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DNA REPAIR GENE POLYMORPHISMS, EXPOSURE TO IONIZING RADIATION, AND THE RISK OF DEVELOPING MALIGNANT NEOPLASIA: META-ANALYSIS

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Nowadays oncological diseases, especially those induced by malignant neoplasms, are Kazakhstan's third-largest cause of death. In the structure of mortality, lung cancer is in the first place (16.5%, 1945 cases), gastric cancer is in second (11.8%, 1411 cases), colorectal cancer is in third (10.7%, 1242 cases), and breast cancer is in fourth (8.2%, 959 cases). The genetic and chromosome mutations induced by lesions on different areas of DNA sequence significantly impact the etiology and pathogenesis of cancer. The most cytotoxic damage pays upon DNA double-strand breaks (DSBs), which cause chromosome aberrations and genome instability, leading to the development of malignant neoplasms [1]. Double-strand break reparation is one of the main protective mechanisms against this process, and the genes regulating DSB reparation play a vital role in early prognostics and diagnostics of cancerous diseases. The difference in the allelic forms of this group of genes directly affects the activity of repair systems and thereby can determine the risk of an increase in the pool of mutations in the genome and the development of tumors.

Single nucleotide polymorphisms (SNPs) are variations of a single nucleotide of a gene in a DNA sequence that can affect both readable (exon) and unreadable (intron) regions of the genome, in one way or another affecting the efficiency of post-translational modifications, of the stability of mRNA folding, and conformations of the quaternary structure of the protein [2]. The results of many modern retrospective studies indicate the correlation of some polymorphisms of DNA repair genes with the development of malignant neoplasms, such as lung cancer, stomach cancer, breast cancer, gliomas, osteosarcomas, etc. This correlation can be explained by the influence of differences in the variations of polymorphic repair genes on the functionality of repair systems. Accordingly, genotyping of polymorphic genes of this group can be used for early cancer diagnosis and prognosis of its clinical course, which can be useful in choosing a strategy and methods of cancer treatment [3].

One of the promising concepts is the creation of panels of single nucleotide polymorphisms for predicting the degree of risk and aggressiveness of cancer, which allow patients to be genotyped according to a determined list of risk or protective genetic markers of malignant neoplasia. Information about the patient's genetics allows for high-risk factors for early cancer detection, which can play a decisive role in the chance of survival [4]. One of the main causes of death in oncological diseases is untimely access to therapy. Later stages of cancer are distinguished by the tendency for malignant cells to invade, their concomitant metastasis, and inflammation of the

lymphatic system. With an increase in the period of development of neoplasia, the effectiveness of therapy and the chances of a cure decrease respectively [5][6]. Remarkably, there are usually no clinical manifestations of oncology at the earliest stages of cancer, and the only possible option for detecting neoplasms during this period is the study of aggravating factors, the main of which is genetic [7]. It is important to note that the effectiveness of therapy is highest in the treatment of cancer in the initial stages [8]. Since cancer cells do not have an invasive course during this period, the risk of spreading metastases and, subsequently, the recurrence of oncological diseases appears to be significantly lower, except for the presence of genetic predispositions to them.

Apart from the early diagnostics, SNP analysis paves the way to personalized medical treatment adapted to the data of patient's genetics. As a mutagen, ionizing radiation also increases the mutations' pool, hence SNPs associated with DNA repair deficiencies can lead to cancer progression. Genetic polymorphisms associated with intrinsic radiosensitivity thus can be used to predict a patient's reaction to the radiotherapy commonly used to target cancer cells. Optimization of the radiation dose according to the genetic background of the patient would also benefit the treatment without the excessive costs of unnecessary assays and procedures [9][10][11]. For instance, patients with SNP variations associated with radiation injury would benefit from such alternatives as treatment with cytotoxic compounds, which suppress the DNA replication of malignant proliferating cells whose genome is severely unstable without the usage of ionizing agents [12]. On the other hand, these patients could be treated with more sophisticated approaches to radiotherapy, including proton therapy which exposure is more limited towards the cancerous cells, whilst adjacent healthy tissue remains unaffected [13]. Improving the accuracy of therapy strategies would significantly increase patients' chances of a cure.

In this meta-analysis, I have assessed the correlation between 16 DNA repair gene polymorphisms, exposure to ionizing radiation, and the risk of developing malignant neoplasms. This report includes a total of 93 case-control studies genotyping cases with different types of malignant tumors, including lung cancer (non-small cell lung cancer and adenocarcinoma), oral cancer, colorectal cancer, glioma, breast cancer, gastric cancer, esophageal adenocarcinoma, head and neck cancer, gastric antrum adenocarcinoma, hepatocellular carcinoma, acute myeloid leukemia, nasopharyngeal carcinoma, bladder cancer, prostate cancer, neuroblastoma, non-Hodgkin lymphoma, osteosarcoma, ovarian cancer, cervical cancer, renal cell carcinoma, chronic myelogenous leukemia, colon cancer, and laryngeal cancer.

The aim of this study was to determine whether APEX1 (rs1130409, rs3136817), BRCA2 (rs15869), ERCC1 (rs3212986, rs11615), ERCC5 (rs17655), hOGG1 (rs1052133), XPD (rs1799793, rs13181), XRCC1 (rs25487), XRCC3 (rs861539), XRCC5 (rs11685387), XRCC6 (rs2267437, rs5751129, rs132770), and LIG4 (rs1805388) affect susceptibility to malignant neoplasms development.

Search strategy. All the analyzed articles were retrieved from PubMed, Scopus, and Web of Science online databases published up to January 2023 in the English language. The following keywords were applied during the data search: "SNP", "DNA repair gene", "association", "case-control study", and "cancer susceptibility".

Eligibility criteria. The final inclusion criteria for the meta-analysis were: (i) case-control study, (ii) no diagnosed cancer in the control group, while study group was clinically diagnosed with cancer, (iii) available genotypes and their allele polymorphisms among the groups, (iv) research on non-familial cases of cancer, (v) studies of gene polymorphisms associated with the repair of double-strand breaks in DNA and ionizing radiation.

Studies that did not meet these criteria were excluded from this meta-analysis.

Data extraction. From the eligible studies, the extracted data included: (i) the first author's name, (ii) the year of the study, (iii) the number of case-control, and (iv) the type of cancer.

Statistical modeling for meta-analysis. Meta-analysis is a statistical method of data analysis that combines the results of different scientific studies on the same issue with the results of varying degrees of error. By performing a meta-analysis, the accuracy of the overall result increases, as various statistical approaches are used that summarize and combine the results of the original

studies into some weighted average. Meta-analysis was performed using the Comprehensive Meta-Analysis software. Data from 93 articles were entered into the software according to the research models: Additive (comparison of mutant and wild-type homozygotes); Dominant (comparison of wild type + heterozygotes and mutant type); and Recessive (comparison of mutant type + heterozygotes and wild type). Results with *p*-value < 0.05 were considered statistically significant publication bias. OR (Odds Ratio) was calculated for checking the difference in odds of exposure between case and control groups. The heterogeneity of publications was calculated by using the I-sq value: an I-sq > 50% was denoted for high heterogeneity, hence a random statistical model was applied. Otherwise, the fixed model was used.

Table 1 Characteristics of the studies of hOGG1 (rs1052133) polymorphism included in the meta-analysis

First author, year	Cases			Controls		
	CC	CG	GG	CC	CG	GG
Canbay et al., 2011	31	40	8	171	69	7
Zhang et al., 2018	82	82	36	73	98	29
Jin et al., 2018	88	114	23	138	56	6
McKean-Cowdin et al., 2009	596	347	52	1150	676	112
Chang et al., 2020	4	45	69	66	236	288
Hassan et al., 2019	264	50	18	40	26	4
Wang et al., 2018	98	217	197	179	567	330
Jin et al., 2019	88	114	23	138	56	6

Table 2 Characteristics of the studies of XPD (rs1799793) polymorphism included in the meta-analysis

First author, year	Cases			Controls		
	GG	GA	AA	GG	GA	AA
Adico et al., 2023	21	37	6	22	39	3
Jelonek et al., 2010	41	59	21	52	58	8
Steck et al., group 1 2014	170	45	5	258	60	3
Steck et al., group 2 2014	136	119	40	230	238	57
Ni et al., 2014	182	26	5	210	27	3
Kabzinski et al., 2015	91	120	20	109	118	2
Chen et al., 2012	155	182	56	177	186	47

Table 3 Characteristics of the studies of XRCC6 (rs5751129) polymorphism included in the meta-analysis

First author, year	Cases			Controls		
	TT	TC	CC	TT	TC	CC
Chin-Mu Hsu et al., 2013	228	58	12	266	28	4
Te-Chun Hsia et al., 2012	290	59	9	642	66	8
Huang et al., 2015	131	35	10	305	40	7
Bau et al., 2008	253	60	5	284	31	3
Rajaej et al., 2014	193	168	46	195	157	43
Yang et al., 2011	106	26	4	502	52	6

Table 4 Meta-analysis of the association between hOGG1 (rs1052133), XPD (rs1799793), and XRCC6 (rs5751129) polymorphisms and cancer risk

Polymorphism	Statistical model	Test of association		Test of heterogeneity	I-sq
		OR	p	Model	
hOGG1 (rs1052133)	Additive (GG vs. CC)	2.039	0.010	Random	82.658
	Dominant (CC+CG vs. GG)	0.639	0.005	Random	63.668
	Recessive (GG+GC vs. CC)	1.507	0.115	Random	93.651
XPD (rs1799793)	Additive (AA vs. GG)	2.017	0.005	Random	51.296
	Dominant (GG+GA vs. AA)	0.639	0.001	Fixed	44.834
	Recessive (AA+GA vs. GG)	1.152	0.057	Fixed	0.000
XRCC6 (rs5751129)	Additive (CC vs. TT)	1.689	0.003	Fixed	41.357
	Dominant (TT+CT vs. CC)	0.647	0.010	Fixed	34.397
	Recessive (CC+CT vs. TT)	1.957	0.000	Random	73.162

A total of 93 articles that assayed the association between 16 SNPs with cancer were determined. Among them, hOGG1 (rs1052133), XPD (rs1799793), and XRCC6 (rs5751129) polymorphisms showed a statistically significant ($p < 0.05$) correlation with the risk of developing malignant neoplasms. Particularly, the hOGG1 (rs1052133) showed that the mutant genotype almost doubles the risk of developing malignant neoplasms (colorectal cancer, glioblastoma, renal cell carcinoma, and chronic myelogenous leukemia). Almost equivalent degree of association was measured with XPD (rs1799793), which showed a significant correlation with colon cancer, colorectal cancer, breast cancer, glioma, and non-small cell lung cancer. The XRCC6 (rs5751129) showed slightly fewer OR, and was correlated with hepatocellular carcinoma, lung cancer, nasopharyngeal carcinoma, oral cancer, and gastric cancer.

All estimated published publications were executed under accredited genotyping methods.

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PHENOTYPIC AND GENOTYPIC ANALYSIS OF ANTI-TUBERCULOSIS DRUG RESISTANCE IN *MYCOBACTERIUM TUBERCULOSIS* ISOLATES IN ASTANA

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Tuberculosis is one of the most lethal infectious in the world. Tuberculosis is caused by the bacterial agent *Mycobacterium tuberculosis*. Current statistical data reports tuberculosis as highly transmissible infection. According to the WHO reports annual transmission is estimated at an average of about 10 million people[1]. In 2020 the number of new cases had decreased wherethrough the COVID-19 pandemic.

Mycobacterium tuberculosis together with *M.bovis, M.africanum, M.caprae, M.canetti*, and others include the Mycobacterium tuberculosis complex. Among the above species, *M.tuberculosis* considers the main contributor to the tuberculosis incidence. *Mycobacterium tuberculosis* is aerobic, small, and rod-like shape bacteria. Non-spore-forming bacillus has a size from 0.2-0.6 um. Bacterial cell walls contain high molecular weight lipids such as cord factor glycolipids and mycolic acids[2]. The bacillus is visible on cultural media in 3-8 weeks while the cell can take typically 18 hours to divide.

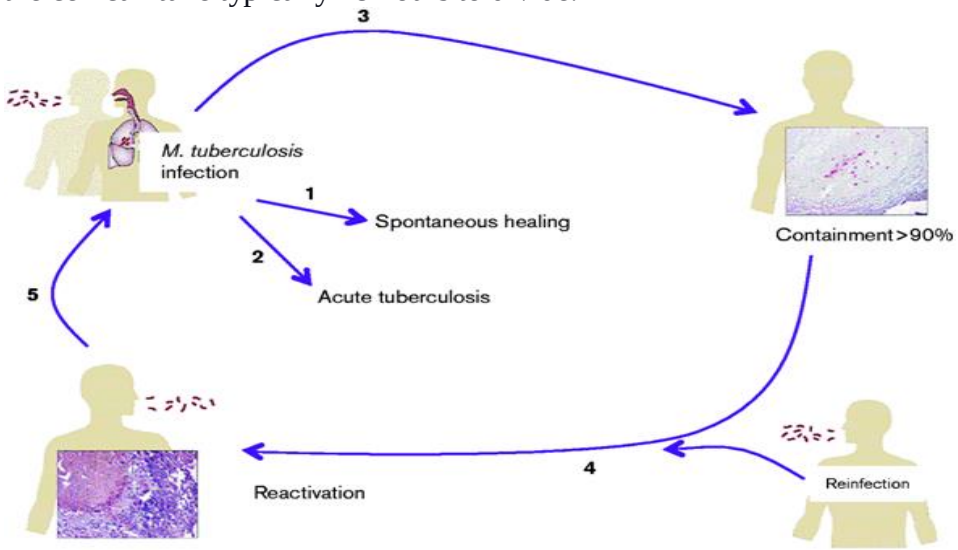

Figure 1 Transmission of tuberculosis[3].