

**Accidental radiation doses and its effects on the
population living near Semipalatinsk Nuclear Test Site**

by

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Abstract

Kazakhstan is a former of Soviet Unions Republic which is located on the middle of Eurasian continent and borders Siberian Russia in the north, China in the east, Kyrgyzstan, Uzbekistan and Turkmenistan in the south, and the Caspian Sea and European Russia in the west. Semipalatinsk region is located on north-east side of the country with mostly the flat steppe area and became under the interest of Soviet Union Military forces as a “uninhabitant” and perfect place for nuclear weapon testing. USSR established Semipalatinsk nuclear test site in 1947 on the August 21st. Since then, 456 nuclear explosions were carried out including 111 atmospheric events between 1949 and 1963.

Purpose of study is the investigations of (1) endothelial dysfunction on population living near Semipalatinsk Nuclear Test Site, and (2) congenital anomalies and congenital anormaries of the circulatory system. These studies are necessary not only to find radiation effects from the nuclear test in Semipalatinsk but also people living in the area of the nuclear test site are very much worrying about its effects for their own and for their children.

In most countries, congenital anomalies remain a relevant public health problem, but they are also an important risk factor for child mortality and disability. Studies in Europe and North America have shown that up to a third of all perinatal losses may be due to anatomical defects. In stillborn infants, congenital anomalies are detected in 15-20 % of the cases. According to the National Center on Birth Defects in the United States each year 10 to 20 million children are born throughout the world with congenital anomalies. congenital anormaries of the circulatory system are one of the leading causes of death in infants, so the timely detection of them is important, and hemodynamic instability can determine the quality of children's lives beginning in the neonatal period. Congenital anormaries of the circulatory system is present from birth in definition. The most practical measurement of congenital anormaries of the circulatory system occurrence is birth prevalence per 1,000 live births. According to the literature, the frequency of congenital anormaries

of the circulatory system in infants is an average of 2 to 5 per 1,000. The estimate of 8 per 1,000 live births is accepted as the best approximation generally.

The lack of a clear trend towards reducing the number of children born with various malformations, including congenital anomalies of the circulatory system, highlights the significance of ongoing research on the subject. In the Republic of Kazakhstan, official statistics on infant mortality show that congenital anomalies were present in up to 22.8% of cases, ranking second among all causes. According to the Ministry of Health of the Republic of Kazakhstan, the incidence of congenital diseases in Kazakhstan is 4%-6%, including congenital abnormalities at 2.5%.

Every year, according to the National Register of Genetics of the Republic of Kazakhstan, from 2,500 to 3,500 children are born in Kazakhstan with congenital and hereditary diseases, constituting a rate ranging from 20.0 to 24.3 per 1,000 live births, and the proportion of congenital malformations among cases of perinatal mortality in a number of ecologically unfavorable regions is highest among conditions associated with perinatal mortality. In 9 % of cases of congenital anomalies of the circulatory system was due to a variety of factors including radiation, viral infections, diseases of the mother during pregnancy, drugs and chemicals, and heavy metals, while only 10 % of cases of congenital anomalies of the circulatory system were caused by chromosomal abnormalities or single gene mutations.

The zones of maximum and high radiation risk are recognized to be in the cities Semey, Ust-Kamenogorsk, Kurchatov, Ridder, and in the regions of East Kazakhstan: Borodulichinsky, Zharminsky, Ayagozky, Glubokovsky, Shemonaikhinsky, and Ulansky areas, but no analysis of the incidence of congenital anomalies, depending on the degree of remoteness from the test site has been recently published. At the same time the highest levels of disease were recorded in the Akmola region at 783.6 cases per 100,000 populations, the South Kazakhstan region - at 967.4, the

Zhambyl region - at 707.0, and in Almaty city - at 788.1. Until now, the frequency of congenital abnormalities have not been fully studied, including malformations of the heart and blood vessels, and their prevalence among the causes of infant mortality in Semey and East Kazakhstan has not been established. Also, the impact of various exogenous and endogenous circumstances, the long term consequences of the activities at the SNTS twenty five years after the test site was closed, the risk of having a baby with a congenital anomaly have been important today.

The definitions of the contribution and mechanisms of action of anthropogenous radiation on human health are complicated. The problems faced by researchers in this field include the high remoteness of the influence, the considerable range of radiation doses, the need to use a dose reconstruction procedure, and the simultaneous influence of radiation and its effects on humans.

According to the literature it is known that the development of malignant tumors is the result of exposure to ionizing radiation during nuclear bombings, accidents and catastrophes, and as a result of nuclear tests. It is very significant impact on the health of the population, according to the known research activity has Semipalatinsk nuclear test site (SNTS). There are the opinions about the possibility of chronic radiation exposure influence (in low doses) led to the development of malignant neoplasm. However, not all researchers concur with this opinion. There are theories of the threshold dose, of the nonlinear interaction of “dose effect”, and the non- threshold linear theory. Nowadays, linear no threshold theory received essential confirmation due to the results of conducted researches for revealing the connection between diagnostic methods using ionizing radiation and the risk of development of malignant neoplasms. Main studies in the region of the Semipalatinsk nuclear test site were also carried out on the basis of the linear non-threshold theory. At the same time, it is impossible to associate many features of cancer morbidity in different regions of the Earth with the state of the natural radiation background. This item is a critically important argument for the threshold theory. When considering the question about the effect of

ionizing radiation on the development of neoplasm the key moment is its mutagenic effect. However, there are different directions of analysis, including mainly the condition of immune system. The concept of genesis of radiation-induced malignant neoplasms can have another aspect - the negative influence of radiation, including chronic low doses, on the morphology and function of the vascular endothelium. The condition of vascular endothelium is considered as a potential modifying factor in the genesis of oncological complications in radiation exposed individuals throughout all their lives (as the result of Semipalatinsk nuclear test site activity).

Despite the long-term activity at SNTS, three decades after it closed, the East Kazakhstan region recorded one of the lowest incidence of congenital anomalies. This suggests that the landfill activity played only a minor role in the relative risk of congenital anomalies in comparison with other risk factors all over Kazakhstan. At the same time, the data suggest that within the East Kazakhstan region, even decades after the closure of the landfill, the highest incidence of morbidities still seem to be observed in the territories of maximum radiation risk.

The history of exposure to ionizing radiation and family radiation history contributes to aggravation of vascular endothelial dysfunction in patients with rectal cancer (differences in the content of circulating endotheliocytes with patients without a radiation history reach 1.53 times, endothelium-dependent vasodilation - 1.34 times).

In conclusion, in our study (1) we found the difference between exposed and non-exposed areas for the factors of endothelial function in the patients with rectal cancer such as ISD (%), WF (mg/ml), CE content and EDVD (%).

(2) there was no difference for the congenital anomalies and congenital anomalies of the circulatory system between exposed and non-exposed area. In this regard, for a better understanding of the effects of SNTS consequences.

The importance of the study is that we found some difference or the factors of endothelial dysfunction in the patients. In the Semipalatinsk area this kind of findings about the differences are rare. The reason is not clear now but we need further systematic research studies should be done to clarify and find its mechanism as the effects from the nuclear tests. On the other hands, in the both of the congenital anomalies and congenital anomalies of the circulatory system we did not find any difference. This is an good information for the people living in these area since it seems no problem from the effects of the nuclear tests.

1. Introduction

1.1 History

Kazakhstan is a former of Soviet Unions Republic is located on the middle of Eurasian continent and borders Siberian Russia in the north, China in the east, Kyrgyzstan, Uzbekistan and Turkmenistan in the south, and the Caspian Sea and European Russia in the west (Fig. 1).

Semipalatinsk region is located on north-east side of the country with mostly the flat steppe area and became under the interest of Soviet Union Military forces as a “uninhabitant” and perfect place for nuclear weapon testing (Fig. 2).

The twentieth century was the century of world nuclear weapons. Developed states conducted an active policy in this direction. USSR established Semipalatinsk nuclear test site in 1947 on the August 21st. Since then, 456 nuclear explosions were carried out including 111 atmospheric events between 1949 and 1963 (Grosche 2011, Takemine et al. 2015) (Fig. 3).



Fig. 1 The map of the Republic of Kazakhstan.

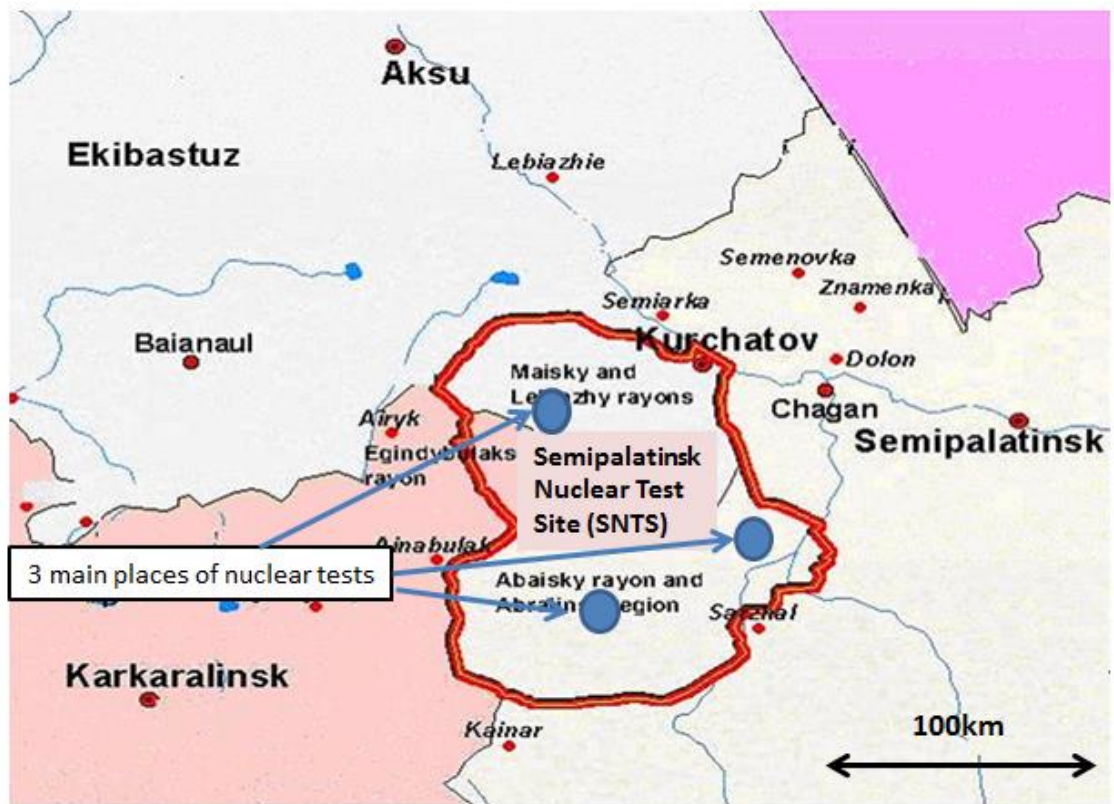
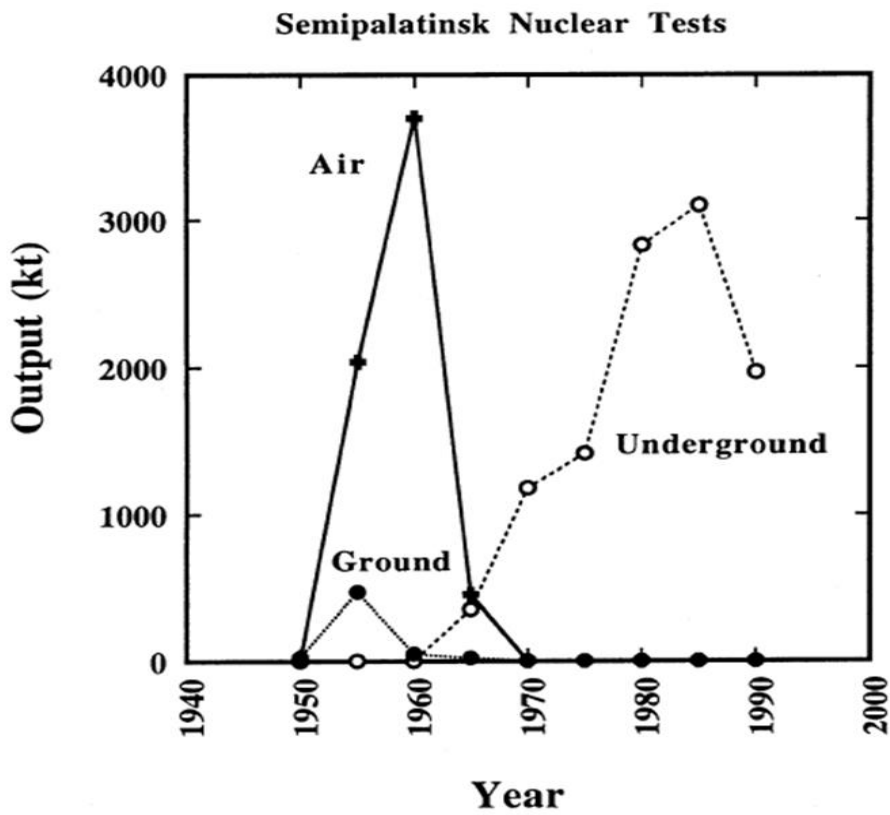


Fig. 2. The map of the Semipalatinsk nuclear test site.



USSR Nuclear Weapons Tests and Peaceful Nuclear Explosions 1949 through 1990, Russian Federal Nuclear Center- VNIIEF, 1996.

Fig.3. History of nuclear experiments in Semipalatinsk (Taira et al. 2011; Kawano et al. 2006; Grosche 2011).

According to the Kazakhstan government, 1.6 million people were subjected to radiation and 1.2 million people are still suffering from its aftereffects. A preliminary study has shown that the exposure to radiation due to the tests has seriously affected the health of the population in the wide areas around the SNTS (Kawano et. al. 2006; Hirabayashi 2008).

The question of assessing radiation doses increased with time. In the first is due - media tools very often had of a lack objective dosimetric information and exaggerate the severity of possible medical after-effects. Secondly, expert of radiation medicine and epidemiology needed reliable information about radiation doses that to determine risks for medical consequences.

After the accident at the Chernobyl Atomic Station, it was on April 26, 1986, interest of scientists increased again of develop and apply the methods of monitoring the population's response to an accidental radiation impact and after nuclear tests.

The first open access papers of evaluate after-effects of accident at Chernobyl were published in 1986-1989. Such publications on tests at the Semipalatinsk nuclear test site, which include information about effects on the residents of surrounding area, were published in 1989-1990 (Stepanenko 2009).

Despite the 1990 termination of the operations of the Semipalatinsk nuclear test site (SNTS) in northeast Kazakhstan — at which the nuclear tests began in 1949 — the health problems of the area's residents who were exposed to radiation from the site and the health problems of their descendants remain. Their health problems include a high rate of malignant neoplasms (Bauer et al. 2005), which are one of the disease classes that are most strongly influenced by ionizing radiation.

This time The Kazakhstan territory has area with high radiation doses as determined by the Kazakhstan government as shown in Fig.4 (Takemine et al. 2015). These areas were determined based on many measurements of the radiation doses. Examples of the tooth enamel and brick dosimetries are shown in the Appendix A.

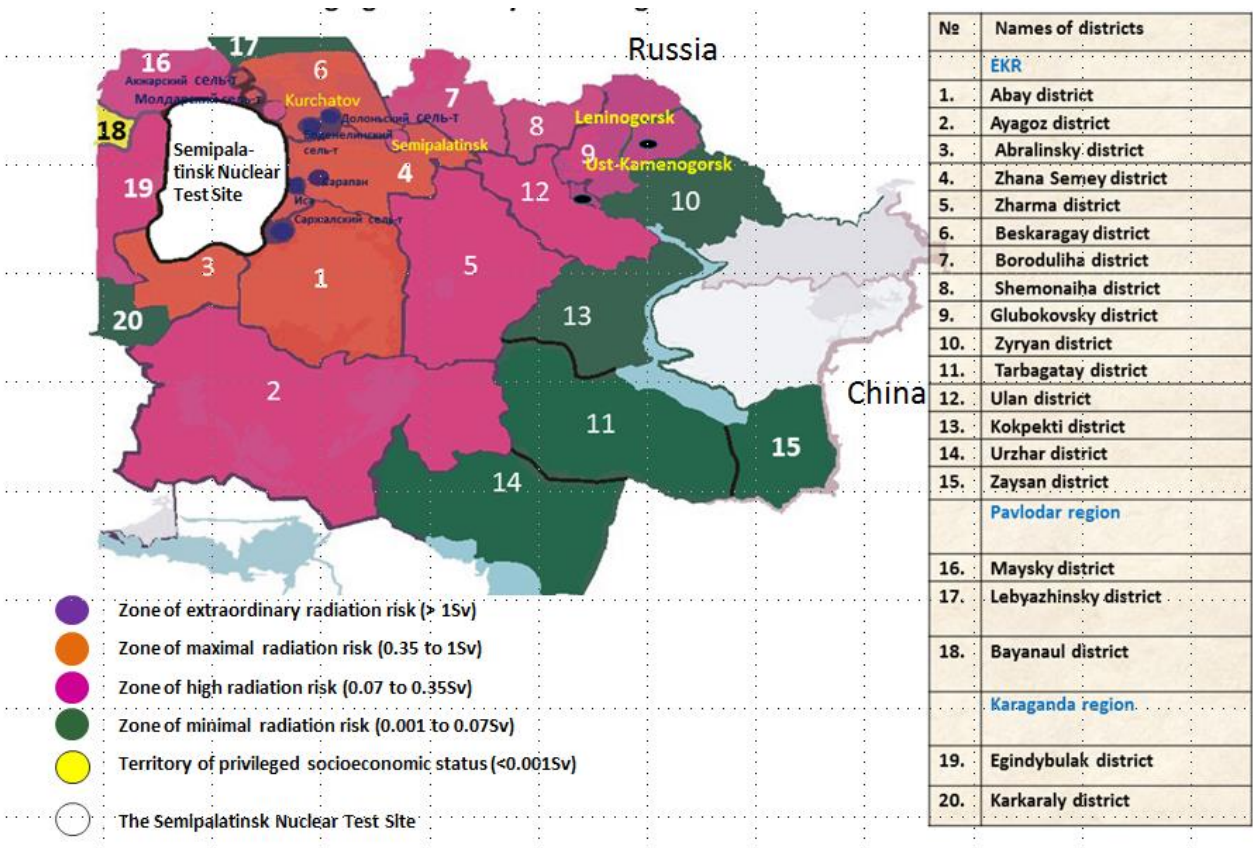


Fig. 4. Schematic ranging of territory according to radiation risk. (Takemine et al. 2015).

1.2. Studies of the impacts of accidental radiation effects

After the nuclear accidents at the Chernobyl nuclear power plant, and then at Fukushima, radiobiologists have the question of how to diagnose the biological consequences of "low doses" (Handkiewicz-Junak et al. 2016).

In radiobiology, the concept of radiation risk is associated with the dose at which the effects under investigation begin to appear (Yarmonenko and Vaison 2004). For all this, the upper limit of "low doses" is determined in different ways, depending on the evaluation criterion. When studying the effect of ionizing radiation on organisms, "low doses" are those that do not cause noticeable disturbances in vital activity. Based on this, some authors suggest to count for "low doses" of a person in the range up to 200mGy - 500mGy for mammals (Hayes 2008; Koterov 2013).

Along with this, there are also microdosimetric studies, according to which a dose can be considered low when the critical target receives on average no more than one radiation event. Therefore, all biological effects and the effects of ionizing irradiation on a living organism are divided into deterministic and stochastic.

Deterministic effects, which manifest themselves in the form of obvious pathology, with significant radiation doses. The peculiarity of such effects is that they assume the presence of a certain minimum threshold, below which the effect is absent, and above - depends on the dose received. Stochastic effects do not have a dose threshold, that is theoretically possible with a "low dose" of irradiation, and the probability of occurrence is less, the lower the dose.

At the present time, in assessing the effects of the effects of ionizing radiation in "low doses", there are three opposite points of view. Some researchers point to the increased risk of "low doses," others reject any features of their effects, while others indicate the existence of radiation hormesis, that is, the positive action of ionizing irradiation.

The absence of peculiarities in the effect of radiation in "low doses" is evidenced by the recognition of a linear no-threshold concept as the basis for the normalization of the radiation factor.

On the positive effect of radiation in small doses and radiation hormesis began to report at the beginning of the development of radiobiology. Many researchers observed the stimulation of various life processes. A detailed review of such works relating to this and subsequent periods is given by the convinced follower of the ideas of radiation hormesis (Vaiserman 2010).

After nuclear accidents, environmental pollution occurs. As a result, radioactive particles enter the body, which in turn leads to beta radiation. As a result of the accident at the Chernobyl nuclear power plant (CNPP), the vast adjoining territories were contaminated with radioactive fallout. Studies on the evaluation of humoral immunity have determined that soil contamination has a strong correlation with the individual dose of ^{137}Cs (McMahon et al. 2014), 25 years after the accident at the CNPP, the doses of internal exposure to residents living in contaminated areas of northern Ukraine are limited but still associated with pollution in Soil of ^{137}Cs . In addition, the cause of internal exposure is the consumption of local products (Kimura et al. 2015).

In 2011, the Fukushima nuclear power plant accident in Japan caused by an earthquake measuring 9.0 magnitude after the tsunami was a reminder that even modern systems are vulnerable to natural disasters (Aitsi-Selmi and Murray 2016). Given that the magnitude of environmental pollution accident at the Fukushima nuclear power plant second after the Chernobyl nuclear power plant, scientists from Japan, reacted sharply and began to study the effect of "low doses" of radiation on the ecosystem. Hiyama et al (2012) studied blue butterflies, permanent inhabitants of the Fukushima Prefecture and concluded that even "low doses" can significantly affect the genetic apparatus, which manifests itself in the form of changes in pattern and color, as well as the shape of the wings, the size of the chest, abdomen. The first generation extended the process of pupation, the

frequency of abnormalities showed a high inverse correlation with the distance of the collection sites from the Fukushima nuclear power plant. A decrease in survival was also observed.

Based on these data, it is impossible to estimate the effect of low doses on the human body, since the cells of the wings of these butterflies are more stable than human cells to short-term high doses of radiation. But we must also take into account that larvae and pupae are more vulnerable to long-term low radiation doses (Hiyama et al., 2012, 2013, 2015).

At the moment, scientifically, no one can provide convincing data that the long-term impact of "low doses" on the population living in the Fukushima area is safe for people's health.

Muller (1928, 1950) found serious consequences after exposure to ionizing radiation in the descendants of irradiated parents. In his experiment, he irradiated - *Drosophila* - with X-rays and found developmental defects and other disturbances in the following generations. Based on this, he came to the conclusion that a "low dose" of irradiation and even a natural radiation with increasing range of norms can lead to induction of cancer and various mutations. His work was awarded the Nobel Prize in Medicine in 1946. In 1950, he warned that radioactive contamination of the lower atmosphere adversely affects the human gene pool (Schmitz-Feuerhake et al. 2016; Muller 1950).

Later Anne Graupner with a group of scientists conducted an experimental study in mice and found that radiation in "low doses" causes genotoxic effects. Radiation damage to DNA is more complex than endogenous, which in turn can lead to an irreversible reorganization of the DNA apparatus (Anne Graupner et al. 2016; Lomax et al. 2013).

In 2001, UNSCEAR presented a report about the health of the survivors of the atomic bombing of Hiroshima and Nagasaki. There, data were presented that the descendants of the surviving mutations in the genetic apparatus were not found (UNSCEAR 2001).

Later, Schmitz-Feuerhake et al. (2016) analyzed the scientific papers on the effect of "low doses" of radiation on the genetic apparatus and concluded that the hereditary defects found were at doses from 1 mSv to 10 mSv.

Radioactive fallout from nuclear explosions has affected the population around the world to some extent. After the Chernobyl nuclear power plant accident in 1986, the inhabitants of Sweden suffered from exposure by ^{137}Cs , after five years, cancer growth was observed (Alinaghizadeh et al. 2016), in Belarus, Ukraine and western Russia, the incidence of thyroid cancer increased sharply in children (Brenner et al. 2011; Cardis et al. 2005; Ivanov et al. 2012; Zablotska et al. 2011). Based on these data, a screening of the incidence of thyroid cancer in Fukushima was carried out, which also showed a high growth of this nosology (Mitsutake et al. 2015).

A lot of different researches of the SNTS have been carried out, the definition of the radioactivity of the environment (Evseeva et al. 2011, 2012; Mitsutake et al. 2015; Taira et al. 2011) and the health status of the population living near the regions. For example, an analysis of radiation risk among the Semipalatinsk historical cohort was conducted in relation to mortality from cardiovascular diseases. A significant high risk was found in people living in the landfill area than among those who lived in the villages of comparison (Grosche et al. 2011). A biomarker of leukemia for a given cohort was determined (Zharlyganova et al. 2008). A study was conducted on the evaluation of polymorphisms of genes that have a potential relationship with thyroid cancer (Sigurdson et al. 2009), and a dose-effect relationship was also established (Zhumadilov 2006).

Rozenson (1997) investigated the relationship between the irradiated population between radiation-induced changes in the immune status and allergic reactions. The author established that a number of individuals irradiated at a dose of more than 1000 mSv had a decrease in immunoregulatory subpopulations with a predominant deficiency of T suppressors with a

simultaneous increase in immunoglobulin of class E, which in turn led to the formation of respiratory allergies and allergic dermatoses.

Iwata et al. (2004) conducted studies on the prevalence of skin cancer in people living near the SNTS. According to their data, even many years after the closure of the polygon, "low doses" may be the cause of the development of this pathology.

According to the long-term results of scientists, the health of the exposed population living in the territories near the Semipalatinsk test site shows an increase in morbidity and mortality rates, a combination of multiple somatic pathology and psycho-organic disorders (Azhmuratova et al. 2011; Apsalikov et al. 2010; Belikhina et al. 2011).

When assessing the hazard of radiation exposure, it is necessary to take into account the accompanying chemical factors, that is, regional features. For the first time, Chaizhunosova (1993) found that the assessment of the risk of radiation exposure should be carried out taking into account the concomitant effects of modifying chemical factors. According to the results of studies, the dose of ionizing radiation on the population of the Maiskyi and Lebyazhye districts was about 30 mSv. Along with this, in the territory of the Maisky district, there was a marked increase in the content of pesticides and mineral fertilizers. As a result, based on the obtained data, the author comes to the conclusion that the combined effect of ionizing radiation and chemical agents leads to a substantial reduction in the thresholds for the main effects of ionizing radiation. This is due to the fact that there was an excess of cancer, as well as congenital malformations in the Maiskyi district where there was a combined radiation - chemical effect. In the Lebyazhye district, where the dose was almost the same as in Maysky, but without pesticide exposure, no such effects were found.

To date, there is no single scientific justification for the pathogenesis of diseases of people living in environmentally unfavorable conditions. Very often, changes from the nervous system are treated as functional. The reported complaints of general weakness, fatigue, headaches, dizziness,

decreased performance (Hirabayashi et al. 2008; Kawano et al. 2006) interpreted by some specialists as a desire to receive benefits or as a manifestation of radiophobia (Apsalikov et al. 2010; Muldagaliev et al. 2012).

We have attracted interest from complaints made by the exposed population, such as: general weakness, fatigue, reduced efficiency. Since similar symptoms were noted according to the authors' data from people living on different continents, but exposed to various hazardous substances. For example, after the atomic bombing of Hiroshima, the syndrome "Genbaku Burabura Byo" (the impact of the atomic bomb) (Hida 2010) in USA, among veterans who fought in the Persian Gulf, this syndrome is called "Gulf war syndrome" (Bertell 1998). The liquidators of the Chernobyl nuclear power plant presented all these symptoms in the form of a psychoorganic syndrome. Therefore, they have been treated annually since 1990 to the present (Lysenko 2007; Krasnov et al. 2015).

It is believed that the nervous system is considered relatively resistant to ionizing radiation (Gus'kova and Shakirova 1998) but it should be noted that the experimental work of Achanta Pragathi and colleagues shows that ionizing radiation contributes to worsening of associative memories (Pragathi et al. 2009).

In Ukraine, the adolescents were examined for determining suicidal tendencies and the presence of depression. In the study group were children who were 6 years of age, in the womb and born 45 weeks after the accident. They have identified psychological problems associated with inadequate environmental assessment (Contis and Foley 2015). Mental health problems have been observed in many residents of the Fukushima prefecture (McMahon et al. 2014).

I also want to note that in our time, in the era of scientific and technological progress, human activity becomes the main source of pollution of the biosphere. In the environment, gaseous, liquid and solid chemical substances that are in waste that enter the soil, air or water, enter the

environment in large quantities, and then, moving along trophic routes, enter the human body (Askarova 2014; Hiyama et al. 2012, 2013, 2015).

Unfortunately, there is no specific data indicating that "low doses" of ionizing radiation may or may not be, one of the causes of "chronic fatigue" of the population. As, basically presented complaints are treated as the desire to receive benefits or psychological violations.

Thus, analysis of literature data suggests that in assessing the effects of irradiation with "low doses", there are three categories of researchers who hold different views. Existing judgments create the problem of "low doses", the study of which is relevant.

2. Two important aspects of the health status of the population of the Republic of Kazakhstan

2.1. Vascular endothelium and its functions in the body

Functions of the endothelium and its control on vascular tone:

The adult human possess approximately 10^{12} vascular endothelial cells (normal functional endothelium), which occupy an area exceeding 1000 m^2 covering the luminal surface of the blood vessels and the vascular smooth muscle. This intact functional endothelium “cellophane lining” has many functions. It is now believed to be active participants in the maintenance of vascular tone and regulation of blood flow (Dinerman et al. 1990).

An important role of endothelium in the regulation of vascular tone was first identified by Furchgott and Zawadzki (1980). They found that nitrogen monoxide synthesized by endothelium, has an effect on modulating the vasodilating effect of acetylcholine.

Endothelium also prevents the platelets and leukocyte activation on the luminal side of the vessel wall and plays a major role in maintaining vascular hemostasis. In addition, the vascular endothelial cells serve as a non-thrombotic barrier separating blood from the vascular smooth muscle, so it enhances the fluidity of blood (Vanhoutte and Houston 1985; Wael Hamdy Sayed Ali Mansy 2004).

Endothelium is most sensitive to the factors, which are released by activated platelets, such as adenosine diphosphate, serotonin, thrombin, etc.). Metabolic products (active forms of oxygen, lipoperoxides, homocysteine, pro-inflammatory and other cytokines) are the other source of external stimuli for endotheliocytes (Tanaka et al. 2009; Victor et al. 2009).

Endothelial cells have sensory properties. They are provided through the presence of many different receptors on cell membranes. The signal is transferred inside the cell by means of a cascade mechanism. The main targets for its functioning locate in the cell nucleus.

Several classes of vascular growth factors are known. In endothelial cells, a number of growth factors are synthesized, in particular platelet growth factor (produced not only by endotheliocytes, but also by platelets); macrophage growth factor; Endothelin 1, 2, 3 (Hu and Huang 2015; Farooqi and Siddik 2015; Lin et al. 2002; Kohan et al. 2011; Rodríguez-Pascual et al. 2011). Fibroblast growth factors, transforming growth factor, etc are nonspecific for endothelium, but synthesized by its cells. As for the influence of these factors on angiogenesis mechanisms, the following features are characteristic:

- Direct stimulation on endotheliocytes
- Paracrine effect of growth factors on endothelial cells
- Synthesis and discharge in the state of hypoxia, for compensation (in case of increased organ mass or functioning)
- The possibility to stimulate angiogenesis under the influence of other factors (some medications, increase in the vascular wall shear stress, etc.)
- Increased permeability of capillary endotheliocytes under the influence of growth stimulators
- Fibrin as a matrix for growth of newly formed vessels;
- The formation of new vessels takes considerable time and requires the action of endothelial growth factors (Kandalajt et al. 2011).

Endothelial growth factors play the role of regulators and stimulators of not only vascular growth, but also of vascular permeability. This mechanism ensures adequate blood supply to body organs, in particular with increasing functional load. Intact endothelium is able to stimulate the increase in the number of appropriate cells for the formation of microcirculatory bed vessels, and also to change the lumen of the muscular type arteries by stimulating or blocking the proliferation

of smooth muscle cells of the vascular wall, and the production of glycosaminoglycans (Koch and Claesson-Welsh 2012; Sa-Nguanraksa and O-Charoenrat 2012; Lafuente et al. 2012).

In the conditions of normal body functioning, endothelium regulates the relationship between proliferation and programmed cell death through apoptosis (Erusalimsky and Kurz 2006; Kontogeorgos and Kontogeorgou 2003).

Mechanisms of apoptosis ensure elimination of damaged cells and cells with a completed life cycle, the main trigger factor in this case is played by a program, which is genetically encoded. However, there are extracellular factors that stimulate the initiation of apoptosis.

Nitrogen monoxide is one of the most important substances released by endothelium, which plays vasodilating, anticoagulant, protective and some other roles (Loscalzo 2013). The first violations of vasodilator vessel reactions associated with endothelial dysfunction, were described in the 1980s. At this time, a weakened or distorted vascular response to acetylcholine was established (Furchgott and Zawadzki 1980). As a result of the subsequent analysis, a very strong vasodilator is produced, which is now classified as gas transporter (Dusting 1989; Long and Berkowitz 1989; Valerio and Nisoli 2015), it is produced by endothelium under normal conditions and mediates the vasodilating effect of acetylcholine. This substance is nitrogen monoxide (NO).

NO is synthesized from L-arginine in a reaction catalyzed by three isoforms of the specialized enzyme – NO-synthase (eNOS) – localized in the Golgi apparatus. It is a cytochrome-P-450 reductase-like enzyme and consists of two analogous subunits, i.e., is a dimer, and shows its activity only in this form (Heiss et al. 2015).

Endotheliocytes and vascular wall cells – platelets – also produce a second powerful physiological vasodilator (antiplatelet prostacyclin), which has antiaggregant and anticoagulant effects. Synthesis of prostacyclin is derived from membrane phospholipids (Villar et al. 2006; Kawabe et al. 2010).

Prostacycline affects cells with the same mechanism as NO does, so the effects of both substances are similar. However, there are also differences - in particular, the reactions are mediated by different messengers of type II, as well as the way energy is obtained by the cell (hydrolysis of GTP – In case of NO and ATP - under the action of prostacyclin) (Shankarraman et al. 2012; Turner and Kinsella 2012).

2.1.1. Changes in the state of endothelium in pathology condition and their pathogenetic role

Endothelial dysfunction is a condition when the entire complex of its properties is violated, which is usually accompanied by the predominance of prothrombotic and vasoconstrictor effects. It develops in the majority of diseases associated with systemic impairment of the entire body's functions – cardiovascular, metabolic, vasculitis, neoplasms (Hadi et al. 2005; Patti et al. 2005; Tousoulis et al. 2010; Natri et al. 2008). The severity of endothelial dysfunction depends on the severity and prevalence of pathological effects produced on vessels and, to a certain extent, on the genetically determined properties of the endothelium, its resistance to negative influences (Joshi et al. 2013).

A very significant point in endothelial dysfunction is a decrease in the bioavailability of NO as a result of the violation of the following mechanisms:

- oxidative stress with intracellular increase in the content of free radicals, in particular superoxidione, decreases the activity of eNOS. As a result, the most powerful and fast reacting vasodilator system turns out to be "off". Simultaneously increases the production of angiotensin II (Silva et al. 2012; Aroor et al. 2013). This mediator promotes the oxidation of NO and potentiates the blockade of its secretion:

- changes in the functional state of the callicrin-kinin system (Sharma and Narayanan 2014);

- decrease in the density of membrane receptors, which leads to activation of NO synthesis (Ramadoss et al. 2013);

- activation of the synthesis of other vasoconstrictors (endothelin) as a result of damage to endotheliocytes;

- an uncontrolled transmembrane current of Ca^{2+} ions into the cell is formed, which can reduce energy production as a result of mitochondrial oxidation blockage (Marzetti et al. 2013).

In case of solid tumors, there is almost always an imbalance between proliferative and metabolic activity of tumor tissues and its blood supply, which leads to local ischemia (Thanan et al. 2014). In all cases this state is accompanied by the development of a local oxidative stress, and in a large sized tumors – by the significant violation of its trophism. An additional confirmation of this is the increase in prothrombotic potential in patients with even relatively small neoplasms compensated in terms of blood supply (Elyamany et al. 2014; Yamashita Y. 2015).

Oxidative stress is one of the main causes of increased risks and prevalence of thrombotic events in malignant neoplasms (Cameron et al. 2016). At the same time, in patients with malignant tumors, the formation of systemic endothelial dysfunction in excess of protective threshold is even more dangerous in terms of the formation of the entire complex of complications and unfavorable outcomes.

2.1.2. Endothelial dysfunction in rectal cancer patients chronically exposed to ionizing radiation

2.1.2.1 Introduction

The main mechanism of the impact of ionizing radiation on the development of a neoplasm is the radiation's mutagen action. However, there are a number of other factors to consider in analyses of this impact, including the condition of the immune systems of the radiation-exposed individuals

(Shankarraman et al. 2012). The genesis of radiation-induced malignant new growths can be expected to have a variety of causes. At the same time, these causes are considered a potentially modifying factor in the genesis of complications of oncological diseases among individuals who are chronically exposed to ionizing radiation over their lifetimes.

Our objective in this study is to detect the features of endothelial function in patients with rectal cancer who were exposed to chronic ionizing radiation as a result of nuclear tests.

2.1.2.2. Patients

We have examined 146 individuals including control (n=40), non-exposed atients (n=36) and exposed patients (n=40). Seventy-six of these individuals were rectal cancer patients. In the present study, we divided these 76 patients into two groups based on their exposure/lack of exposure to radiation from the nuclear tests: The 40 exposed patients were exposed to chronic ionizing radiation from nuclear tests conducted at the Semipalatinsk Nuclear Test Site (SNTS) in northeast Kazakhstan during the years 1949 to 1989. Radiation doses for the people living in emergency zones with the maximum radiation risk from the SNTS during the dose-forming nuclear tests (i.e., irradiation from low to high doses) were evaluated by the Scientific Research Institute for Radiation Medicine and Ecology Kasakhstan (Bauer et al. 2005; Gordeev et al. 2002). In 2006 the doses were re-evaluated and estimations for inhabitants of the most exposed Dolon village ranged about 250 to 400 mSv (Stepanenko et al. 2006). There were also actual dose measurements by Electron Spin resonance (ESR) measurements of the tooth enamels collected from exposed people in this area. For example Zhumadilov and co-workers determined a mean cumulative dose of 74 ± 35 mSv (Zhumadilov et al. 2006; Zhumadilov et al. 2007). A review of the dosimetry studies of the Dolon village was made by Stepanenko et al. (2006) and one of every village in this area was given by Shinkarev (2013).

The other patients were the 'Non-Exp group' (n=36 patients); they had spent all of their lives living in a region of radiological safety, i.e., the city of Almaty, which is more than 700 km away from the SNTS. The ages of the 76 patients ranged from 51 to 65 years old. The average ages were 61.2 ± 2.1 years in the total group, 61.4 ± 1.1 years in the Exp group, 60.9 ± 1.3 years in the Non-Exp group, and 57.6 ± 1.4 years in the control group.

The study inclusion criteria for patients were as follows: (1) age from 50 to 65 years, (2) having a verified diagnosis of one or more malignant neoplasms on the basis of a morphological examination, (3) not having undergone specific anti-tumor therapy at the time of the initial examination for the present study, (4) not having undergone any diagnostic procedures associated with exposure to ionizing radiation during the prior 6 months, and (5) providing informed consent to participate in the study and for the anonymous use of their data in scientific publications. Our initial examination was performed after the clinical diagnosis was verified, before specific antitumor treatment such as chemotherapy and radiation therapy was conducted, and before any surgical intervention was performed. For the verification of rectal cancer, non-radiological methods such as magnetic resonance imaging and endoscopic methods have been used for the beginning with the outpatient diagnostic stage.

We also examined a control group of 70 apparently healthy adults who had lived all of their lives in regions of radiological safety and who did not have any history of radiotherapy. Chosen was a random sample of clinically healthy individuals from 50 to 65 years of age, who did not have difficult current and/or complicated chronic diseases, exacerbations of chronic diseases, acute conditions, malignant neoplasms (including in the past) at the time of medical examination in Almaty.

The exclusion criteria were the presence of severe somatic comorbidities including arterial hypertension (class II or higher), ischemic heart disease, bronchial asthma, chronic

obstructive pulmonary disease, chronic kidney disease with renal insufficiency, cardiac insufficiency of any origin above functional class I; chronic infectious diseases (tuberculosis, brucellosis, etc.); acute infectious diseases; conditions accompanied by a fever at the time of the initial examination; refusal to participate in the study at any stage.

2.1.2.3. Methods of investigation

Indicators of vascular-platelet hemostasis

For our analysis of vascular-platelet hemostasis in the three groups, we determined the level of platelet aggregation induced by adenosine diphosphate (ADP) using the method devised by Barkagan et al. (1999). The defined parameters of vascular-platelet hemostasis were as follows: the index of spontaneous platelet aggregation (ISA), the total index of aggregation (TIA), and the index of spontaneous disaggregation (ISD) in the blood. The level of von Willebrand factor (WF) in the blood was also measured. The study was conducted on formalized platelets using a ristomycin test.

Methods for the investigation of endothelial function

To investigate the endothelial function of the controls and the rectal cancer patients who were exposed/not exposed to radiation, we determined the content of exfoliated (circulating) endotheliocytes in the peripheral blood (CE) by isolation of endothelial cells together with platelets, followed by precipitation using platelet ADP, as described (Hladovec 1978), the content of metabolites of nitric oxide (NO) (met. NO) in the blood by spectrophotometry (Molina et al. 1995), and the rate (percentage) of endothelium-dependent vasodilation (EDVD) by ultrasound, based on reactive hyperemia by Doppler-ultrasound investigation (Celermajer 1995). Measurements of the

diameter of the brachial artery during the sample were carried out on an ultrasound machine ACUSON 128 (USA), using a linear sensor with a phased array at a frequency of 7 MHz.

Doppler echocardiography test with reactive hyperemia on the brachial artery (endothelium-dependent reaction)

Changes in the diameter of the brachial artery during a test with reactive hyperemia (endothelium-dependent reaction) were performed on the ACUSON 128 US-based ultrasound machine using a linear phased array sensor at a frequency of 7 MHz. The time between samples with reactive hyperemia and nitroglycerin intake was 10 min. The arterial diameter was measured in the immediate vicinity of the selected anatomical marker.

The measurements were performed by a linear method and in the modification of DA Zateyshchikov, which consists in measuring the diameter of an artery using two points, established by an ultrasound cursor: one - on the border of the adventitia-media of the anterior wall of the artery, the other on the border of the media-adventitia of the posterior wall. The image of the vessel was automatically synchronized with the R wave of the ECG. The diameter of the brachial artery was the average value calculated from the three cardiac cycles. The flow-dependent dilatation as a characteristic of the endothelium-dependent response was calculated, equal to the ratio of changes in the diameter of the brachial artery during reactive hyperemia to the diameter of the artery at rest, expressed as a percentage of the original diameter.

Determination of the content of desquamated endotheliocytes in the blood

The quantitative determination of circulating (desquamated) endotheliocytes in the blood was performed according to the method of Hladovec et al, (1978). The method is based on the

isolation of endothelial cells together with platelets, followed by the deposition of platelets with ADP.

Blood from the ulnar vein was taken in an amount of 5 ml, in a tube with 3.8% citric sodium, in a ratio of 1: 9. The blood was centrifuged for 15 minutes at 200 g. Then 1 ml of plasma was mixed with 0.2 ml of the sodium salt of adenosine diphosphate (Na-ADP) at a concentration of 1 mg / ml, and then again centrifuged in the previous regime. The platelet-free supernatant was centrifuged at 200 g for 15 min to precipitate endotheliocytes, the supernatant plasma was removed, the Goryaev chamber was filled with a final suspension. The number of endotheliocytes was counted in 2 nets of the chamber by the method of phase contrast microscopy. Taking into account the ratio between the number of cells in the grid and the volume of the Goriaev chamber, the volume of the resulting suspension and the volume of plasma, the result was multiplied by 104 / 1 in counting the number of endothelial cells.

Determination of von Willebrand Factor on Formalized Platelets

As a material for the study, citrated platelet-poor blood plasma is used.

Fixed platelets are thawed, centrifuged at 1000 rpm (240 d) for 20 minutes, the supernatant drained, the platelets resuspended in 1 ml of the suspension solution (to an optical density of 1.0). The optical density is measured on a photoelectric colorimeter with a green filter (640 nm) in a 2 ml cuvette.

To 1 ml of the plate suspension thus prepared is added 0.6 ml of physiological sodium chloride solution, 0.2 ml of diluted twice with physiological sodium chloride solution of the poorly studied platelet plasma and 0.2 ml of ristomycin solution. The optical density is recorded, then the mixture is poured into a cuvette for 5 ml and stirred for 2 minutes using a magnetic stirrer. Again

transferred to a cuvette for 2 ml and the optical density is again measured. The agglutination index (IA) is calculated.

The percentage of VF is determined by the calibration curve. If in the course of the research results go beyond the calibration curve, the investigated plasma will dilute twice with physiological sodium chloride solution before determination and the found value of the VF (according to the calibration schedule) is multiplied by 2.

To construct a calibration curve, prepare mixture from 10 samples of normal platelet-poor plasma which has got from healthy people aged 20-30 years. Dilutions from this mixture in the suspension solution are made 2, 4 and 8 times. Dilution 1: 2 is taken as 100% activity of VF, dilution 1: 4 - for 50% and 1: 8 - for 25% of the activity of this factor. Each sample was examined three times according to the procedure described above. The average value is calculated. The calibration curve is constructed in the bilogarithmic coordinate system. The new calibration curve is constructed for each newly prepared suspension of fixed platelets and a series of ristomycin.

2.1.2.4. Results

The results of our analysis of the numerical ratings of vascular-platelet hemostasis and the condition of the endothelium in the Exposed, Non-Exposed and control groups are shown in Table 1.

Table 1 Means and standard errors of vascular-platelet hemostasis and endothelial function by groups of the rectal cancer patients and the control group.

Indicator	Groups			Statistical significance of difference of means (p-values from two-sided t-test)			
	Control (G1:n=70)	Non-Exposed Patients (G2: n=36)	Exposed Patients (G3: n=40)	G2 vs. G1	G3 vs. G1	G2+G3 vs. G1	G3 vs. G2
	M1± m	M2± m	M3± m				
ISA (%)	41.2± 3.4	54.7 ±5.5	60.3± 6.1	0.037	0.006	0.002	0.495
TIA (%)	60.5 ±5.1	74.8 ±6.6	79.7 ±6.3	0.086	0.018	0.014	0.591
ISD (%)	19.7± 2.0	13.5± 1.0	9.8 ±0.7	0.006	<0.001	<0.001	0.002
WF(mg/ml)	51.7± 2.6	69.6 ±4.2	89.5 ±6.3	<0.001	<0.001	<0.001	0.009
CE content [for 1000 platelets]	2.2 ±0.1	4.8± 0.3	8.1± 0.5	<0.001	<0.001	<0.001	<0.001
met. NO content (mcg/ml)	41.3 ±2.4	59.1± 3.3	54.6 ±7.8	<0.001	0.103	0.002	0.595
EDVD (%)	18.6 ±1.0	12.2± 1.0	8.8± 0.7	<0.001	<0.001	<0.001	0.005

M1, M2, M3: the average values in the respective groups (G1, G2 and G3) of number series; m: the standard error for each group. ISA: index of spontaneous platelet aggregation, TIA: total index of aggregation, ISD: index of spontaneous disaggregation, WF: von Willebrand factor, EDVD: endothelium-dependent vasodilation; p-value or probability value – statistical hypothesis testing; CE – circulated endothelicytes; met.NO – metabolites of Nitrogen Oxyde.

The ISA values were in the range of 21%–58% in the control group, 48%–75% in the Non-Exposed group, and 53%–81% in the Exposed group. There were significant differences in the ISA values between both groups of patients and the control group ($M2/M1=1.33$; $M3/M1=1.46$).

Significant differences in ISA values between the radiation-exposed and unexposed patients were not found. Significant differences in the average TIA values were observed between all patients ($M2+M3$) or exposed patients alone ($M3$) and control group; $M2+M3/M1=1.24$; $M3/M1=1.32$. However, no significant difference was observed for the other values $M2/M1$ and $M3/M2$. The ISD values of both the Exp (8%–13%) and Non-Exp (10%–18%) patients were significantly reduced compared to those of the control subjects (14%–31%). Each of the between-group differences ($M1/M2=1.46$; $M1/M3=2.00$ and $M2/M3=1.38$) were significant. The WF content was significantly higher in both the Exp group (89.5 mg/ml) and Non-Exp group (69.6 mg/ml) compared to the control group (51.7 mg/ml) ($M2/M1=1.35$; $M3/M1=1.73$). The difference between the two groups of patients was also significant ($M3/M2=1.29$).

Our analysis of several indices of vascular-platelet hemostasis thus revealed the activation of aggregation mechanisms in both groups of patients with malignant neoplasms. However, the question of the origin of this activation against the background of the disaggregation disorders remains. Is the activation a manifestation of the primary disorders of the structure and function of platelets, or is it a consequence of the secondary pathological activation of platelets by the action of non-platelet factors? The reduction of the levels and the significance of the differences between the two patient groups in terms of TIA against ISA is evidence of a possible role of external influences on the thrombocytes' condition.

It is known that the aggregation function of platelets is closely associated with the condition of the vascular endothelium (Forconi et al. 2013). We thus hypothesized that one of the possible reasons for the increase in aggregation and the reduction of the disaggregation ability of

platelets in the radiation-exposed patients with malignant neoplasms would be structural and functional disorders of the endothelium. To test this hypothesis, we conducted several laboratory and statistical analyses.

Significant differences were revealed among all three groups in terms of the content of circulating endothelial cells (i.e., CE) in the peripheral blood. The extent of the excess of this indicator over the control group was for exposed patients 3.68 times, and for the unexposed 2.18 times. In addition, the content of CE differed significantly in the group of patients with a history of radiation compared to patients without a radiation history ($M3/M2 = 1.69$). The endothelium damage in the radiation-exposed individuals may thus occur before the development of their cancer, or the neoplastic process may affect the condition of endothelial cells. However, whatever the mechanisms are, the result is decreased resistance of endothelial cells due to the combination of chronic radiation exposure and the malignant neoplasm.

The content of NO metabolites in the blood of both the Exposed and Non-Exposed patients, as an indicator of the function of the vascular endothelium, was increased. This phenomenon, which reflects the pathological mechanisms of the overproduction of NO by the endothelium in the presence of local or systemic inflammation, hypoxia, and the activation of lipid peroxidation, is well known (Lacroix et al. 2012). However, the average NO metabolite content of the radiation-exposed patients was not significantly lower than that of the Non-Exp patients ($M2 / M3=1.08$).

The degree of EDVD is the parameter that most clearly defines the presence of endothelial dysfunction, and in the present study the degree of EDVD was significantly lower in patients than controls and underwent the most significant decrease in the patients who were chronically exposed to the nuclear site radiation.

Thus, all of the laboratory and instrumental data obtained in the present study confirmed the presence of endothelial dysfunction in the patients with malignant neoplasms and most of them suggest a greater degree of endothelial dysfunction in the patients who were subjected to chronic radiation exposure as compared to the non-exposed patients.

To determine the relationship between the condition of the endothelium and vascular-platelet hemostasis, we conducted a correlation analysis, the results of which are summarized in Table 2. In both the Exposed and Non-Exposed patients, significant correlations were revealed between the content of endothelial cells in the blood and the EDVD values and indices of hemostasis. The correlation coefficients of the indices of hemostasis with the content of NO metabolites were significantly smaller than with the content of endothelial cells in the blood and the EDVD values.

Table 2 The coefficients of correlations between the parameters of endothelial function and vascular-platelet hemostasis in the Exp and Non-Exp patients

Indices of endothelial function	Indices of vascular-platelet hemostasis			
	ISA	TIA	ISD	WF
Exposed Patients (G3: n=40)				
CE content	0.55	0.57	-0.44	0.76
	<i>p</i> =0.034	<i>p</i> =0.030	<i>p</i> =0.037	<i>p</i> =0.009
met. NO content	0.50	0.59	-0.28	0.32
	<i>p</i> =0.037	<i>p</i> =0.031	<i>p</i> =0.067	<i>p</i> =0.053
EDVD	-0.64	-0.70	0.73	-0.60
	<i>p</i> =0.022	<i>p</i> =0.017	<i>p</i> =0.011	<i>p</i> =0.030
Non- Exposed Patients (G2: n=36)				
CE content	0.34	0.40	-0.27	0.45
	<i>p</i> =0.050	<i>p</i> =0.044	<i>p</i> =0.061	<i>p</i> =0.039
met. NO content	0.27	0.32	-0.15	0.19
	<i>p</i> =0.061	<i>p</i> =0.053	<i>p</i> =0.075	<i>p</i> =0.070
EDVD	-0.36	-0.18	0.31	-0.33
	<i>p</i> =0.055	<i>p</i> =0.073	<i>p</i> =0.054	<i>p</i> =0.051

A common feature of all of the results of the correlation analysis in the chronically radiation-exposed patients (Exposed group) was significantly greater correlations between the indices of endothelial function and the hemostasis system.

2.1.2.5. Discussion

In oncology, the vascular endothelium is thought to be mainly a producer and a target organ for a large number of biologically active agents that define the conditions of tumor growth. Mainly these agents are stimulators and inhibitors of neovascularization or some cytokines (Polet et al. 2013; Goveia et al. 2014; Carman et al, 2015). However, other properties are most essential for the endothelium: barrier function, the regulation of the vascular wall's tone, the rheological properties of blood, and hemostasis (Huck et al. 2014; Turner et al. 2012).

Systemic reactions of the endothelium to various pathological states are expressed primarily as circulatory and hemostasis disorders (Fisher 2008; Kvolik et al. 2010). Hemostasis disorders may play an essential role in both the pathogenesis of neoplasms and their hematogenic dissemination (Gay et al. 2011).

Our present findings revealed signs of endothelial dysfunction in both groups of patients — those who had been chronically exposed to radiation and those who had not. These signs included a decrease in endothelium-dependent vasodilatation (Xu et al. 2014) and an increased content of circulating endotheliocytes in the blood, and also an increase in one of the major endothelial components of the hemostasis system, i.e., von Willebrand's factor (Huck et al. 2014).

Prior analyses of a number of indicators in groups of oncological patients confirmed the existence of dependence between the status of endothelial function and that of hemostasis, indicating that the endothelium provides the most important mechanisms of hemostasis (Pak et al. 2016; Aird 2015).

Thrombotic complications remain one of the leading causes of death of patients with cancer, observed from 20% up to 30% of all cancer-related deaths (Elyamany et al. 2014; Heit 2015). These complications are usually associated with the activation of coagulative hemostasis, and the corrective treatment is directed toward this activation (Franchini et al. 2015). However, the essential and leading role of the vascular platelet link of hemostasis (which is a target for the development of a neoplasm) should not be ignored, and all methods of oncological treatment should include a consideration of this aspect of hemostasis (Cameron et al. 2016; Falanga et al. 2015; Mezouar et al. 2016).

An even higher degree of the vascular endothelium damage has been revealed in rectal cancer patients who were affected by radiation from the SNTS compared to non-exposed patients. Ionizing radiation appears to aggravate the extent of disturbances of endothelial function and to cause a decrease in the control of the formation of platelet blood clots, disturbing the rheological properties of blood and reducing microcirculation. The cause of functional lesions and the death of cancer patients may thus be the multiple thromboses of small vessels, not occlusions of large vessels.

There are a large number of factors that counteract and promote metastasis of malignant neoplasms. However, the tumor cell spreading by the hematogenous pathway must pass through the endothelial layer and the basal membrane of the vessel in order to penetrate the tissues in all cases. Disturbances in the structure, trophism, and other components of endothelial function may promote the spread of hematogenous metastases (Pacia et al. 2015).

Ionizing radiation can thus have another negative oncological effect - promoting tumor growth activation and/or the risk of metastasis through the formation of endothelial dysfunction.

2.1.2.6. Conclusion

Hemostatic disturbances are one of the most important consequences of the neoplastic process and the reason for a large number of treatment failures. The essential cause of hemostasis disorders is the presence of regular changes of endothelial function. Endothelial dysfunction and the accompanying circulation disturbances also promote the dissemination of tumor cells and their penetration into tissues along with the development of remote metastases. An especially high risk of similar complications may occur among patients who are treated surgically.

The prognoses of cancer patients may be improved by a further clarification of disturbances of the vasotonic and hemostatic functions of the endothelium, and the development of approaches directed to their correction. Patients with an increased risk of the development of endothelial dysfunction should be carefully monitored.

2.2. Congenital anomalies of the circulatory system

2.2.1. Introduction

A congenital anomalies of the circulatory system is a problem with the structure of the heart. It is present at birth. Congenital anomalies of the circulatory system are the most common type of birth defect. The defects can involve the walls of the heart, the valves of the heart, and the arteries and veins near the heart. They can disrupt the normal flow of blood through the heart. The blood flow can slow down, go in the wrong direction or to the wrong place, or be blocked completely.

Doctors use a physical exam and special heart tests to diagnose congenital anomalies of the circulatory system. They often find severe defects during pregnancy or soon after birth. Signs and symptoms of severe defects in newborns include:

- Rapid breathing

- Cyanosis - a bluish tint to the skin, lips, and fingernails
- Fatigue
- Poor blood circulation

Many congenital heart defects cause few or no signs and symptoms (National Heart, Lung, and Blood Institute).

In most countries, congenital anomalies remain a relevant public health problem, but they are also an important risk factor for child mortality and disability. Studies in Europe and North America have shown that up to a third of all perinatal losses may be due to anatomical defects. In stillborn infants, congenital anomalies are detected in 15-20 % of cases. According to the National Center on Birth Defects in the United States each year 10 to 20 million children are born throughout the world with congenital anomalies (Knowles et al. 2005). congenital anomalies of the circulatory system are one of the leading causes of death in infants, so the timely detection of them is important, and hemodynamic instability can determine the quality of children's lives beginning in the neonatal period. congenital anomalies of the circulatory system is present from birth in definition. The most practical measurement of congenital anomalies of the circulatory system occurrence is birth prevalence per 1,000 live births (Mason et al. 2005). According to the literature (Chaix 2016), the frequency of congenital anomalies of the circulatory system in infants is an average of 2 to 5 per 1,000. The estimate of 8 per 1,000 live births is accepted as the best approximation generally (Bernier et al. 2010).

The lack of a clear trend towards reducing the number of children born with various malformations, including congenital anomalies of the circulatory system, highlights the significance of ongoing research on the subject. In the Republic of Kazakhstan, official statistics on infant mortality show that congenital anomalies were present in up to 22.8% of cases, ranking second among all causes. According to the Ministry of Health of the Republic of Kazakhstan, the

incidence of congenital diseases in Kazakhstan is 4%-6%, including congenital abnormalities at 2.5% (Statistical summary of Republic Kazakhstan, 2008-2013).

Every year, according to the National Register of Genetics of the Republic of Kazakhstan, from 2,500 to 3,500 children are born in Kazakhstan with congenital and hereditary diseases, constituting a rate ranging from 20.0 to 24.3 per 1,000 live births, and the proportion of congenital malformations among cases of perinatal mortality in a number of ecologically unfavorable regions is highest among conditions associated with perinatal mortality (Igisinov et al. 2013). In 9 % of cases of congenital anomalies of the circulatory system was due to a variety of factors including radiation, viral infections, diseases of the mother during pregnancy, drugs and chemicals, and heavy metals, while only 10 % of cases of congenital anomalies of the circulatory system were caused by chromosomal abnormalities or single gene mutations (Chaix et al. 2016; Chernyh et al. 2012; Hoffman and Kaplan 2002).

It is known, that 468 nuclear tests were performed at the Semipalatinsk Nuclear Test Sites (SNTS) before 1990 caused irreparable damage to human health and the environment and caused an increase in overall morbidity and mortality (Katayama et al. 2006; Law of the Republic of Kazakhstan, 1992 explained in Takemine et al. 2015). About 54 % of the area occupied by the nuclear test sites was in East Kazakhstan. The zones of maximum and high radiation risk are recognized to be in the cities Semey, Ust-Kamenogorsk, Kurchatov, Ridder, and in the regions of East Kazakhstan: Borodulichinsky, Zharminsky, Ayagozky, Glubokovsky, Shemonaikhinsky, and Ulansky areas (Law of the Republic of Kazakhstan 2014), but no analysis of the incidence of congenital anomalies, depending on the degree of remoteness from the test site has been recently published. At the same time the highest levels of disease were recorded in the Akmola region at 783.6 cases per 100,000 populations, the South Kazakhstan region - at 967.4, the Zhambyl region - at 707.0, and in Almaty city - at 788.1. Until now, the frequency of congenital abnormalities have

not been fully studied, including malformations of the heart and blood vessels, and their prevalence among the causes of infant mortality in Semey and East Kazakhstan has not been established. Also, the impact of various exogenous and endogenous circumstances, the long term consequences of the activities at the SNTS twenty five years after the test site was closed, the risk of having a baby with a congenital anomaly have been important today.

The aim of this study was to determine the incidence of congenital malformations and congenital anomalies of the circulatory system in Kazakhstan and in the East Kazakhstan region among children aged 0 to 14 years.

2.2.2. Materials and methods

The prevalence rates of congenital anomalies and of CHD were studied in the Republic of Kazakhstan (16 regions) and all the cities and regions of the East Kazakhstan region. The standard WHO definition was used (2015): "Congenital anomaly - a persistent morphological changes in the body of the organ or a large part of the body, appearing most often in utero, is outside the normal variations of the structure and violates its function" (WHO 2015). The study is based on official statistical data reported on patient's chart number 12 of the Ministry of Health of the Republic of Kazakhstan on the prevalence of congenital anomalies and congenital anomalies of the circulatory system over a 6-year period (2007-2012) (Statistical summary, 2014). In Kazakhstan data congenital anomalies of the circulatory system were tabulated however it mainly indicate congenital anomalies of the circulatory system. Also, data from the statistical compilation titled "Health of the Republic of Kazakhstan and activities of the healthcare organizations" for the period 2007-2012 were used (Statistical summary, 2008-2013). The study included congenital malformations, deformations and chromosomal abnormalities in children aged 0-14 years, which are classified

according to ICD-10 as - Q00-Q99, as well as congenital heart disease and diseases of circulatory system in children aged 0 to 14 years, classified in accordance with the ICD-10 as - Q20-Q28.

2.2.3. Results

As results, it was found that the highest incidences of congenital anomalies over the study period were observed in the Zhambyl, South Kazakhstan, North Kazakhstan, Akmola and Mangistau regions. The East Kazakhstan region, where most of the SNTS was located, had a long-term average incidence almost three times lower than the national average and six times lower than the Zhambyl region, where the incidence rate in this period was the highest in Kazakhstan (Table 3).

Table 3. The incidence of congenital anomalies per 100,000 population per year in Kazakhstan by region. 2007 to 2012.

Region. city	Long-term average annual value	Coefficient	95 % CI		P
Atyrau	309.7	20.0	-47.4	87.5	0.457
West Kazakhstan	364.6	162.0	-63.7	31.3	0.397
Karaganda	380.1	38.0	12.5	63.4	0.014
East Kazakhstan	394.9	-10.7	-33.8	12.3	0.266
Almaty	485.5	-44.9	-108.1	18.3	0.120
Aktobe	572.8	-10.6	-32.4	11.1	0.247
Kyzyl-Orda	628.9	23.3	-54.3	7.6	0.105
Astana	636.7	13.5	-64.7	91.8	0.656
Kostanai	734.8	167.5	104.0	231.1	0.002
The Republic of Kazakhstan	1040.8	56.7	34.4	79.0	0.002
Pavlodar	1081.9	169.2	95.2	243.3	0.003
Almaty	1163.7	116.5	-88.9	322.0	0.191
Mangistau	1352.3	237.1	-25.5	499.8	0.066
Akmola	1566.2	-41.3	-175.3	92.5	0.439
North Kazakhstan	1771.1	55.2	-347.8	458.2	0.723
South Kazakhstan	1855.0	101.0	22.1	179.9	0.024
Zhambyl	2403.4	69.0	-78.7	216.7	0.264

In the Fig.5 there is incidence of congenital anomalies in Kazakhstan by region per 100,000 population per year (the red bar shows exposed region).

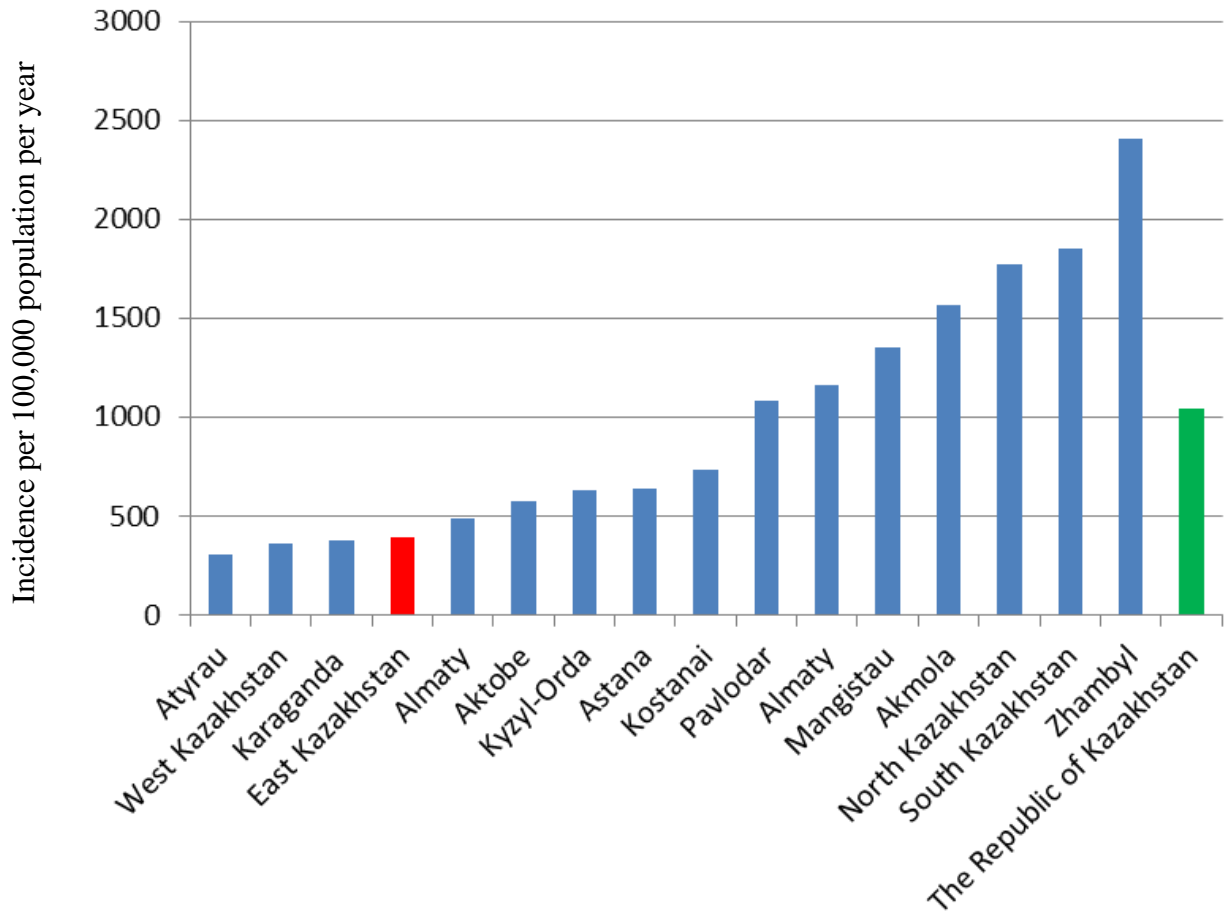


Fig. 5 The incidence of congenital anomalies in Kazakhstan by region. (2007 to 2012).

The red bar shows exposed region.

Moreover, the incidence of congenital anomalies in the East Kazakhstan region had a tendency to decrease, although this tendency did not reach statistical significance. It is interesting to note that none of the administrative units of the republic showed statistically significant trends in reducing the incidence of congenital anomalies. In addition, the South Kazakhstan, Pavlodar, Kostanay and Karaganda regions showed statistically significant increases in incidence over the study period, which resulted in an increase in incidence at the national level by an average of 56.7 (95 % CI: 34.4-79.0) cases per 100,000 population per year. However, the significant increase in the reported incidence was probably due to the improved diagnosis of congenital anomalies, and was not the result of a true increase in incidence. The differences between the incidence of the region ranked first and that ranked last was eight-fold, which is an unlikely result.

In the territory of East Kazakhstan, the highest incidence rates of congenital abnormalities have been reported in the cities of Ridder, Kurchatov, and Ust-Kamenogorsk, and in the Glubokoe and Zharma areas. All of these areas have an average annual incidence above average for the area, which suggests the negative impact of the landfill. At the same time, in some rural areas assigned to the zone of maximum and increased risk, the incidence was significantly lower, which, however, may be due in part to the lower diagnostic capabilities in these areas (Table 4).

In the Fig. 6 there is incidence of congenital anomalies in the East Kazakhstan region per 100,000 population per year (the red bar show exposed areas more than 0.07Sv).

Table 4. The incidence of congenital anomalies per 100,000 population per year in the East Kazakhstan region. 2007 to 2012.

District. city	Long-term average annual value	Coefficient	95% CI		p
Tarbagatai	152.6	16.8	-4.6	38.4	0.095
Kurchum	179.3	17.7	-40.8	76.2	0.449
Ayagoz	186.9	17.4	-20.0	54.9	0.265
Caton-Karagay	189.0	3.1	-47.1	53.3	0.872
Kokpekty	198.2	10.4	-44.7	65.6	0.627
Zaysan	206.9	10.3	-9.9	30.6	0.231
Urjar	237.5	46.0	-20.4	112.5	0.127
Ziryanovsk	240.7	20.2	-40.9	81.5	0.418
Ulan	241.7	27.1	-62.8	117.2	0.449
Boroschlihinsk	270.0	13.5	-20.8	47.9	0.336
Semey	296.3	-17.1	-63.2	28.8	0.359
Shemonaikha	308.0	-0.5	-11.7	10.6	0.901
Beskaragai	316.1	14.6	-37.1	66.3	0.477
May	320.6	16.8	-43.9	77.6	0.484
Zharma	337.2	70.1	23.7	116.4	0.014
Kurchatov	341.9	-128.6	-232.4	-24.9	0.026
Glubokovoe	352.6	61.5	-215.3	92.1	0.328
Ust-Kamenogorsk	493.7	25.4	-32.9	83.9	0.293
Ridder	968.9	-304.1	-469.0	-139.2	0.007

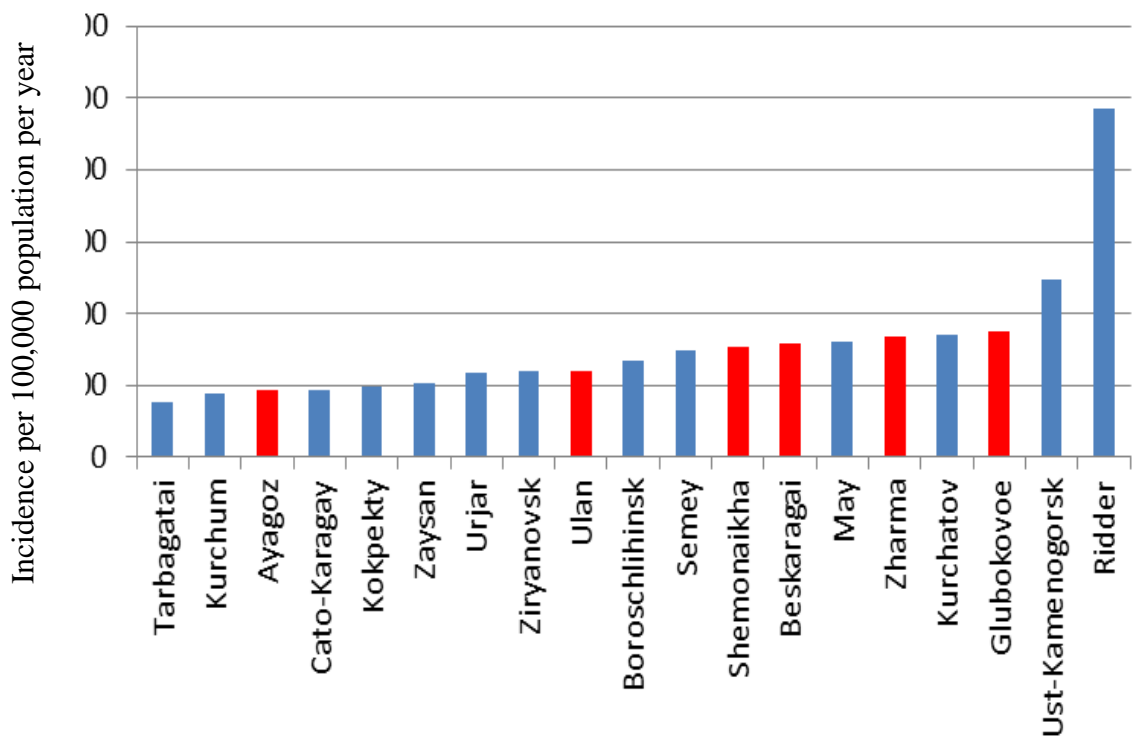


Fig. 6. The incidence of congenital anomalies in the East Kazakhstan region (2007 to 2012). Red bars show exposed areas more than 0.07Sv.

The Zharma region showed an increase in incidence. Considering that opposing trends recorded in ecologically unfavorable surrounding areas, we believe that the identified trends can be regarded as the result of random variation or regression to the mean.

The highest incidences of congenital anomalies of the circulatory system over the study period were observed in the Akmola, Almaty, South Kazakhstan, Pavlodar and Mangistau regions. The East Kazakhstan region, where SNTS is located, had a long-term average incidence almost 2 times lower than the national average and 3.5 times lower than the Akmola region, where the incidence rate in this period was the highest in Kazakhstan (Table 5).

In the Fig. 7 there is incidence of congenital anomalies of the circulatory system in Kazakhstan per 100,000 population per year (the red bar shows exposed region).

Table 5. The incidence of congenital anomalies of the circulatory system per 100,000 population per year in Kazakhstan. 2007 to 2012

Region, City	<u>Long-term</u>	<u>Coefficient</u>	95% CI		p
	<u>average</u> <u>annual</u> value				
Almaty	125.5	0.62	-26.6	27.9	0.064
Atyrau	129.4	-40.5	-80.0	-1.03	0.046
Karaganda	176.8	-47.6	-95.5	-0.32	0.051
East Kazakhstan	213.6	-54.6	-87.7	-21.5	0.010
West Kazakhstan	236.9	-52.0	836	-20.5	0.010
Aktobe	247.9	-61.7	-96.4	-27.0	0.008
Kyzylorda	277.2	-59.7	1 14.1	-5.25	0.038
North Kazakhstan	328.7	94.4	-295.2	106.2	0.261
Astana	330.4	-113.9	-178.1	-49.7	0.008
Mangistau	388.4	-123.6	-166.0	-81.3	0.001
The Republic of Kazakhstan	416.3	-71.9	-117.2	-26.6	0.012
Kostanay	431.8	82.5	29.7	135.2	0.012
Zhambyl	571.3	-205.7	-344.5	-67.0	0.015
South Kazakhstan	606.6	-76.6	-151.4	-1.97	0.046
Pavlodar	617.5	18.7	-13.1	50.6	0.078
Almaty	679.7	-139.7	-262.4	-17.1	0.034
Akmola	773.8	-48.4	-194.5	97.7	0.410

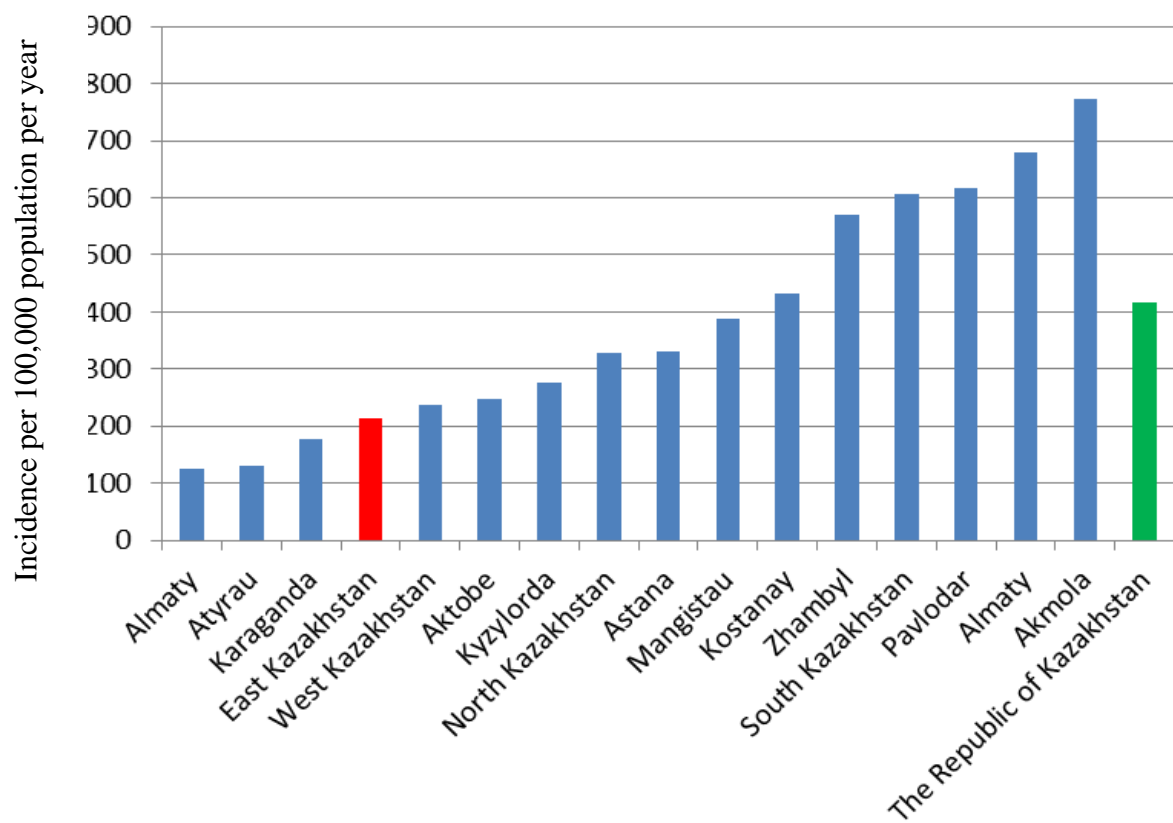


Fig. 7. The incidence of congenital anomalies of the circulatory system in Kazakhstan (2007 to 2012). The red bar shows exposed region.

Kazakhstan region showed a statistically significant downward trend on average of 54.6 (95% CI: 21.5-87.7) per 100,000 population per year. Statistically significant reductions in incidence were observed in the Atyrau, West Kazakhstan, Aktobe, Kyzylorda, Mangystau, South Kazakhstan, and Zhambyl regions, as well as in the cities of Astana and Almaty. The only region where an increase was recorded during the period was Kostanay. At the national level a downward trend in congenital anomalies and diseases of the circulatory system was also registered (Table 5).

The highest rates of incidence of anomalies of the circulatory system over the study period in the East Kazakhstan region were registered in the cities of Kurchatov, Ridder, Ust-Kamenogorsk, Semey and districts of Zharma, Glubokoe, i.e. in ecologically disadvantaged areas that are experiencing the most serious consequences of the SNTS activities. None of the administrative and territorial indicators of East Kazakhstan showed statistically significant changes in the dynamics of the incidence of abnormalities of the circulatory system (Table 6).

In the Fig. 8 there is incidence of congenital anomalies of the circulatory system in the East Kazakhstan region per 100,000 population per year (red bars show exposed areas more than 0.07Sv).

Table 6. The incidence of congenital anomalies of the circulatory system per 100,000 population per year in the East Kazakhstan region. 2007 to 2012

District. city	Long-term average annual value	Coefficient	95 % CI		p
Caton-Karagay	44.0	-0.4	-8.9	7.5	0.879
Ayagoz	44.2	6.7	-4.0	17.5	0.159
Beskaragai	49.0	-4.8	-18.1	8.4	0.372
Shemonaikha	54.0	-5.2	-23.4	12.8	0.464
Kurchum	58.1	-3.9	-17.9	9.9	0.471
Ulan	68.8	20.3	-12.0	52.8	0.156
Kokpekty	73.4	6.0	-25.8	37.9	0.624
Urjar	75.0	20.0	-7.9	48.1	0.118
May	78.6	-8.1	-32.6	16.4	0.409
Tarbagatai	79.9	2.8	-5.94	11.7	0.400
Boroduliha	83.2	12.0	-15.4	39.5	0.291
Ziryanovsk	83.9	3.0	-25.1	31.1	0.782
Zaysan	87.1	3.3	-11.0	17.7	0.552
Semey	88.0	2.6	-7.0	12.3	0.493
Zharma	88.6	17.4	1.1	33.7	0.041
Glubokoe	89.4	2.4	-1.6	6.5	0.170
Ridder	90.7	-3.1	-19.1	12.8	0.614
Ust-Kamenogorsk	15.9	0.2	-22.8	23.2	0.982
Kurchatov	188.2	-71.7	-127.1	-16.3	0.023

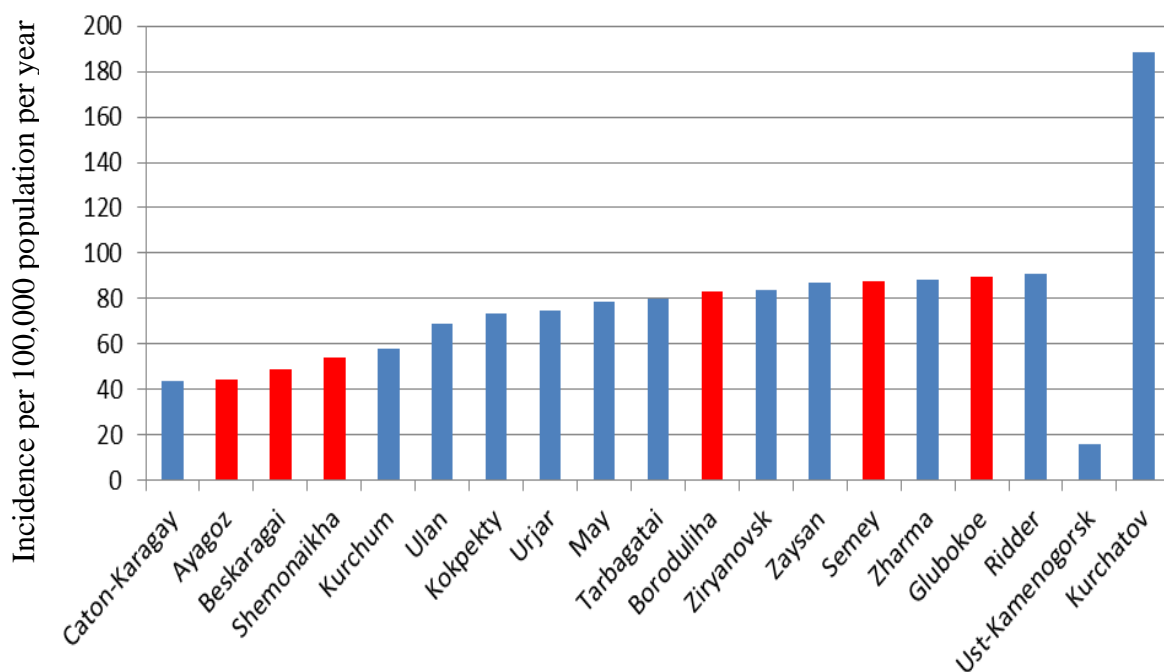


Fig. 8. The incidence of congenital anomalies of the circulatory system in the East Kazakhstan region (2007 to 2012). Red bars show exposed areas more than 0.07Sv. 1,

2.2.4. Discussion

The results of our study show that the consequences of the activities of the Republic of Kazakhstan SNTS currently play a minor role. Regions with the maximum levels of morbidity due to congenital anomalies in general and to anomalies of the circulatory system are in opposite parts of the country, while the East Kazakhstan region has one of the lowest morbidity rates in Kazakhstan. Moreover, this situation is unlikely to be related to the features and capabilities of diagnosis, as in East Kazakhstan, diagnostic medical staff has a pronounced wariness related to birth defects because of the ecological trouble the region.

At the same time at the regional level, the degree of influence of the impacts of the landfill is much more significant. The highest long-term incidence rates were recorded in urban and rural areas in this region and these areas also showed an larger maximum radiation risk. This variability in incidence can hardly be explained by varying diagnostic capabilities.

The results of the environmental study should be interpreted with caution, and the main features of the design of environmental studies should be taken into account. We used official statistics as our data, and thus the quality of our results depends on the quality of the reporting documentation. In addition, no information on the radiation levels in the study area was available, which made it impossible to analyze the link between radiation and congenital anomalies. On the other hand, this relationship is not in doubt, and the purpose of our study was to investigate the effects of the activity at the landfill on the incidence of congenital anomalies decades after the closure of the landfill. Another drawback of this study is our dependence on the reporting format adopted in the Republic of Kazakhstan; namely, the incidence was reported in children ranging in age from 0 to 14 years, which makes it impossible to compare the data with the results of most of the foreign and Russian studies (Chernyh et al., 2012; Postoev et al., 2014), which focused on the

perinatal prevalence of congenital anomalies and twenty-eight percent of all major congenital anomalies consist of heart defects (Dolk et al., 2011).

A report about prevalence rates of congenital anomalies of the circulatory system in newborns varied widely and depends to some extent, lesion inclusion and exclusion criteria (Baird et al., 1991). Different methods as certainment (e.g., physical examination, echocardiography, and registry data) yield varying prevalence rates of congenital anomalies of the circulatory system in infancy (Warnes et al., 2001). However, we did not find studies about prevalence among the regions of one country.

Nevertheless, we did not set an aim to compare our results with those of other countries, and the different regions of Kazakhstan and East Kazakhstan shared the reporting format, which allowed; us to make comparisons within Kazakhstan, though these were not necessarily very informative.

2.2.5. Conclusion

It should be noted that, despite the long-term activity at SNTS, three decades after it closed, the East Kazakhstan region recorded one of the lowest incidence of congenital anomalies. This suggests that the landfill activity played only a minor role in the relative risk of congenital anomalies in comparison with other risk factors all over Kazakhstan. At the same time, the data strongly suggest that within the East Kazakhstan region, even decades after the closure of the landfill, the highest incidence of morbidities is still observed in the territories of maximum radiation risk.

3. Future perspectives, toward epidemiological analysis based on individual retrospective dosimetry

Epidemiological “case-control” technique is one of the important instruments for estimation of health consequences of large scale radiation accidents. The technology of “case-control” epidemiological study needs individual approaches to assessments of absorbed doses among the investigated population. Another important condition – it is application to the same method of individual dose reconstruction for all persons included to such type of epidemiological study. There is only one way how apply the same method of individual dose reconstruction to all members of cohort – it is to develop and to realize the computational approaches of dose reconstruction using radioecological models and with accounting for individual information obtained by individual questioning/investigation.

On the other hand, any computational dose estimation needs instrumental verification in order to be sure in reliability of computed dose values. This instrumental verification can be based on the different sources of experimental data – a) available results of “on site” individual dose measurements (these data, as a rule, are very limited due to unexpected irradiation of humans at the moment of accident); b) results of application of instrumental dose reconstruction methods: Electron Spin Resonance (ESR) dosimetry with human tooth enamel and Retrospective Luminescence Dosimetry (RLD).

Since the primary days after the Chernobyl accident and in the future period, the main goals of long-term investigations, scientific and practical activities in the field of retrospective dosimetry were the development of approaches to assessments of individual absorbed doses among inhabitants living on the territories, contaminated by radionuclides as a result of the Chernobyl accident (Tsyb et al. 1998; Stepanenko et al. 2007, 2008).

Development and application of individual instrumental and computational methods of retrospective dosimetry allows dosimetrical support of “case-control” epidemiological studies and determination of persons with highest individual doses for implementing of individual prophylactic and medical measures (Davis et al. 2004; Davis et al. 2006; Kopecky et al. 2006).

The experience gained in the investigations of Chernobyl accident consequences assessment and corresponded retrospective dosimetry techniques studies have discovered the capability of its applications in solving topical tasks on the dose estimations among the population located near the Semipalatinsk nuclear test site (SNTS) (Hoshi et al. 2006); Stepanenko et al. 2006-a, 2007).

Currently, the dose assessments among the population near the Semipalatinsk Test Site area were rather contradictory (Lindholm et al. 2002; Hoshi et al. 2006) that do not allowed confident conclusions about real consequences of the tests based on the epidemiological studies.

The application of individual retrospective dosimetry methods can be useful for preparation of readiness to irradiation dose assessment in possible future radiation accidents: nuclear technologies continue developing and expanding, and the list of industrial risks of radiation accidents is added by those associated with potentially challenges of nuclear terrorism.

4. Discussion

In oncology, the vascular endothelium is thought to be mainly a producer and a target organ for a large number of biologically active agents that define the conditions of tumor growth. Mainly these agents are stimulators and inhibitors of neovascularization or some cytokines (Polet et al. 2013; Goveia et al. 2014; Carman et al. 2015). However, other properties are the most essential for the endothelium: barrier function, the regulation of the vascular wall's tone, the rheological properties of blood, and hemostasis (Garaliene 2006; Púzserová 2008).

Systemic reactions of the endothelium to various pathological states are expressed primarily as circulatory and hemostasis disorders (Fisher 2008; Kvolik et al. 2010). Hemostasis disorders may play an essential role in both the pathogenesis of neoplasms and their hematogenic dissemination (Gay et al. 2011).

Our present findings revealed signs of endothelial dysfunction in both groups of patients — those who had been chronically exposed to radiation and those who had not. These signs included a decrease in endothelium-dependent vasodilatation (Xu et al. 2014) and an increased content of circulating endotheliocytes in the blood (Machalińska et al. 2011), and also an increase in one of the major endothelial components of the hemostasis system, i.e., von Willebrand's factor (Huck et al. 2014).

Thus, an inappropriate increase in the vascular endothelium damage rate has been revealed in rectal cancer patients who were affected by anthropogenous radiation at medium or high doses.

Prior analyses of a number of indicators in groups of oncological patients confirmed the existence of dependence between the status of endothelial function and that of hemostasis, indicating that the endothelium provides the most important mechanisms of hemostasis (Pak et al. 2016; Aird 2015).

Thrombotic complications remain one of the leading causes of death of patients with cancer, observed from 20% up to 30% of all cancer-related deaths (Elyamany et al. 2014; Heit 2015). These complications are usually associated with the activation of coagulative hemostasis, and the corrective treatment is directed toward this activation (Franchini et al. 2015). However, the essential and leading role of the vascular platelet link of hemostasis (which is a target for the development of a neoplasm) should not be ignored, and all methods of oncological treatment should include a consideration of this aspect of hemostasis (Cameron et al. 2015; Falanga et al. 2015; Mezouar et al. 2016).

Ionizing radiation appears to aggravate the extent of disturbances of endothelial function and to cause a decrease in the control of the formation of platelet blood clots, disturbing the rheological properties of blood and reducing microcirculation. The cause of functional lesions and the death of cancer patients may thus be the multiple thromboses of small vessels, not occlusions of large vessels.

There are a large number of factors that counteract and promote metastasis of malignant neoplasms. However, in all cases, the tumor cell spreading by the hematogenous pathway must pass through the endothelial layer and the basal membrane of the vessel in order to penetrate the tissues. Disturbances in the structure, trophism, and other components of endothelial function may promote the spread of hematogenous metastases (Pacia et al. 2016).

The effect of ionizing radiation can thus have another negative oncological effect - promoting tumor growth activation (Treppe et al. 2015) and / or the risk of metastasis (Zang et al. 2016) through the formation of endothelial dysfunction.

Hemostatic disturbances are one of the most important consequences of the neoplastic process and the reason for a large number of treatment failures. The essential cause of hemostasis disorders is the presence of regular changes of endothelial function. Endothelial dysfunction and the

accompanying circulation disturbances also promote the dissemination of tumor cells and their penetration into tissues along with the development of remote metastases (Arnes et al. 2012; Ramcharan et al. 2015). An especially high risk of similar complications may occur among patients who are treated surgically.

The prognoses of cancer patients may be improved by a further clarification of disturbances of the vasotonic and hemostatic functions of the endothelium, and the development of approaches directed to their correction. Patients with an increased risk of the development of endothelial dysfunction should be carefully monitored.

It is known that thrombotic complications are the second most common direct cause of deaths of oncologic patients (Elyamany et al. 2014; Franchini et al. 2015). Taking into account the use of modern methods of treatment the patients with distant metastases, this factor comes to the fore (Epstein and O'Reilly 2012; Trujillo Santos 2012). The risk of cancer spread (metastasing) in the presence of evident endothelial increases due to three mechanisms – the increase of the permeability of the endothelium for the cellular elements of the tumor (Rebelo et al. 2009), the increase of thromboembolic potential and the negative impact of endothelial dysfunction on the state of the immune system as a result of cytokine imbalance (Poher et al. 2009).

Besides, it should be mentioned that according to the data of most researches the endothelial dysfunction also conduces the neovascularization of metastatic masses (Arnes et al. 2012; Ramcharan et al. 2015).

5. Conclusions

In this paper, the effects of radioactivities from the nuclear explosions spread from the nuclear test site of the Former Soviet Union have been studied. The reasons are not only to find the radiation effects from the radioactivity and but also to explain for the people living in these are whether the areas are safe or not.

There are two findings, firstly (1) we found the difference between exposed and non-exposed areas for the factors of endothelial function in the patients with rectal cancer such as ISD (%), WF(mg/ml), CE content and EDVD (%) and also found all of these factors are statistical significant between patients and healthy people. Secondly, (2) we found no difference for the congenital anomalies and congenital anormaries of the circulatory system between exposed and non-exposed area.

For the first cases we found the difference for the factors of the endothelial function between the patients living in the exposed area and not exposed area. The reasons are not clear now, however findigs of such differencs are very rare. Thereofere for the understandings of the effects of SNTS consequences it is necessary and important to continue the study to find its reasons and mechanizms.

For the second cases, it is important and useful because we can explain the people living in these areas that it had not been any problems to live in until now and after now.

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Appendix A

A. Retrospective dosimetry methods in cases of large scale radiation accidents.

A.1. Chernobyl accident. Thyroid gland irradiation: example of individual dose reconstruction and verification

For retrospective assessment of individual absorbed doses in the thyroid gland, a semi-empirical computational model within the international project on epidemiological study of radiation dependence of thyroid gland incidence rate on the contaminated territories of the Bryansk region was developed and used (Stepanenko et al. 2004, 2008; Stepanenko 2015). In addition to this model the results of individual questioning/investigation was accounted for individual dose assessments. Any computational dose estimation needs instrumental verification in order to be sure in reliability of computed dose values. In a case of thyroid gland internal irradiation by ^{131}I the verification of applied semi-empirical computational model was performed using available results of “direct” measurements of ^{131}I activity measurements. The comparison between individual absorbed doses in thyroid gland computed by semi-empirical model with doses accessed using available “direct” measurements of ^{131}I activity in thyroid gland of the same persons was conducted (Stepanenko et al. 2004) as shown in Fig. 9 as an example.

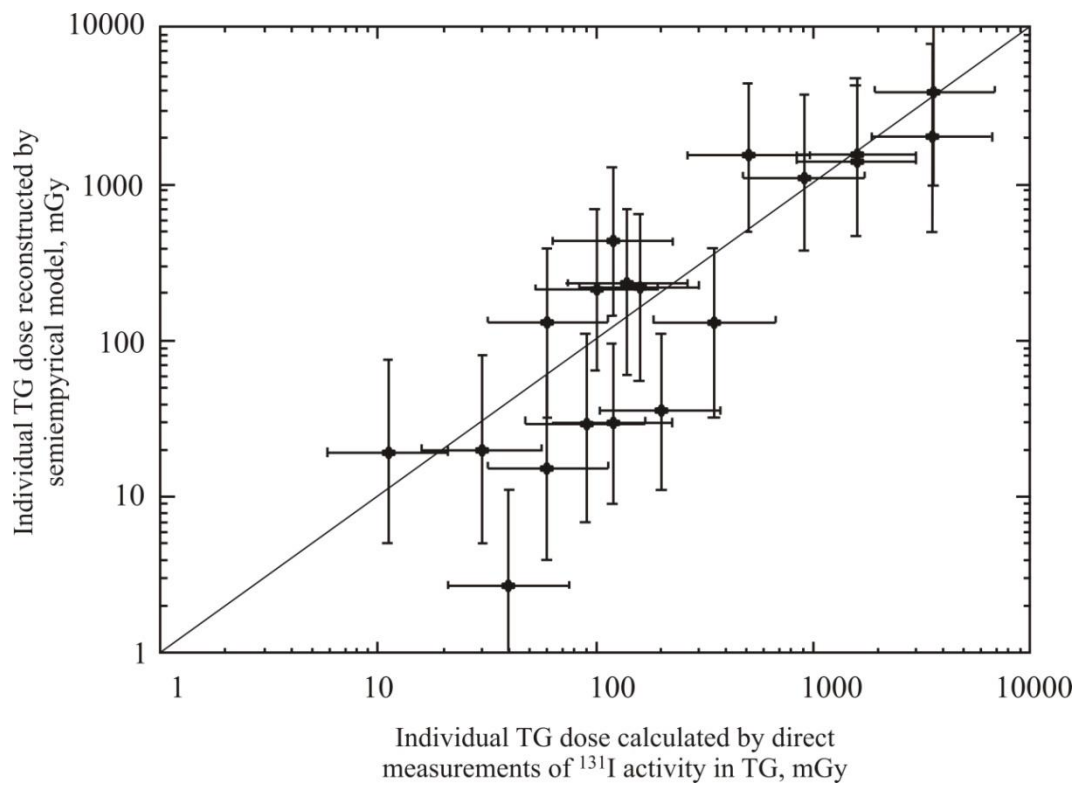


Fig. 9. Comparison between individual absorbed doses in thyroid gland computed by semi empirical computational model with doses assessed by direct measurements of ¹³¹I activity in thyroid gland of the same persons. Standard geometrical deviations of individual dose values are indicated in the figure (Stepanenko et al. 2004).

The following principal conclusion was made as a result of this study: it was found that reconstructed individual doses in thyroid gland has a very high level of on homogeneity of individual dose distributions: the majority of examined persons received quite low doses and only few of them received irradiation doses, highly exceeding the average and median values. As an example, Fig. 10 shows statistical distribution of reconstructed individual absorbed doses in the thyroid gland among persons residing on contaminated territories of the Bryansk region and included to the epidemiological study (Davis et al. 2004; Kopecky et al. 2006; Stepanenko 2015). This is the demonstration of importance of individual dose reconstruction in a case of large scale radiation accident: individual approach allows determining the persons with highest individual doses - for implementing among them the individual prophylaxis and medical measures.

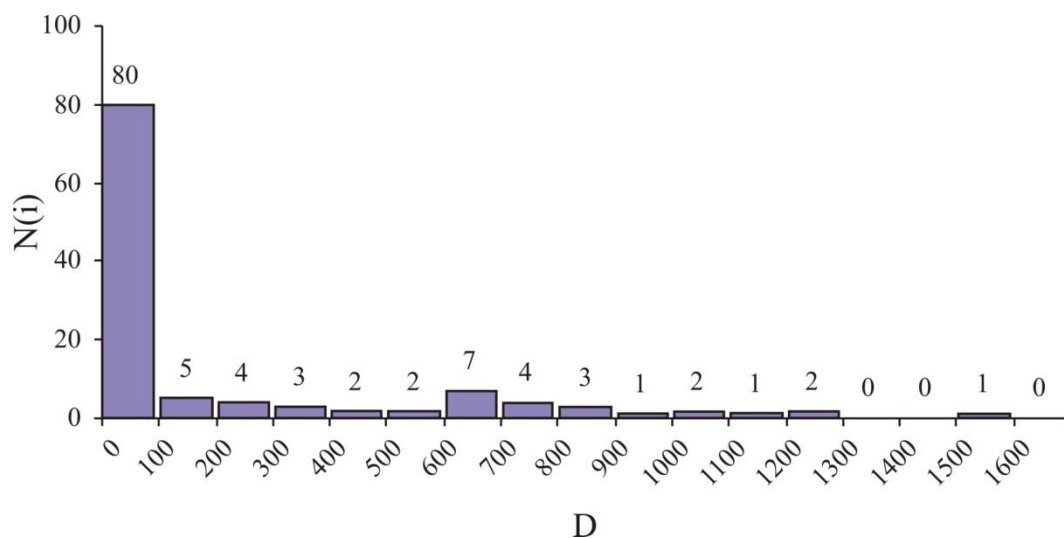


Fig. 10. The example of statistical distribution of reconstructed individual thyroid absorbed doses (D , mGy) among persons included to the epidemiological study in Bryansk region, Russia (the persons with the age up to 20 years old at the moment of the accident). $N(i)$ is the number of examined persons in various ranges of individual doses. The precise number of examined persons for various dose ranges, D , is indicated above the histogram columns (Davis et al. 2004; Kopecky et al. 2006; Stepanenko 2015).

A.2. Chernobyl accident. Whole body irradiation: example of individual accumulated dose reconstruction and verification

For retrospective assessment of individual accumulated doses in whole body (WB), the corresponding model within the international project on epidemiological study on contaminated territories of the Bryansk region was developed and used (Davis et al. 2006; Stepanenko 2015). In addition to this model the results of individual questioning/investigation was accounted for individual retrospective dose assessments.

As it was in a case with retrospective thyroid dose estimations, the following principal conclusion was made: it was found that reconstructed accumulated whole body (WB) individual doses has an uneven statistical distributions of WB individual doses: the majority of examined persons received quite low doses and only few of them received irradiation doses, highly exceeding the average and median values. As an example, statistical distribution of reconstructed accumulated WB individual doses of external irradiation among persons residing on contaminated territories of the Bryansk region and included to the epidemiological study are shown in Figs. 11 and 12 (Stepanenko 2015). This is the demonstration of importance of individual dose reconstruction in a case of large scale radiation accident: individual approach allows determining the groups of persons with highest individual doses - for implementing among them the individual countermeasures for reducing further additional irradiation.

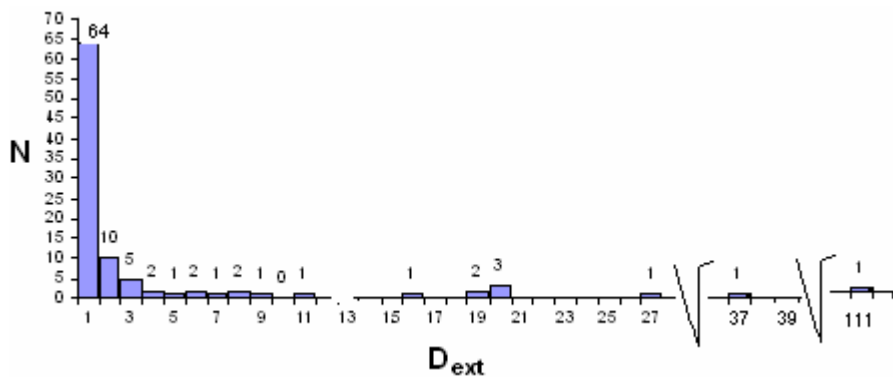


Fig. 11. Statistical distribution of individual accumulated WB external doses among investigated persons (“controls” – healthy persons). Total number of persons– 98. Numbers of persons (N) in different dose intervals (D_{ext} mGy) are indicated above the corresponding columns. Minimal dose – 0.08 mGy, maximal dose – 111 mGy. Mean dose – 4.0 mGy, median dose – 0.78 mGy.

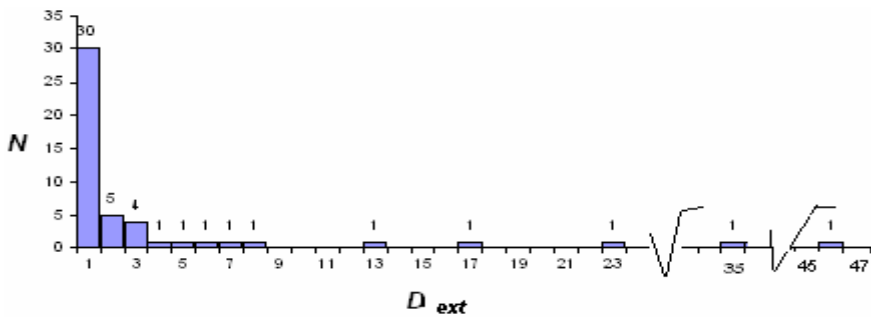
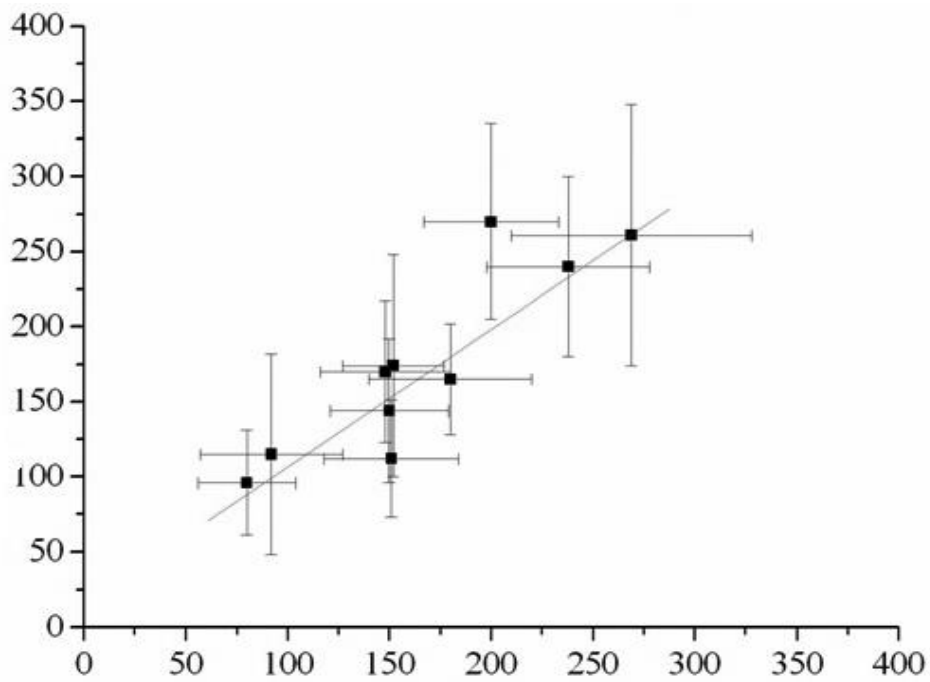


Fig. 8. Statistical distribution of individual accumulated WB external doses among investigated persons (“cases” – persons with confirmed diagnosis of thyroid cancer). Total number of persons– 49. Numbers of persons (N) in different dose intervals (D_{ext}, mGy) are indicated above the corresponding columns. Minimal dose – 0.12 mGy, maximal dose – 46 mGy. Mean dose – 3.8 mGy, median dose – 0.90 mGy.

As it was pointed out above, any computational dose estimation needs instrumental verification in order to be sure in reliability of computed dose values. In a case of whole body external irradiation, the instrumental verification was performed by two steps and using two instrumental methods: a) first step -verification of computed values of external accumulated doses for different localities using application of Retrospective Luminescence Dosimetry (RLD) method; b) second step - verification of computed values of external accumulated individual doses using Electron Spin Resonance (ESR) dosimetry method with human tooth enamel. The descriptions of developed methods of RLD and ESR dosimetry in application to Chernobyl accident are presented in (Bailiff et al. 1996, 2004-a, 2005; Ivannikov et al. 2000, 2004, 2006; IAEA 2002).

The correlation between experimental estimation of accumulated external doses (method RLD with recalculation of dose in the bricks to dose in the air) and corresponding calculated accumulated external doses in air at different localities of contaminated territory in Bryansk region, Russia is shown in Fig. 13 (Bailiff et al. 2004-a; Stepanenko 2015).

D_{cal}



D_{ex}

Fig. 12. Comparison between experimental estimations of accumulated external doses (method RLD with recalculation from dose in brick to dose in the air) and corresponding calculated accumulated external doses in the air at the same 10 sampling points (localities) of contaminated territory in Stariy Vishkov settlement, Bryansk region, Russia. D_{ex} – doses based on RLD data, mGy; D_{cal} – calculated doses, mGy. Coefficient of correlation is equal to 0.86.

A.3 ESR method.

Results of comparisons between calculated accumulated individual whole body doses and individual accumulated external doses, which were estimated using ESR dosimetry method with human tooth enamel for the same 10 persons, were presented in the papers (Stepanenko et al. 2003; Stepanenko et al. 2007-a; Stepanenko 2015). It was found that calculated doses were estimated in the range from 52 to 203 mGy, and the values of doses estimated by ESR method were in the range from 52 to 203 mGy. It was concluded that uncertainties of “ESR doses” and calculated doses are comparable. The coefficient of correlation between individual “ESR doses” and calculated doses for the same persons is equal to 0.71. The obtained results are confirming the importance the usage of instrumental dose estimations (RLD and ESR) in order to be sure in reliability of calculated dose values – as it was demonstrated by example of external dose estimations among persons living in territories contaminated following the Chernobyl accident.

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Appendix B

B. List of papers of Rakhypbekov Tolebay

B.1. Papers the topics of which are related with the thesis application. No 1, 2, 3 are the papers for this Ph.D.

1. Tolebay Rakhypbekov, Valerii Stepanenko, Kassym Zhumadilov, Importance of applications of individual retrospective dosimetry methods in cases of large scale radiation accidents, *Advances in ESR Applications*, 33, 14-19, 2017. 查読有
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