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ASSOCIATION BETWEEN EXPOSURE TO IONIZING RADIATION AND THE DEVELOPMENT OF CARDIOVASCULAR DISEASES: A LITERATURE REVIEW

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Abstract

Introduction. Pathology of the cardiovascular system is the leading cause in the structure of the causes of death in all countries of the world in recent decades. The impact of ionizing radiation on the cardiovascular system is a complex process that includes various molecular and cellular mechanisms that lead to tissue damage and disruption of their functions. The aim of our research was the analysis and evaluation of modern literature data on the possible association between exposure to ionizing radiation and the development of diseases of cardiovascular system.

Search strategy. For the search and analysis of scientific data, we used databases and web resources: MEDLINE, Pubmed, Google Scholar, Cyberleninka, and eLIBRARY. 124 literary sources were identified, of which 48 publications were the basis of the analytical material for this article.

Results. The development of circulatory diseases due to radiation exposure is based on damage to the vascular intima, primarily in the coronary arteries, changes in the endothelium associated with the accumulation of reactive oxygen species, and low-intensity inflammation leading to the development of atherosclerosis. Acute radiation injury to the heart is associated with inflammation and mitochondrial dysfunction, while chronic radiation injury is associated with myocardial fibrosis. High doses of radiation to the cardiovascular system are typically associated with radiation therapy for cancers such as breast or lung cancer. Low doses of radiation are typical for radiation situations associated with occupational exposure to ionizing radiation, as well as for residents of radiation-contaminated, environmentally unfavorable areas due to nuclear weapons testing or radiation accidents.

Conclusion. The results of the literature review demonstrate a clear link between radiation exposure over a wide range of doses and excess risks of circulatory diseases, primarily coronary heart disease, stroke, myocardial infarction, and hypertension.

***Key words**: ionizing radiation, circulatory system diseases, radiation doses, mortality, morbidity.*

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Резюме

СВЯЗЬ МЕЖДУ ВОЗДЕЙСТВИЕМ ИОНИЗИРУЮЩЕГО ИЗЛУЧЕНИЯ И РАЗВИТИЕМ СЕРДЕЧНО-СОСУДИСТЫХ ЗАБОЛЕВАНИЙ: ОБЗОР ЛИТЕРАТУРЫ

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Введение. Патология сердечно-сосудистой системы является лидирующей причиной в структуре причин смерти во всех странах мира в последние десятилетия. Воздействие ионизирующего излучения на сердечно-сосудистую систему является сложным процессом, включающим разнообразные молекулярные и клеточные механизмы, приводящие к повреждению тканей и нарушению их функций. Целью исследования явился анализ и оценка современных литературных данных о возможной связи между воздействием ионизирующей радиации и развитием патологии сердечно-сосудистой системы.

Стратегия поиска. Для поиска и анализа научных данных использовались базы данных и веб-ресурсы: MEDLINE, Pubmed, Google Scholar, Cyberleninka, eLIBRARY. Было выявлено 124 литературных источника, из которых 48 публикаций легли в основу аналитического материала данной статьи.

Результаты. В основе развития болезней системы кровообращения при радиационном воздействии лежат повреждение интимы сосудов, в первую очередь, коронарных артерий, изменения в эндотелии, связанные с накоплением активных форм кислорода, а также малоинтенсивное воспаление, ведущее к развитию атеросклероза. Острое лучевое повреждение сердца связано с воспалением и митохондриальной дисфункцией, а хроническое с фиброзом миокарда. Высокие дозы облучения сердечно-сосудистой системы связаны, как правило, с лучевой терапией онкологических заболеваний, таких как рак молочной железы или рак легкого. Низкие дозы облучения характерны для радиационных ситуаций, связанных с профессиональным воздействием ионизирующей радиации, а также для жителей радиационно-загрязненных экологически неблагоприятных территорий вследствие испытаний ядерного оружия либо радиационных аварий.

Заключение. Результаты обзора литературных источников свидетельствуют о связи между радиационным воздействием в широком диапазоне доз и избыточными рисками болезней системы кровообращения, в первую очередь, ишемической болезни сердца, инсультами, инфарктом миокарда и артериальной гипертензией.

***Ключевые слова**: ионизирующая радиация, болезни системы кровообращения, дозы облучения, смертность, заболеваемость.*

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Түйіндеме

ИОНДАУШЫ РАДИАЦИЯНЫҢ ӘСЕРІ МЕН ЖҮРЕК-ҚАНТАМЫР АУРУЛАРЫНЫҢ ДАМУЫ АРАСЫНДАҒЫ БАЙЛАНЫС: ӘДЕБИ ШОЛУ

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Кіріспе. Соңғы онжылдықтарда жүрек-қантамыр жүйесі патологиясы әлемнің барлық елдерінде өлім себептері құрылымында жетекші орын алады. Иондаушы сәулеленудің жүрек-қантамыр жүйесіне әсері — ұлпалардың зақымдануы мен олардың қызметінің бұзылуына әкелетін алуан түрлі молекулалық және жасушалық механизмдерді қамтитын күрделі үдеріс. Зерттеудің мақсаты – иондаушы радиацияның әсері мен жүрек-қантамыр жүйесі патологиясының дамуы арасындағы мүмкін байланысты сипаттайтын қазіргі заманғы әдеби деректерді талдау және бағалау.

Іздеу стратегиясы. Ғылыми деректерді іздеу және талдау үшін MEDLINE, PubMed, Google Scholar, Cyberleninka, eLIBRARY деректер базалары мен веб-ресурстары пайдаланылды. 124 әдеби дерек анықталып, олардың ішінде 48 жарияланым осы мақаланың талдамалық материалының негізіне алынды.

Нәтижелер. Радициялық әсер кезінде қанайналым жүйесі ауруларының дамуында ең алдымен коронарлық артериялар интима қабатының зақымдануы, белсенді оттегі түрлерінің жиналуымен байланысты эндотелий өзгерістері,

сондай-ақ атеросклероздың дамуына алып келетін төмен қарқынды қабыну үрдістері маңызды рөл атқарады. Жедел радиациялық жүрек зақымдануы қабынумен және митохондриялық дисфункциямен байланысты болса, созылмалы зақымдану миокард фиброзына әкеледі. Жүрек-қантамыр жүйесінің жоғары дозада сәулеленуі көбінесе сүт безі обыры немесе өкпе обыры сияқты онкологиялық ауруларды сәулелік терапиямен емдеуге тән. Төмен дозалар, әдетте, иондаушы радиацияның кәсіптік әсерімен немесе ядролық қару сынақтары мен радиациялық апаттар салдарынан экологиялық қолайсыз, радиациялық ластанған аймақтарда тұратын халыққа тән.

Қорытынды. Әдеби деректерге жасалған шолу радиациялық әсердің кең дозалық ауқымында жүрек-қантамыр жүйесі ауруларының, ең алдымен ишемиялық жүрек ауруы, инсульт, миокард инфарктісі және артериялық гипертензияның артық қаупімен сөзсіз байланысты екенін көрсетеді.

Түйінді сөздер: *иондаушы радиация, қанайналым жүйесі аурулары, сәулелену дозалары, өлім-жітім, сырқаттанушылық.*

Дәйексөз үшін:

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Introduction

The effect of ionizing radiation on the human body in most cases is manifested by an increased risk of developing malignant neoplasms [13]. This effect has been demonstrated in a number of studies, most notably in the Life Span Study (LSS) cohort study of the health status of survivors of the bombing in Japan [29]. A series of reports found that there was a 17% excess risk of cancer among the affected population. Furthermore, it was demonstrated that the excess relative risk (ERR) per Gy was 0.42 Gy-1 (95% CI 0.32–0.53) for all solid cancers among the affected population of Japan.

One area of interest has been determining the radiation dose that is a factor in adverse prognosis [31]. In the aforementioned LSS study, the minimum dose range associated with an increased risk of ERR was 0–0.2 Gy for malignant tumors. For a long time, possible non-oncologic effects of ionizing radiation were virtually excluded. However, modern epidemiological data, particularly studies among atomic bomb survivors, indicate an increased risk of cardiovascular diseases CVD [6,21].

It is well known that cardiovascular pathology has been the leading cause of death worldwide in recent decades [45]. The main known modifiable risk factors for circulatory system diseases include nicotine addiction, diabetes mellitus, arterial hypertension, excess weight, hypercholesterolemia, and elevated levels of low-density lipoproteins [43]. The risks of developing CVD when exposed to ionizing radiation have not been sufficiently studied. They are primarily associated with diagnostic procedures and radiation treatment of oncological diseases, since in these cases the radiation doses are clearly defined and belong to the high-dose range (> 5 Gy) [40]. Exposure to such radiation doses causes damage to the structures of the heart, as well as the coronary, carotid, and other large arteries [3]. The effects of ionizing radiation on the cardiovascular system are complex, involving a variety of molecular and cellular mechanisms that lead to tissue damage and dysfunction. Key mechanisms include endothelial cell damage, accelerated atherosclerosis, inflammation, oxidative stress, fibrosis, and alterations in metabolic pathways [38, 7].

The aim of our research was the analysis and evaluation of modern literature data on the possible association between exposure to ionizing radiation and the development of diseases of cardiovascular system.

Search strategy

For the search and analysis of scientific data, we used databases and web resources: MEDLINE, Pubmed, Google Scholar, Cyberleninka, and e-LIBRARY. For the literature review, we used sources published from 1998 to 2025. Scientific articles were used that correspond to the topic and the basic context of the study. During the selection of literature for writing an article, preference was given to publications in peer-reviewed publications. During the primary analysis, a general array of articles was selected, which was filtered for compliance with keywords and context. As a result of the primary selection, 124 literary sources were identified, of which 45 publications were the basis of the analytical material for this article.

Inclusion criteria: reports of randomized and cohort studies, systematic reviews and meta-analyses, diagnostic and treatment protocols, and articles in English. Exclusion criteria: personal communications, newspaper publications, abstracts, and articles with fuzzy conclusions.

Results and discussion

Pathogenetic mechanisms of cardiovascular pathology development under the influence of ionizing radiation

Radiation-induced circulatory pathology, according to many studies, is associated with acute exposure to high doses of radiation [21, 26]. The effect of high doses of ionizing radiation on blood vessels is well illustrated by the example of radiation therapy for cancer, which is accompanied by damage to the vascular intima. At the level of large vessels, such damage is similar to atherosclerotic lesions. Similar changes are observed, for example, in the coronary arteries during the treatment of lung or mediastinal cancer, as well as in peripheral arteries during the treatment of corresponding cancer sites. At the microvascular level, endothelial damage is observed, leading to damage to internal organs such as the kidneys, skin, and brain [1].

The early development and progression of atherosclerotic cardiovascular diseases is primarily based on the development of endothelial dysfunction with the accumulation of reactive oxygen species in endothelial cells, as well as chronic low-intensity inflammation, which plays a key role in atherogenesis [38]. Thus, a number of studies, including experimental ones, have shown that exposure to high radiation doses can lead to

an increase in the levels of adhesion molecules, such as intracellular adhesion molecule 1 (ICAM-1), vascular adhesion molecule 1 (VCAM-1), E-selectin, and platelet endothelial adhesion molecule (PECAM-1) [5, 44]. In addition, another probable mechanism of dysfunction has been shown: a decrease in the activity of thrombomodulin and an increased formation of von Willebrand factor, one of the key factors of endothelial dysfunction [41].

In recent years, the concept of radiation-induced heart disease, which occurs as a result of radiation therapy, has emerged. In an experimental study on mice irradiated with a dose of 30 Gy of 60Co γ-rays, a significant number of inflammatory cells was detected, and after one and a half months, an increase in hypertrophied cardiomyocytes and increased myocardial fibrosis. Furthermore, radiation-induced heart disease was associated with the expression of the Cmpk2, Ifit3, Dhx58, Slc2a1, and Thbs1 genes. The results of the study allowed the authors to conclude that acute radiation injury to the heart is associated with inflammation and mitochondrial dysfunction, while chronic radiation injury is associated with myocardial fibrosis [23, 32]. Diffuse fibrosis, following high-dose exposure, affects not only the myocardium but also the pericardium, causing pericardial adhesions, microvascular damage, damage to the intracardiac conduction system, and valvular stenosis, as well as stenosis of the coronary, carotid, and other major arteries. These effects can occur both in humans receiving radiation therapy and in experimental animals [2].

Effects of high doses of ionizing radiation on the cardiovascular system

High risks of radiation-induced cardiac pathology are associated with postoperative radiation therapy for malignant breast neoplasms. Doses to individual parts of the heart muscle during this type of treatment can exceed 40 Gy with fractionated double irradiation of 20 Gy. When calculated for the entire heart muscle, this dose corresponds to 1-2 Gy [32]. Mortality rates from circulatory diseases in women who underwent surgery and radiation exposure were almost 30% higher than in women who received surgery alone [8]. Adverse effects on the heart are observed more often with left-sided neoplasms than with right-sided cancers. Radiation doses to the heart in patients with left-sided tumors undergoing radiation therapy are higher than in patients with right-sided tumors undergoing radiation therapy [10]. This is confirmed by the results of a large-scale epidemiological study of 72,000 breast cancer patients with a 30-year follow-up period. In this cohort, women with left-sided cancers (average radiation dose greater than 6 Gy) had an increased risk of coronary heart disease, pericarditis, and valvular defects compared to patients with tumors located on the right (average radiation dose to the heart of approximately Gy) [26].

Some studies have reported involvement of the immune system in response to exposure to ionizing radiation. In particular, variations in T-cell and B-cell populations depending on radiation doses were found in Japanese atomic bomb survivors [16]. This relationship is especially pronounced with irradiation of the bone marrow or the whole body. It is assumed that radiation exposure causes death of monocytes in the arterial intima, which is associated with the development of atherosclerosis [19]. Monocyte adhesion is associated with radiation-induced aging of the vascular endothelium [24]. With regard to arterial hypertension, the kidneys are considered to be the main target organ for radiation exposure, which is confirmed both by experimental studies and in a study conducted in a cohort of atomic bomb survivors in Japan [12, 17].

Effects of low doses of ionizing radiation on the cardiovascular system

There is evidence that cardiovascular diseases may also be associated with lower levels of radiation exposure, particularly occupational exposure [18, 20, 11]. Some studies conducted in the last decade suggest an excess radiation-related risk at doses received in occupational settings or in unfavorable environmental conditions (<0.5 Gy/L) [20, 21, 22], but the existence of such risks and their magnitude remain unclear. The primary cause of damage to the vascular network is systemic hypoxia, which affects the function of many organs, primarily the myocardium and brain. At moderate radiation doses averaging approximately 50 cGy, the cardiovascular risks for exposed individuals were comparable to those associated with cancer [22].

Cohorts of atomic bomb survivors in Japan

Ecological studies examining the relationship between morbidity and mortality from cardiovascular disease and radiation exposure primarily include studies on cohorts of individuals who survived the atomic bombing in Japan and who received relatively high doses of external gamma radiation in a single instance. For example, the Life Span Study (LSS) cohort study revealed an excess of mortality associated with cardiovascular disease and stroke [35]. These studies have reliably established a link between ionizing radiation from nuclear testing and mortality from the main circulatory diseases – stroke and coronary heart disease (CHD). Thus, the ERR for ischemic stroke was 0.04 Gy-1 (95% CI -0.1, 0.2), for hemorrhagic stroke 0.05 Gy-1 (95% CI -0.06-0.17), while this indicator was 0.58 (95% CI 0.45-0.72) for all cases of CVD [36].

Another study conducted in the same cohort found increased risks of LSS, arterial hypertension, and acute coronary syndrome, but these indicators were not statistically significant [47]. These risks were significantly increased among cohort members exposed in early childhood, but among individuals exposed in utero, the risks of CVS were significantly lower. It should be noted that cohort members exposed in utero had lower doses than those exposed in childhood [39].

According to the study by Preston D.L. et al. (2003), in the LSS cohort, the excess relative risk (ERR) estimates were 0.17 with 90% CI (0.08–0.26) for all circulatory diseases and 0.12 (90% CI, 0.02–0.22) for stroke for the period from 1968 to 1997 [31]. In the study by Takahashi et al., who also studied this population, an increased risk of developing valvular heart disease, more often of rheumatic genesis, was established. Thus, the ERR/Gy for rheumatic heart diseases was 0.96 Gy-1 (95% CI 0.28–1.92), while for coronary heart disease only a slight increase was observed - 0.03 Gy-1 (95% CI -0.08–0.15) [37].

It should be noted that the unique situation of the atomic bomb survivors in Japan was that ionizing radiation was not the only factor. The victims also suffered burns, multiple injuries to various organs and bones, and severe stress, which could have affected their health and led to the development of cardiovascular diseases in subsequent years.

Persons exposed to occupational radiation

Adverse effects of radiation exposure have been identified not only among those affected by nuclear weapons testing, but also among occupational groups. For example, the International Nuclear Worker study (INWORKS) found a significant increase in the risk of cardiovascular diseases (CVD), including coronary heart disease (ERR 0.18; 95% CI 0.004–0.36), acute myocardial infarction (ERR 0.26; 95% CI 0.003–0.51), and chronic cerebrovascular diseases (ERR 0.5; 95% CI 0.12–0.94) [11].

In 2007, the International Agency for Research on Cancer (IARC) conducted a large-scale study examining the risk of various diseases among nuclear energy workers in fifteen countries. The study's results suggested increased risks of mortality from CVD in general, cerebrovascular diseases, and certain circulatory diseases, but not from heart failure or deep vein thrombosis; however, the results were not statistically significant [42].

Another significant group of professionals exposed to single-dose radiation is the Chernobyl disaster liquidators. The dose range was very wide. In this group, the risks of not only mortality but also cardiovascular disease (CVD) incidence related to radiation exposure were studied. This cohort exhibited an excess incidence of coronary heart disease and stroke, and a link was established between these and exposure to ionizing radiation. However, no such link was found for arterial hypertension [17].

The effects of ionizing radiation on circulatory diseases have been studied in considerable detail using workers at the Mayak Production Association in the Chelyabinsk Region, who produce nuclear weapons components and isotopes, as well as store and recycle spent nuclear fuel. A distinctive feature of radiation exposure for this group is the relatively high average whole-body dose (approximately 0.5–0.6 Gy) that accumulated over a long period of time. Furthermore, the majority of this dose was delivered via α-emitting plutonium radioisotopes, representing internal doses, primarily to the liver. In this cohort of professionals, trends toward increased coronary heart disease and cerebral vascular pathology, both for morbidity and mortality, were also identified [4]. A study including representatives of the Mayak cohort of workers demonstrated dose-dependent trends for CHD (ERR 0.06 Gy-1; 95% CI 0.001–0.13) and cerebrovascular disease (ERR 0.00 Gy-1; 95% CI -0.06–0.08) [4]. An excess relative risk of cardiovascular mortality per Sievert was also found in a group of UK radiation industry workers (ERR 0.25 Sv−1), but this figure was of borderline significance [28].

In a cohort study conducted in China, it was found that long-term exposure to low doses of ionizing radiation is also a risk factor for the development of hypertension (RR = 2.09; 95% CI: 1.40–3.06). The fundamental fact is the establishment of a linear increase in risk depending on the dose. Thus, the average dose (5.17–20.00 mSv) caused an increase in RR of 2.70 (95% CI: 1.39–4.99); a high dose (48.33–110.84 mSv) was characterized by the maximum RR, amounting to 3.05 (95% CI: 1.46–5.96) [46].

Population of radioecologically unfavorable territories

The least accurate determination of radiation doses is characteristic of cohorts of residents of areas exposed to radiation from nuclear weapons testing or radioecological disasters. This is due to significant uncertainties associated with population migration, different dietary habits and lifestyles, and the need to calculate doses retrospectively using a survey of exposed individuals, which is associated with memory errors. For example, in a cohort of individuals exposed to radiation in the Southern Urals (the Techa River cohort), significantly elevated excess relative risks of mortality from all circulatory diseases (ERR 0.24 Gy−1) and, in particular, coronary heart disease (ERR 0.40 Gy−1) were found. However, when calculating the indicator for the entire population (exposed + unexposed), it increased significantly – up to 3.15 Gy−1 for diseases of the circulatory system, 3.22 Gy−1 for cardiac pathology and 2.96 Gy−1 for stroke [15].

Results of studies published in recent decades assessing the health status of the population living in the Semipalatinsk Nuclear Test Site (SNTS) also demonstrate a clear link between radiation exposure and the risk of developing CVD. A cohort study that included residents of Kazakhstan exposed to radiation as a result of nuclear weapons tests at the Semipalatinsk nuclear test site compared with unexposed residents from 1960 to 1999 found that radiation doses ranged up to 0.63 Gy to the whole body. Overall, the exposed population showed high mortality from cardiovascular diseases, significantly exceeding that in the unexposed cohort. However, no clear dose-response relationship was found for all cardiovascular diseases, heart disease, and stroke [14]. Long-term exposure to low and medium doses of ionizing radiation was shown to result in an increased ERR among the general population living in the area of 3.15 Gy-1 (95% CI 2.48–3.81). This study also found an increased relative risk of stroke among the affected population.

This relationship was confirmed in another study that included patients injured in ground-level explosions and their descendants [34]. The authors found that patients exposed to radiation were younger than those not exposed (mean age 63 years versus 64 years, $p < 0.001$) and had a higher prevalence of almost all comorbidities. Furthermore, exposed patients had a higher risk of stroke mortality than non-exposed patients.

Of particular interest are studies assessing the role of radiation exposure and the risk of developing arterial hypertension (AH). Currently, there is no doubt that AH is one of the main risk factors for the development of the most significant CVDs, as well as mortality due to CVDs in the world. Thus, a series of LSS studies determined the association of radiation exposure not only with the risk of developing AH (ERR was 0.07 Gy-1 with 95% CI -0.22, 0.55) [36], but also with the progression of organ damage mediated by AH (ERR 0.360 Gy-1; 95% CI 0.1-0.68) [37]. An increased risk of developing AH was also established among residents affected by the activities of the STNPS; thus, the study by *Markabayeva A. et al.* also established an excess relative risk of developing AH [25].

Conclusion

Our literature review demonstrates a clear link between radiation exposure over a wide range of doses and increased risks of circulatory diseases, primarily coronary heart disease, stroke, myocardial infarction, and hypertension. The development of circulatory diseases due to radiation exposure is primarily due to damage to the

vascular intima, primarily in the coronary arteries, changes in the endothelium associated with the accumulation of reactive oxygen species, and low-grade inflammation leading to the development of atherosclerosis. Acute radiation injury to the heart is associated with inflammation and mitochondrial dysfunction, while chronic radiation injury is associated with myocardial fibrosis. High doses of cardiovascular radiation are typically associated with radiation therapy for cancers such as breast or lung cancer. Low doses of radiation are typical for radiation situations associated with occupational exposure to ionizing radiation, as well as for residents of radiation-contaminated ecologically unfavorable areas due to nuclear weapons testing or radiation accidents.

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