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CARCINOGENICITY OF IONIZING RADIATION: A LITERATURE REVIEW

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ABSTRACT

Relevance: *According to WHO, malignant neoplasms rank second in population mortality structure due to a constantly increasing influence of technogenic factors that have a direct carcinogenic effect on the body and suppress defense mechanisms. Ionizing radiation plays a special role in the development of cancer. It is used in industry, agriculture, medicine, and scientific research as a diagnostic tool in modern healthcare and radiation therapy for cancer treatment. The consequences of radiation influence are not only the result of a direct effect on the body but also a delayed one through generations of parents and grandparents. According to the radiobiological hypothesis, any level of radiation, no matter how small, poses a risk of long-term consequences, including cancer, in exposed people and their descendants of the first two generations. That is, cancerous tumors are likely consequences of the influence of radiation. Despite various theories of the biological effect of low doses of ionizing radiation, most authors attach primary importance to DNA damage in the manifestation of genetic effects (the concept of non-threshold mutational action).*

The study aimed to *highlight the role of ionizing radiation in tumorigenesis.*

Methods: *Data from MEDLINE, Embase, Scopus, PubMed, and Cochrane Central Register of Controlled Trials was analyzed to select and analyze relevant information over the past 10 years using such keywords as "gamma irradiation," "spontaneous oncogenesis," and "prevention of oncogenesis."*

Results: *Radiation exposure may increase the risk of cancer development due to epigenetic changes leading to increased genomic instability (GI) and/or specific suppression of tumor suppressor genes. Changes in the TP53 gene network expression occur; the most significant genes as predictors of carcinogenesis are ST13, IER3, BRCAI, LRDD, and MRAS. Epigenetic changes also influence individual susceptibility to radiation-induced cancer. In addition to the mutagenic effects of ROS and AFN, there is also evidence that oxidative stress plays a fundamental role in epigenetic modifications.*

Conclusion: *As a result of radiation exposure, damage occurs that causes genetic and epigenetic changes, leading to changes in the level of protein expression due to changes in the methylation of cytosine residues in DNA, modification of histones, and regulation of microRNA expression.*

Keywords: *gamma irradiation, spontaneous oncogenesis, prevention of oncogenesis.*

Introduction: Oncological diseases remain one of the most important problems of modern health care and medicine. According to the Minister of Health of the Republic of Kazakhstan, at the end of 2022, "in Kazakhstan, oncological diseases ranked 7th among all diseases, while circulatory system diseases ranked 2nd in mortality. As of today, over 205,000 patients with cancer are under dynamic follow-up in Kazakhstan. Besides, more than 37 thousand new cases are detected annually. Of these cases, 56% are people of employable age." The generally recognized reason for such morbidity and mortality from malignant neoplasms (MN) is a constantly growing influence of technogenic factors. They have a direct carcinogenic effect on the human body and suppress its protective mechanisms, primarily immune reactivity. Ionizing radiation occupies a special place among factors contributing to MN development. The scientific and technological achievements increase the number and power of radiation sources, including nuclear power stations and various less-capacity sources widely used in industry, medicine, and science.

The first test nuclear explosion at the Semipalatinsk Test Site occurred on August 29, 1949. The power capacity of the first bomb was 22 kilotons. In total, from 1949 to 1989, at least 468 nuclear tests, both surface and underground, have been carried out at this test in Kazakhstan. During the period of unprecedented nuclear weapons tests, the radioecological situation in the region changed dramatically, affecting the morbidity indicators, the course of certain nosological forms, and a higher contribution to radiation-induced pathologies. Recent research revealed a higher frequency of MNs, hereditary pathologies, and general somatic diseases among the population exposed to radiation. The age at exposure, the time from the exposure, and the radiation dose were found to influence cancer morbidity and mortality. In a directly irradiated population, the cancer pathologies are dominated by MNs of the digestive and respiratory organs. In contrast, cancers of the breast, female genital organs, lymphoid and hematopoietic tissues, eye, brain, and other parts of the central nervous system, as well as bones and articular cartilag-

es, prevail in the descendants of the second and third generations [1-4].

The study aimed to highlight the role of ionizing radiation in tumorigenesis.

Materials and methods: Data from MEDLINE, Embase, Scopus, PubMed, and Cochrane Central Register of Controlled Trials was analyzed to select and analyze relevant information over the past 10 years using such keywords as "gamma irradiation," "spontaneous oncogenesis," and "prevention of oncogenesis."

Results:

Carcinogenicity. Radiation-induced cancer

Vast accumulated experimental material and clinical observations show that MNs can develop in almost any body tissue under the influence of ionizing radiation. However, the most common are MNs of the skin and bones, endocrine-dependent tumors (ovarian, breast, thyroid, and prostate cancers), and leukemias [5].

The absorbed dose and several other factors, like inherited body type, sex, age, and others, determine the probability of developing radiation-induced solid tumors and leukemias. The immunological and hormonal status, vascular trophism, cell kinetics, and other features can decisively affect tumor incidence [6-10]. Cancer was once considered a "genetic accident" that results from accumulating random (stochastic) DNA mutations. The stochastic effects, currently more associated with ionizing radiation effects, appear as mutations and then develop into latent genome damage and clinical manifestations such as oncological and genetic pathologies. Currently, there is a broad consensus that cancer is a result of both genetic and epigenetic changes. Several studies indicate that cancer is a failure of genome regulation due to the malfunction of mechanisms that regulate the antimutation activity and prevent epigenetic modification [11, 12]. Sharp changes in DNA methylation are common in cancer and are considered early events in many cancer cases. They appear even more frequent than genetic mutations [13-15]. Loss of methylation throughout the genome, especially in repetitive elements [16], contributes to gastrointestinal neoplasms and is a main sign of cancer [17, 18]. Over 300 genes and gene products are epigenetically altered in various types of human cancer [19]. A meta-analysis of altered genes in colorectal cancer confirms their involvement in oncogenesis [20].

The role of tumor suppressor gene hypermethylation in radiation-induced cancer was demonstrated. Suppression of the suppressor genes has been demonstrated in the studies in mouse models of radiation-induced lymphoma, lung tumors in rats, and lung adenocarcinoma in workers at the "Mayak" plutonium plant in Russia [21, 22]. The aberrant hypermethylation was observed in many patients with renal cell carcinoma living in areas radioactively contaminated after the Chornobyl Atomic Power Station accident [23]; the DNA hypermethylation of tumor suppressor genes was found in workers exposed to radon in uranium mines [24].

The above results indicate that radiation exposure, although generally considered pathogenic due to DNA damage such as deletions and point mutations [25], may also increase cancer risk due to epigenetic changes that increase genomic instability (GI) and/or the specific suppression of tumor suppressor genes.

It is now recognized that epigenetic and genetic changes are involved in cancer initiation and progression [26, 27]. Epigenetic changes also affect individual susceptibility to radiation-induced cancer. Differences in sensitivity to radiation between individuals or groups of individuals may be associated with gender, age at exposure, health status, genetic and epigenetic changes, lifestyle, and age lived [28].

Several studies have shown that epigenetic regulation underlies the radiation-induced instability of the transgenerational genome [29-33], i.e., radiation-induced damage can induce GI. Small doses of ionizing radiation induce cellular replication of primary and delayed dysgenic effects, resulting in a poly-genomic imbalance in the body and dysfunction of cells, tissues, and organs. This affects the differentiation processes by reducing the biological stability of the organism and increasing the risk of stochastic diseases, including MNs [34, 35]. At the cytogenetic level, the transmissible chromosomal instability is transmitted through the parents' irradiated germ cells to their offspring's somatic cells [36].

The most relevant radiation-induced changes include 1) radiation-induced epigenetic effects, i.e., changes in the gene expression, e.g., by altering the structure of DNA and chromatin without altering the DNA sequence; 2) nonlinear responses, such as non-target effects (NTES), i.e., effects observed in cells not directly exposed to radiation (side effects, BE) or occurring in the offspring of irradiated cells or observer cells (GI), as well as (radio)-adaptive response. All these NTES can be described as the expression of inter- or intracellular signaling and are considered particularly relevant for cellular response to low-dose radiation [8].

Molecular mechanism of radiation oncogenesis

Ionizing radiation can cause various DNA changes, including base damage, sugar-phosphate backbone damage, single-strand breaks, double-strand breaks (DSBs), and the DNA-DNA cross-links and DNA-protein cross-links. The clustered DNA lesions, such as complex DSBs and non-DSB clustered lesions, are the most biologically significant radiation-induced DNA damage [37-40]. Unrepaired or incorrectly repaired DNA damages cause changes in DNA sequence, the genetic mutations,

which are the main cause of harmful biological effects, and lead, even at low doses, to an elevated incidence of MNs and hereditary diseases inherent in the population [41]. The most common consequence of wrong reparations is the loss of heterozygosity. In addition to the gene with broken DNA, heterozygosity extends to proximal and distal genes. Wrong reparation leads to deletions and reciprocal translocations. They inactivate suppressor genes and proto-oncogenes, which leads to the induction of MNs (leukemias, lymphomas, and others). Expression of the TP53 gene network changes. The ST13, IER3, BRCAI, LRDD, and MRAS genes are the most significant predictors of carcinogenesis [8]. Structural and functional disorders of the genome of immunocompetent cells include an increased number of proliferating cells with CD71 marker and $CD95^+$ and $CD16^+$ cells, which are markers of readiness for apoptosis [42].

Main mechanisms of radiation-induced genetic and epigenetic changes

It is well known that ionizing radiation can cause DNA damage through direct accumulation of energy in DNA and indirect action of active chemical particles formed near DNA [38]. Radiation with high linear energy transfer (LET) mainly causes direct DNA damage, while radiation with low LET mainly leads to indirect DNA damage by free radicals in water. These radicals are formed by water radiolysis. Under aerobic conditions, these free radicals convert into reactive oxygen species (ROS); organic radicals appear, which produce peroxyl radicals and hydroperoxides [43]. Reactive nitrogen species (ANS), generated by radiation, produce nitric oxide, which reacts with superoxide radicals to form peroxynitrite [44]. The radiation quality modulates the output and spatial distribution of ROS and ANS. They can cause several changes, including DNA breaks, base damage, and destruction of sugars, which, if not addressed, can lead to genetic mutations in surviving cells. ROS can be generated directly by radiation and indirectly through mitochondrial damage. This activates the signal pathway that supports the elevation of ROS due to increased oxidase expression and creates a cycle of high oxidative stress, i.e., an excess of ROS/ANS, not compensated through mechanisms of antioxidant cell protection [45].

In addition to ROS and ANS mutagenic effects, there is evidence of a fundamental role oxidative stress plays in epigenetic modifications [46, 47]. Oxidative stress can modify the epigenome through various mechanisms, the most important of which include DNA base oxidation and changes in mitochondria, the primary target being the CpG sites, especially in CpG islets [48-50].

Discussion: Children exposed to radiation or radiation-chemical effects or born from irradiated or chemically exposed parents are at risk of developing stochastic pathologies, including genetic diseases, undifferentiated mental retardation, malignant neoplasms, leukemias, etc. According to international organizations [10], these effects can theoretically be caused by exposure of any magnitude. Stochastic effects, which are now largely attributed to the impact of ionizing radiation or other chemical, physical, and biological agents, reappear in various mutations. They increase the likelihood of spontaneous mutations registered under natural conditions and expressed as hidden genomic damage, ultimately resulting in oncological or genetic pathology.

Ionizing radiation causes direct damage to cell DNA and indirect cell damage by ROS impact. The resulting mutations of all types – chromosomal and genomic, single- and two-strand breaks (or other changes), – and cell repair disorders can lead to cell apoptosis, chromosomal instability, mutation, and/or oncogenesis.

The study of direct radiation effects in modern radiobiology and radiation medicine pays much attention to the dynamics of free radical oxidation of lipids, which are important energy substrates, and their role in developing "genome instability." The descendants of exposed persons present a pathological imbalance of "peroxidation/antioxidative defense" at the cellular (chromosomal aberrations, mutations, iatrogenic cell death, etc.) and cytogenetic levels. Chromosomal instability is transmitted through parental germ cells and manifests in somatic cells of the descendants. Low-intensity ionizing radiation does not kill the body cells but modifies cell-tissue processes. It activates free radical mechanisms, increases DNA breaks' frequency, accelerates aging, and intensifies apoptosis and compensatory cell proliferation.

The body responds by activating the reparative and compensatory-restorative processes. The genomic DNA repair system is an anti-mutagenic defense mechanism that restores the broken and/or lost DNA strands. The level of such protection is determined by genetic characteristics (how effectively the genotype of an individual or species forms the antitumor immune system, the genome repair system) and the intensity of oxidative stress – the lipid peroxidation and antioxidative defense ratio and interrelation.

These environmental risk factors affect the genetic apparatus responsible for precisely reproducing features and traits in generations and regulating all body processes. These factors underlie the current increase in the frequency of mutations, congenital deformities, and MNs. The most important environmental risk factors include air and drinking water pollution. Among the consequences are carcinogenesis, mutagenesis, embryo- and gonadotropic effects of physical and chemical agents, and relevant effects with long-term implications.

Since radiation acting independently or in combination with other exo- and endogenous factors increas-

es the risk of free radical and genomic damage, the descendants of exposed parents are at high risk of genetic consequences. Radiation-induced changes in the body have a phase character: at different times after the irradiation of parents, they are manifested by activation or inhibition of adaptive and, most importantly, reparative processes. Therefore, the study of the genesis and development of spontaneous MNs in descendants of irradiated parents is one of the priorities of radiation medicine. Prevention of such induced pathologies is a primary task of radiobiology, radiation medicine, oncology, and pediatrics.

Conclusion: Consequently, radiation-induced oxidative stress plays an important role in the epigenetic landscape of the entire genome [51]. This landscape is formed by cross-coupling effects of DNA methylation and histone and non-coding RNA (particularly microRNAs) modification [52, 53]. Genetic and epigenetic mechanisms may have a common origin in radiation-induced ROS/AFN and be the basis of the observed nonlinear phenomena. The carcinogenic effect of ionizing radiation is implemented through DNA damage, either direct or mediated by generated free radicals (ROS/AFN).

These damages might cause genetic and epigenetic changes that affect protein expression levels due to alterations in cytosine residues' methylation in DNA, histone modification, and microRNA expression regulation [54]. Finally, the results of this literature review (knowledge of mechanisms of carcinogenesis) allow the use of primary prevention strategies in the field of carcinogenesis from the points of genetic and/or epigenetic paradigms to contribute to the identification of innovative "informational" therapeutic strategies [55].

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АНДАТПА

ИОНДАУШЫ СӘУЛЕЛЕНУДІҢ КАНЦЕРОГЕНДІЛІГІ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *ДДҰ деректері бойынша халық өлімінің құрылымында қатерлі ісіктердің (МНТ) үлесі екінші орында. Оның себебі – организмге тікелей канцерогенді әсер ететін және қорғаныс механизмдерін басатын техногендік факторлардың әсерінің үнемі артуы. Қатерлі ісіктің дамуында иондаушы сәулелер ерекше рөл атқарады. Ол өнеркәсіпте, ауыл шаруашылығында, медицинада және ғылыми зерттеулерде, заманауи денсаулық сақтауда диагностикалық құрал ретінде, сондай-ақ қатерлі ісіктерді емдеуге арналған сәулелік терапияда қолданылады. Радиациялық әсердің салдары денеге тікелей әсер етудің нәтижесі ғана емес, сонымен бірге ата-аналар мен ата-әжелер ұрпақтары арқылы кейінге қалдырылады. Радиобиологиялық гипотезаға сәйкес, сәулеленудің кез келген деңгейі, қаншалықты аз болса да, ұзақ мерзімді салдарлардың, соның ішінде қатерлі ісіктің, зардап шеккен адамдарда және олардың алғашқы екі ұрпақтарының ұрпақтарында қауіп төндіреді. Яғни, радиация әсерінің салдары қатерлі ісік болуы мүмкін. Иондаушы сәулеленудің төмен дозаларының биологиялық әсерінің әртүрлі теорияларының болуына қарамастан, авторлардың көпшілігі генетикалық әсерлердің көрінісінде ДНҚ-ның зақымдалуына бірінші кезектегі мән береді (табалдырықсыз мутациялық әрекет тұжырымдамасы).*

Зерттеудің мақсаты *– ісік пайда болудағы иондаушы сәулеленудің рөлін көрсету.*

Әдістері: *MEDLINE, Embase, Scopus, PubMed, Cochrane бақыланатын сынақтардың орталық тізілімінің деректеріне талдау «гамма-сәулелену», «стихиялы онкогенез», «онкогенездің алдын алу» кілт сөздерін пайдалана отырып, соңғы 10 жылдағы сәйкес ақпаратты таңдау және талдау үшін жүргізілді.*

Нәтижелер: *радиациялық әсер эпигенетикалық өзгерістерге байланысты қатерлі ісіктің даму қаупін арттыруы мүмкін, бұл геномдық тұрақсыздықтың (GI) жоғарылауына және/немесе ісік супрессоры гендерінің спецификалық басылуына әкеледі. TP53 гендік желісінің экспрессиясында өзгерістер орын алады; канцерогенездің болжаушылары ретінде ең маңызды гендер ST13, IER3, BRCA1, LRDD, MRAS болып табылады. Эпигенетикалық өзгерістер жеке адамның радиациядан туындаған ісікке бейімділігіне де әсер етеді. ROS және AFN мутагендік әсерлерінен басқа, тотығу стрессінің эпигенетикалық модификацияларда іргелі рөл атқаратыны туралы дәлелдер де бар.*

Қорытынды: *Сәулелену әсерінің нәтижесінде генетикалық және эпигенетикалық өзгерістерді тудыратын зақымданулар пайда болады, бұл ДНҚ-дағы цитозин қалдықтарының метилденуінің өзгеруіне, гистондардың модификациясына және микроРНҚ экспрессиясының реттелуіне байланысты белок экспрессиясының деңгейінің өзгеруіне әкеледі.*

Түйінді сөздер: *гамма-сәулелену, спонтанды онкогенез, онкогенездің алдын алу.*

АННОТАЦИЯ

КАНЦЕРОГЕННОСТЬ ИОНИЗИРУЮЩЕГО ИЗЛУЧЕНИЯ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *По данным ВОЗ, злокачественные новообразования (ЗНО) находится на втором месте в структуре причин смертности населения. Поводом для этого служит постоянный рост влияния техногенных факторов, оказывающих прямое канцерогенное воздействие на организм и подавляющих защитные механизмы. Особая роль в развитии ЗНО отводится ионизирующему излучению. Оно используется в промышленности, сельском хозяйстве, медицине и научных исследованиях, как диагностическое средство в современном здравоохранении, а также в лучевой терапии – для лечения ЗНО. Радиационное облучение оказывает не только прямое действие на организм, но и отсроченное, через поколения родителей и прародителей. Согласно радиобиологической гипотезе, любой сколь угодно малый уровень облучения представляет риск возникновения отдаленных последствий, в том числе*

ЗНО, у облучённых людей и их потомков первых двух поколений. То есть ЗНО являются вероятными последствиями влияния радиации. Несмотря на существование различных теорий биологического действия малых доз ионизирующего излучения, большинство авторов придают повреждению ДНК первостепенное значение в возникновении генетических эффектов (концепция беспорогового мутационного действия).

***Цель исследования** – освещение роли ионизирующей радиации в онкогенезе.*

***Методы:** Проведен анализ данных MEDLINE, Embase, Scopus, PubMed, Cochrane Central Register of Controlled Trials для отбора и анализа релевантной информации за последние 10 лет по ключевым словам: «гамма-облучение», «спонтанный онкогенез», «профилактика онкогенеза».*

***Результаты:** Радиационное воздействие может повышать риск развития рака из-за эпигенетических изменений, приводящих к увеличению геномной нестабильности и/или специфическому подавлению генов-супрессоров опухоли. Происходят изменения экспрессии генной сети TP53; наиболее значимыми в качестве предикторов канцерогенеза являются гены ST13, IER3, BRCA1, LRDD, MRAS. Эпигенетические изменения также влияют на индивидуальную восприимчивость к радиационно-индуцированному раку. Помимо мутагенного действия активных форм кислорода и азота, есть также доказательства того, что окислительный стресс играет фундаментальную роль в эпигенетических модификациях.*

***Заключение:** В результате воздействия радиации происходят повреждения, вызывающие генетические и эпигенетические изменения, приводящие к изменению уровня экспрессии белков вследствие изменения метилирования остатков цитозина в ДНК, модификации гистонов и регуляции экспрессии микро-РНК.*

***Ключевые слова:** гамма-облучение, спонтанный онкогенез, профилактика онкогенеза.*

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