ABSTRACT

dissertation work by Ilbekova Kuralay Baqytbekkyzy on the topic: "Assessment of the risk of malignant neoplasms in the population living near a radioactive waste storage facility and improvement of effective methods for its reduction", submitted for the degree of Doctor of Philosophy (PhD) under the educational program 8D10102 – "Medicine".

Relevance of the study:

The Republic of Kazakhstan is one of the world's leaders in uranium reserves and production volumes [1]. The Shu-Sarysu, Syrdarya, and Northern regions are the largest uranium mining centers; the mining and processing processes carried out here can create new sources of radiation contamination, which requires ensuring radiation safety through continuous monitoring and effective management.

Uranium mining facilities and radioactive waste storage facilities (RWS) increase the likelihood of negative impacts on the health of the population in nearby settlements due to radiation. The increasing incidence of malignant neoplasms has increased the need to study radiation risks in uranium mining regions [2, 3]. Furthermore, the migration of man-made radionuclides and heavy metals along the water-soil-plants-food chain reinforces the need to assess their impact on health and radiation dose [4]. Long-term exposure to uranium compounds can cause stochastic effects, including malignant neoplasms, genetic mutations, and a range of somatic pathologies [5, 6]. According to IARC, cancer incidence and mortality are important and objective indicators of exposure to ionizing radiation [7].

The etiology of malignant neoplasms (hereinafter referred to as MN) is associated with anthropogenic pollution, exposure to ionizing/ultraviolet radiation, viral agents, and behavioral risk factors (smoking, poor diet, stress, etc.). MN incidence is an important environmental indicator of the carcinogenic impact of ecological factors on the population [8, 9].

The State Healthcare Development Program for 2020-2025 aims to improve the health of children and young people and reduce the risk of premature mortality in those aged 30-70 years from cardiovascular, oncological, respiratory diseases, and diabetes. The SWOT analysis identifies air, soil, and water pollution as threats. Therefore, studying the influence of radiation factors on the development of cancer in residents of settlements located near uranium-mining waste disposal facilities in the Akmola region is relevant [10].

Studying cancer incidence in residents living near uranium mining areas is a complex, interdisciplinary task. A key component is predicting the groups most vulnerable to radiation risk, which ensures the timely detection, prevention, and treatment of radiation-induced tumors. These studies form the basis for systemic monitoring and surveillance in affected areas, contributing to improved quality of life and a reduction in mortality [11, 12]. Thus, studying the incidence of cancer among the population living near a radioactive waste storage facility, improving prevention methods and reducing its prevalence, and identifying radiation risk factors is a pressing scientific and practical task.

The aim of the study is to assess the risk of cancer in the population exposed to man-made factors at a radioactive waste storage facility and to propose ways to improve the effectiveness of measures aimed at reducing this risk.

Objectives:

1. To analyze the radiation situation in areas located within the impact zone of the RWS, including external radiation levels and radionuclide content in environmental objects.
2. To assess the incidence rates of malignant neoplasms in the population of settlements in the Akmola region located within the impact zone of the RWS, over time.
3. To develop a predictive model for the prevalence of malignant neoplasms among the population of the study areas based on a time series analysis, taking into account the identified epidemiological risk factors.
4. To study the uranium and creatinine levels in the urine of residents of settlements located near the RWS, and compare the results with those of a control group not exposed to elevated background radiation.

5. To develop and scientifically substantiate a set of measures aimed at reducing the risk of cancer in the population living in the area affected by radioactive waste, including recommendations for monitoring, prevention, and early detection.

Object of the study:

The main group was the population of settlements in the Akmola region located near the RWS and exposed to elevated background radiation. The control group consisted of the population of the city of Akkol, located far from the zone of man-made radiation exposure.

Research materials The study materials included the electronic registry of cancer patients of the Republic of Kazakhstan, data on the population size and its socio-demographic characteristics (Bureau of National Statistics), scientific data from the radiation safety service, archival materials from medical institutions, state archives, civil registry offices (CRO), the author's own materials, as well as the results of an additional clinical study to determine the uranium content in biomaterial.

Research methods:

Study design - observational / retrospective / cohort study.

The following were used: Radiation-epidemiological analysis (assessment of the relationship between radiation and cancer incidence, calculation of lifetime and attributable risk, SIR); dosimetry (assessment of levels of exposure to ionizing radiation); Mathematical modeling (predicting the probability of cancer based on radiation dose); regression analysis (assessing the impact of risk factors on health and survival); and analysis of extensive and intensive cancer incidence rates. The study included a clinical determination of uranium content in biomaterial. The following software packages were used for data processing: STATA 16.0, IBM SPSS Statistics 22.0, and Microsoft Excel 2019.

Scientific novelty of the study:

1. For the first time, a comprehensive assessment of the cancer risk of the population living in the zone of influence of the RWS was conducted, taking into account the radiation situation, biomonitoring, and long-term dynamics of cancer incidence.

2. For the first time, standardized incidence rates (SIRs) were calculated by age group, and population categories with exceeded expected levels of cancer incidence were identified. Associations between cancer incidence and indicators of man-made radiation exposure were assessed, including the radiation situation in the area and the duration of residence in the affected zone.

3. For the first time, a predictive model for the dynamics of cancer prevalence up to 2030 was developed based on mathematical modeling, assessing key sites (tumors of the digestive system, respiratory system, mammary gland, and male genital organs).

4. For the first time, a study of uranium concentration in urine with normalization by creatinine was conducted in cancer patients and healthy individuals of the study and control groups.

5. For the first time, a set of measures for the medical service of settlements located near the RWS has been proposed and scientifically substantiated, including an algorithm for the early detection of malignant neoplasms and a system for forming groups with increased oncological risk.

Theoretical significance of the work.

The theoretical significance of this study lies in the development of scientifically sound approaches to assessing cancer incidence in the population living in the RWS zone. The results expand our understanding of the mechanisms underlying cancer risk from exposure to low doses of ionizing radiation, clarify the role of length of residence and age factors, and provide a theoretical basis for further research in radiation oncology, medicine, and radiobiology.

Practical significance

• The developed guidelines can be used in the practical activities of medical organizations and contribute to improving the effectiveness of early detection and monitoring of malignant neoplasms; their implementation in the clinic is confirmed by an implementation certificate.

• The study results can be used by health authorities to plan measures to reduce cancer risk, early diagnosis, and screening in high-risk groups.

• The developed guidelines can be included in regional sanitary and epidemiological surveillance programs.

• Determining uranium concentrations in the population's biomaterials allows for the improvement of the monitoring system and the identification of groups at highest risk.

• Predictive models make it possible to assess the future burden on the healthcare system and adjust preventive measures.

• The dissertation materials can be used in university educational programs and in the development of regional radiation safety standards.

Part of the work was completed under scientific grant No. 237 of the Ministry of Education and Science of the Republic of Kazakhstan dated March 26, 2018. "Research and development of methods for reducing the radiation risk of the population living in the zone of influence of radioactive waste storage facilities" at the Research Institute of Radiobiology and Radiation Protection of the Astana Medical University, 2018-2020.

The main provisions submitted for defense:

1. An assessment of the radiation situation in populated areas located within the impact zone of the radioactive waste disposal facility revealed areas with exceeded permissible levels of external irradiation and radon concentrations: dose rates reached 2.9 μSv/h, radon concentrations up to 840 Bq/m³, and annual effective doses of 7-28 mSv/year, significantly exceeding the national average.

2. From 2014 to 2023, the average annual incidence rate of malignant neoplasms among the population living near the radioactive waste disposal facility was 309.4 per 100,000, exceeding both the control group and regional levels. Elevated standardized incidence rates (SIRs) were found in the 18-34, 35-50, and 51-70 age groups, with the highest number of cases occurring among residents with a residence period of more than 10 years. The five-year survival rate was 43%, with the highest mortality observed in the first 2-3 years after diagnosis and in individuals over 70 years of age (HR=1.38).

3. A predictive model was constructed using mathematical modeling, revealing a steady increase in the prevalence of malignant neoplasms in the study group – approximately 15-18% by 2030 – with a continued predominance of tumors of the digestive system, respiratory system, breast, and male genital organs.

4. A clinical study of uranium concentrations in urine normalized to creatinine revealed statistically significant differences between the study and control groups ($p=0.005$), confirming the impact of living in a zone of man-made radiation exposure on the level of internal radiation.

5. Based on the results of the study, a clinical algorithm for the early diagnosis of malignant neoplasms was developed for healthcare workers (general practitioners, therapists, oncologists, and oncourologists) in settlements located near the RWS, including the formation of high-risk oncological groups, optimization of patient routing, and recommendations for dynamic monitoring, aimed at increasing the effectiveness of early detection of malignant neoplasms.

Conclusions:

1. In settlements located in the impact zone of radioactive waste tailings storage, external radiation levels and radon concentrations exceed the national average; annual effective doses reach 7-28 mSv/year, compared to the national average of 1-4 mSv/year.

2. In the study group living near the tailings ponds, the average annual incidence rate of malignant neoplasms for 2014-2023 was 309.4 per 100,000 population, which is 1.06 times higher than in the control group (292.8 per 100,000) and exceeds the average levels in the Akmola region by 1.3 times and the average for the Republic of Kazakhstan by 1.6 times. The greatest excess of the standardized incidence rate (SIR) above the expected level was found in the age categories 18-34 years (SIR=1.34), 35-50 years (SIR=2.51), and 51-70 years (SIR=1.44), indicating a greater vulnerability of the working-age population to adverse environmental factors.

In the structure of oncological incidence in the study group, stomach, lung, breast, and male reproductive organ cancers were quantitatively predominant. For three localizations (stomach, lung, and breast), incidence rates in the study and control groups were comparable ($RR\approx1.01$; $p>0.05$), indicating the absence of statistically significant differences between the groups. An

increase in the relative risk of incidence was noted for prostate cancer (RR≈1.9); however, the interpretation of this indicator is limited by the small number of observations in the control group.

3. A predictive model developed using mathematical modeling showed that by 2030, the prevalence of malignant neoplasms among the population living near the radioactive waste tailings pond could increase by 15–18% if current man-made radiation conditions persist. Moreover, tumors of the digestive and respiratory systems, mammary glands, and male reproductive organs predominate in the predicted incidence structure.

4. An analysis of uranium concentrations in urine, normalized for creatinine, revealed statistically significantly higher uranium levels in residents living near the radioactive waste tailings pond compared to the control group: 0.18 μg/L in patients with cancer (0.03 μg/L in controls) and 0.05 μg/L in healthy individuals (0.04 μg/L in controls). Normalization for creatinine confirmed this difference (p=0.005). The identified differences indicate a statistical association between elevated urinary uranium levels and residence near RWS, confirming the need to establish a critical population group with increased cancer risk and to strengthen medical dosimetric monitoring.

5. Based on the study results, a medical care algorithm was developed for the population living in the RWS impact zone. This algorithm aims to create targeted screening programs and expand existing programs for the early diagnosis of the most common malignant neoplasms, including identifying high-risk groups and optimizing patient routing for suspected cancer.

Implementation of research results into practice. The results of comprehensive radioecological monitoring and analysis of cancer incidence in the population served as the basis for the development of the following methodological recommendations:

1. "Ways and Methods for Reducing Radiation Risks and Somatic Morbidity in the Population Living in the Zone of Influence of Man-Made Radiation Factors," dated September 21, 2020. (Appendix A).

2. "Analysis of Cancer Incidence and Mortality in the Population Living Near Mothballed Uranium Mines, and Methods for Minimizing Negative Man-Made Factors" (Astana, 2024), dated October 4, 2024. (Appendix A). These methodological recommendations are proposed for physicians conducting routine observation and screening among population groups exposed to radiation. These recommendations have been officially implemented in the practical activities of the following medical institutions in the region:

- State Enterprise on the Right of Economic Management "Stepnogorsk City Multidisciplinary Hospital" (Appendix B);
- State Enterprise on the Right of Economic Management "Stepnogorsk City Polyclinic" (Appendix B);
- Regional Health Department of the Akimat of Kyzylorda Region (Appendix B).

3. In addition, the recommendations have been incorporated into the educational and scientific programs of the Scientific Research Institute of Radiobiology and Radiation Protection of the Astana Medical University, where they are used to train specialists in radiation medicine. The validity of the developments is confirmed by the following author's certificates:

- No. 18553 dated June 9, 2021 (Appendix C);
- No. 50119 dated October 2, 2024 (Appendix C).

Presentation and discussion of research results

The main results of this work were reported and discussed at the following international and national conferences:

1. Proceedings of the X International Scientific and Practical Conference with International Participation "Medical, Biological and Environmental Problems in Uranium Mining Regions" dedicated to the 20th anniversary of the Research Institute of Radiobiology and Radiation Protection of NCJSC "Astana Medical University" (Astana, April 18-19, 2024);

2. Proceedings of the VIII National Scientific and Practical Conference "Medical, Biological and Environmental Problems in Uranium Mining Regions with International Participation" (Nur-Sultan, March 11-12, 2021).

Publication of research results.

Ten scientific papers have been published on the topic of the dissertation, including 4 articles in peer-reviewed scientific journals indexed in the Scopus and Web of Science databases with an impact factor above zero, 4 articles in scientific journals recommended by the Committee for Quality Assurance in Science and Higher Education of the Ministry of Science and Higher Education of the Republic of Kazakhstan, as well as 2 abstracts published in the proceedings of international scientific and practical conferences.

Personal contribution of the dissertation candidate.

The author independently collected materials, including biological sampling, performed laboratory determination of uranium content in urine with creatinine normalization, processed and analyzed the data, assessed cancer incidence rates and risk factors, developed an algorithm for medical care for healthcare workers, and formulated the provisions submitted for defense, conclusions, and practical recommendations.

Volume and structure of the dissertation.

This dissertation consists of a title page, table of contents, a list of normative references, definitions, notations and abbreviations, an introduction, 6 chapters, a conclusion, practical recommendations, a list of references, and appendices. The dissertation comprises 171 pages and includes 30 figures, 32 tables, and a bibliography of 225 sources.