CC genotype, there is an increased chance of developing a cancerous tumor (OR = 1.23 [95% CI 0.81 – 1.87]). However, these effects were not significant (Table 4).

Table 4. Frequency of genotypes and alleles of XRCC1 polymorphism in patients with breast cancer and the control group.

Polymorphism	Case		Control		P-value	OR (95% CI)
XRCC1 rs 25487						
T>C Gln399Arg Genotypes, n (%)	n = 124		n = 354			
TT	20	16,13	56	15,82		
TC	55	44,35	175	49,43	0,349	0,82 (0,54 – 1,23)
CC	49	39,52	123	34,74	0,384	1,23 (0,81 – 1,87)
TT+ TC		60,96		64,34	0,385	0,82 (0,54 – 1,24)
Alleles, n (%)						
T		37,82		40,54		
C		62,18		59,46		
XRCC1 rs1799782						
G>A Arg194Trp Genotypes, n (%)	n = 206		n = 358			
GG	182	88,35	322	89,9		
GA	23	11,16	36	10,05	0,671	1,12(0,65 - 1,95)
AA	1	0,48	0	0	0,365	5,23(0,21 – 128,38)
GA +AA	24	11,65	36	10,03	0,572	1,18(0,68 – 2,04)
Alleles, n (%)						
G		93,93		94,97		
A		6,07		5,03		

Lys751Gln XPD polymorphism (rs13181, rs1799793). When comparing the frequency of polymorphic gene variants in patients with the control group, no significant changes were detected. The T/T genotype was detected in the patient sample in 27.86% of cases, in the control group in 28.79% of cases. 48.73% of women with breast cancer had the heterozygous T/G genotype; in the control group, the frequency of heterozygous carriers of the minor allele was slightly higher, which suggested a protective effect of the heterozygous genotype. 21.05% of healthy women were homozygous for the G allele; in the group of patients, the frequency of this genotype was 24.38% (Table 5).

The search for associations of the XPD G751T polymorphism with breast cancer did not produce significant results. The T/G genotype showed a protective effect (OR = 0.90 CI 0.64 – 1.28), which was slightly enhanced in the recessive genetic model (OR = 0.82 CI 0.54 – 1.25, P = 0.389) (Table 5).

Table 5. Frequency of genotypes and alleles of XPD polymorphism in patients with breast cancer and the control group.

Polymorphism	n	%	n	%	P-value	OR (95% CI)
	Case n = 201		Control n = 323			
XPD Lys751Gln						
Genotypes, n (%)						
T/T	56	27,86	93	28,79		1
T/G	97	48,73	162	50,15	0,591	0,90 (0,64 – 1,28
G/G	49	24,38	68	21,05	0,389	1,21 (0,80 – 1,84)
G/G и T/G	152	75,6	256	79,01	0,389	0,82 (0,54 – 1,25)
Alleles, n (%)						
G		51,73		53,87		1
T		48,27		46,13		
XPD Asp312Asn						
Genotypes,, n (%)	n=203		n=352			
CC	71	34,97	100	28,341		
CT	97	47,78	180	51,14	0,481	0,87 (0,62– 1,23)
TT	35	17,24	72	20,45	0,374	0,81 (0,52 – 1,27)
TT и CT	132	64,53	252	71,59	0,187	0,74 (0,51 – 1,07)
Alleles, n (%)						
C		58,87		53,98		
T		41,13		46,02		

XPD polymorphism rs1799793 (Asp312Asn). The results of genotyping of the XPD Asp312Asn gene polymorphism (Table 6) were as follows: 34.97% homozygotes for the C allele in the cohort of patients, while in the group of healthy women 28.34%; heterozygous carriers of the minor allele among sick women - 47.78%; among healthy people - 51.14%. 17.24% of women with breast cancer and 20.45% of women in the control group had two copies of the T allele. Comparative analysis showed that women with one (OR=0.87 (CI: 0.62–1.23)) or two copies of the minor are less likely to develop cancer than with two wild-type C alleles (OR=0.81 (CI) : 0.52 – 1.27) However, the results were not significantly significant (p = 0.374), and no significant associations were identified in any genetic models (Table 5).

Haplotype analysis Asp312Asn/Lys751Gln XPD B XRCC1 Arg194Trp + Gln399Arg. The analysis included only those subjects for whom genotypes were identified for all polymorphic variants of these genes: 124 women with breast cancer and 311 from the control group. We found a significant effect (p = 0.017) of the XPD haplotype Asp312Asn +G751T (OR=2.14, CI1.16 – 3.95), which is enhanced by the combination of two haplotypes XRCC1 Arg399Gln-Arg194Trp (T/C+G/G) and XPD Lys751Gln -and Asp312Asn (G/G +TC) OR= 2.65 CI 1.12 – 6.28 (P = 0.029) (Table 6).

Table 6. Frequency of haplotypes XRCC1 Arg194Trp/ Gln399Arg and XPD Asp312Asn/ Lys751Gln their effect on the risk of developing breast cancer in patients with breast cancer and the control group.

	breast cancer (n =124)		control (n =311)		P-value	OR (95% CI)
Haplogroup	n	%	n	%		
XRCC1 Arg194Trp + Gln399Arg						
TC/GG	51	41,13	134	43,09	0,748	0,92 (0,61 – 1,41)
XPD Asp312Asn + Lys751Gln						
CC/TG	21	16,94	27	8,68	0,017	2,14 (1,16 – 3,95)
TC/GG +CC/TG	11	8,87	11	3,53	0,029	2,65 (1,12 – 6,28)

The efficiency of DNA repair in cells is one of the determining factors in preventing the development of cancer [15]. It has been suggested that functional disruptions in highly conserved DNA repair processes resulting from polymorphic variations may increase genetic susceptibility to breast cancer (BC) [10, 16, 17].

XPD/ERCC2 is an evolutionarily conserved 5′ to 3′ ATP-dependent helicase that contains a 4FeS cluster in the HD1 helicase domain [18]. This protein is part of transcription factor IIH (TFIIH), which is required for both DNA repair and transcription. A number of studies have reported a significant association between the XPD gene polymorphisms Asp312Asn and Lys751Gln and cancer risk [11, 19]. However, the results were inconsistent and contradictory. XPD polymorphism was studied in 206 women of the Chechen population with a confirmed diagnosis of breast cancer and 359 healthy women. The data obtained did not reveal a significant association with the risk of developing breast cancer. The TT and TC genotypes of the XPD codon 751 polymorphism showed a protective effect against breast cancer at a trend level ($P \leq 0.481$). As shown by the analysis of the association of carriage of alleles and genotypes of another polymorphic region of XPD Asp312Asn with the risk of developing breast cancer in women, the contribution of the XPD gene to the development of breast cancer is apparently not determined by the influence of its Lys751Gln polymorphism. The G/G genotype shows an increased risk of developing breast cancer, but the resulting value was not significantly significant. At the same time, statistical analysis based on variations in XPD Asp312Asn + Lys751Gln haplotypes showed that the combination CC (XPD Asp312Asn) + TG (XPD Lys751Gln) has significant differences between the group of women with breast cancer and the corresponding control group ($P = 0.017$).

The group 1 gene X-ray crossover complementary (XRCC1) is critical for proper repair of DNA damage such as single-strand DNA breaks. The functional polymorphism of the XRCC1 gene Arg399Gln and Arg194Trp has been widely studied in many types of cancer [6, 7, 8], including breast cancer (BC) [20]. A nonsynonymous polymorphism in XRCC1, 399 G → A, has been shown to reduce the efficiency of such DNA repair and is associated with the risk of certain cancers [21]. Our study did not provide reliable evidence of the relationship between the genotypes of the Gln399Arg XRCC1 polymorphism and breast cancer, despite the fact that the CC genotype greatly increased the risk of developing breast cancer, but the effect was not significant. At the same time, a reverse effect of the heterozygous CT genotype was noted at the trend level; however, there is no association between the XRCC1 Gln399Arg polymorphism and breast cancer.

For another common polymorphism, XRCC1 Arg149Trp, no significant differences in the allelic and genotypic distribution of the polymorphism could be detected between the two groups. We found that women carrying at least one variant allele of the

XRCC1Arg194Trp polymorphism may have an increased risk of developing breast cancer. But more research is needed to confirm this association. There were no significant effects of XRCC1 Arg194Trp/ Gln399Arg haplotypes. At the same time, analysis of combinations of the XRCC1 Arg194Trp and Gln399Arg haplotypes with the XPD Asp312Asn + Lys751Gln haplotypes shows that the intergenic interaction of the XPD(CC+TG) and XRCC1(TC+GG) polymorphisms may be associated with an increased risk of breast cancer in Chechen women (p=0.029) . In summary, our results showed that individual variants in breast cancer susceptibility lead to a small increase in risk, but a combination of these variants can lead to a significant increase in risk.

Oxidative stress is an imbalance between the production and accumulation of free radicals and reactive metabolites, commonly known as “reactive oxygen species.” Many studies [22, 23] that examined the relationship between exposure to reactive oxygen species, genotype and risk of breast cancer have shown that both ROS-generating factors (cigarette smoking and exogenous hormones) and factors counteracting ROS generation (fruit consumption and vegetables), can interact with endogenous sources of pro- and antioxidants and modify the effect of genetic polymorphisms on the risk of developing breast cancer [22, 23]. As indicators of oxidative stress, we assessed CAT gene polymorphisms (rs4756146 and rs1001179) as potential markers of early disease onset.

To date, only a small number of studies have assessed the individual or combined effects of the CAT SNPs rs4756146 and rs1001179 on breast cancer risk [22; 24]. In the present study, insignificant associations of breast cancer genotype CC of the rs4756146 CAT polymorphism with breast cancer were noted. However, in light of the nonsignificant odds ratio and little evidence of association between the rs4756146 polymorphism, these results may be due to chance. A statistically significant positive association was observed for women with more than one CAT allele variant (rs1001179).

The results may indicate that lower ROS scavenging may increase the risk of breast cancer. However, given the lack of data on other markers of oxidative stress, these results require further confirmation. The incidence of breast cancer continues to increase worldwide. Population-based screening is available in many countries but may not be the most efficient use of resources, so interest in risk-based/stratified screening has increased significantly in recent years. An important part of risk-based screening is the inclusion of mammographic density and single nucleotide polymorphisms in risk prediction models, which should be combined with classical risk factors [25].

Inherited genetic pathogenic variants account for a relatively small proportion of all breast cancer cases (4–5%), and most women who develop breast cancer do not have a pathogenic variant in the active gene. Individual variants in breast cancer susceptibility (single nucleotide polymorphisms) also lead to a small increase in risk, but a combination of these variants can lead to a significant increase in risk. It is obvious that populations differ in the genotype and allele frequencies of various SNPs, as well as in the degree and nature of the relationship of the genotype or allele with the development of the disease [26]. However, SNP allele frequencies show significant differences between different populations, even in control groups, making it imperative to conduct studies of this type on a population-by-population basis in an attempt to identify “population-specific markers.”

The results of the present population-based study showed that individual variants in breast cancer susceptibility (single nucleotide polymorphisms) may lead to a small increase, and the combination of these variants may lead to a significant increase in risk.

However, there are some limitations of this study. First, given the retrospective nature of this study, the results need to be confirmed by larger prospective studies. Second, statistical power was significantly reduced in subgroup analyzes due to the small sample size.

4 Conclusions

Thus, analysis of the joint carriage of alleles/genotypes of the studied polymorphic regions in patients and healthy individuals revealed combinations of haplotypes of the XRCC1 Arg194Trp/Gln399Arg and XPD Asp312Asn/Lys751Gln gene haplotypes that are positively associated with breast cancer. Combinations of two haplotypes XRCC1 Arg399Gln-Arg194Trp (T/C+G/G) and XPD Lys751Gln and Asp312Asn (G/G +TC)– turned out to be a breast cancer risk marker.

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