STATUS OF FACTORS OF INNATE IMMUNITY IN EXPOSED PEOPLE WHO SUBSEQUENTLY DEVELOPED CANCER

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Currently, cancer is the major cause of mortality and disability among the working age population of the developed countries. Early diagnosis of tumors, that involves monitoring the health of people exposed to radiation, is one of the most pressing challenges faced by radiation medicine. The study was aimed to perform quantification and functional assessment of the system of neutrophil granulocytes, monocytes and natural killers (NK cells) in people who were diagnosed with tumors after chronic radiation exposure. Certain factors of innate immunity were assessed in 104 people, chronically exposed to low-dose radiation over a wide dose range. Of them 34 exposed individuals were later diagnosed with malignant tumors (MTs). We assessed the number of white blood cells, neutrophil granulocytes, eosinophils, basophils, monocytes and NK cells ($CD16^+/CD56^+$ lymphocytes) in peripheral blood, as well as phagocytic, lysosomal activity and intracellular oxygen-dependent metabolism of neutrophils and monocytes. Individuals, chronically exposed a few years before the development of MTs, showed a significant increase in the phagocytosis rate of monocytes (median 10.50 AU vs. 6 AU; $p = 0.05$) and lysosomal activity of neutrophils (median 482 AU vs. 435.5 AU; $p = 0.03$) compared to patients with no MTs. Assessment of the the dose–response relationship in exposed people, who subsequently developed cancer, revealed a significant increase in the phagocytosis rate of monocytes as a function of the accumulated dose to thymus and peripheral lymphoid organs ($\rho = 0.45$; $p = 0.009$), and the increase in phagocytic activity of neutrophils with the increase in the accumulated dose to red bone marrow ($\rho = 0.44$; $p = 0.01$).

Keywords: chronic radiation exposure, carcinogenesis, neutrophils, monocytes, natural killers

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СОСТОЯНИЕ ФАКТОРОВ ВРОЖДЕННОГО ИММУНИТЕТА У ОБЛУЧЕННЫХ ЛИЦ, ВПОСЛЕДСТВИИ ЗАБОЛЕВШИХ РАКОМ

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В настоящее время онкологические заболевания являются одной из ведущих причин смертности и инвалидизации среди зрелого трудоспособного населения в развитых странах. Одной из актуальных задач радиационной медицины является ранняя диагностика опухолевых заболеваний на основе мониторинга состояния здоровья людей, подвергшихся радиационному воздействию. Целью исследования было оценить количественные и функциональные показатели системы нейтрофильных гранулоцитов, моноцитов и натуральных киллеров у лиц, подвергшихся хроническому радиационному воздействию и впоследствии заболевших опухолевыми заболеваниями. Проведено исследование отдельных факторов врожденного иммунитета у 104 человек, подвергшихся хроническому низкоинтенсивному радиационному воздействию в широком диапазоне доз. Из них у 34 облученных лиц позднее были диагностированы злокачественные новообразования (ЗНО). Проведена оценка количества лейкоцитов, нейтрофильных гранулоцитов, эозинофилов, базофилов, моноцитов и НК-клеток ($CD16^+/CD56^+$-лимфоциты) в периферической крови, а также фагоцитарная, лизосомальная активность и интенсивность внутриклеточного кислородозависимого метаболизма нейтрофилов и моноцитов. У лиц, подвергшихся хроническому радиационному воздействию за несколько лет до развития ЗНО, наблюдалось значимое повышение интенсивности фагоцитоза моноцитов (медиана — 10,50 усл. ед. против 6 усл. ед.; $p = 0,05$) и лизосомальной активности нейтрофилов (медиана — 482 усл. ед. против 435,5 усл. ед.; $p = 0,03$) по сравнению с пациентами без ЗНО. При анализе дозовых зависимостей у облученных лиц, впоследствии заболевших онкологическими заболеваниями, обнаружены увеличение интенсивности фагоцитоза моноцитов в зависимости от дозы облучения тимуса и периферических лимфоидных органов ($\rho = 0,45$; $p = 0,009$), а также повышение активности фагоцитоза нейтрофилов с увеличением накопленной дозы облучения красного костного мозга ($\rho = 0,44$; $p = 0,01$).

Ключевые слова: хроническое радиационное воздействие, канцерогенез, нейтрофилы, моноциты, натуральные киллеры

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It is believed that genetic and epigenetic alterations induced by exposure to ionizing radiation may contribute to the development of malignant tumors (MTs). There is no doubt that the functional state of the body's defense systems, such as DNA repair, cell cycle arrest, antioxidant system and anti-tumor immunity, plays a vital part in malignant transformation of cells. When the defense mechanisms are effective, radiation exposure may result in no pathological changes, however, inefficiency of a particular defense system results in the risk of cancer.

Systemic immunity plays an important role in body's defense against cancer [1]. In particular, neutrophils, monocytes and natural killers (NK cells) are able not only to recognize, lyse, and eliminate tumor cells and mutant cells from the body, but also to regulate the function of other immunocompetent cells (macrophages, T and B cells, eosinophils, basophils) due to production of chemokines, pro- and anti-inflammatory cytokines, prostaglandins, leukotrienes [2, 3]. Furthermore, activated macrophages can exhibit antitumor activity due to lysing enzymes and free radicals that damage tumor cells, and produce TNFα, the antitumor cytokine [4].

In the residents of coastal villages located along the Techa River (South Ural), who had been exposed to low-dose radiation due to the discharge of liquid radioactive waste in the Techa River by the Mayak Production Association for a long time, the changes in their immune system were detected in the form of reduced white blood cell count (mainly due to neutrophils and lymphocytes), increased neutrophil lysosomal activity, certain suppression of monocyte intracellular oxygen-dependent metabolism, and the shift in cytokine balance towards pro-inflammatory response [5, 6]. Furthermore, exposed individuals with obligate precancerous conditions showed the increased absolute and relative natural killer blood cell counts ($CD16^+/CD56^+$ cells) compared to exposed patients with no precancerous conditions [7]. Epidemiological studies of the cohort of people exposed on the Techa River revealed the increased risk of morbidity and mortality from malignant neoplasms and leukemia [8, 9].

The study was aimed to perform quantification and functional assessment of the system of neutrophil granulocytes, monocytes and natural killers in people who were diagnosed with cancer after chronic radiation exposure.

METHODS

The system of neutrophil granulocytes, monocytes and natural killers was assessed in 104 people, chronically exposed to low-dose radiation due to the discharge of radioactive waste in the Techa River by the Mayak Production Association in the 50–60-ies of the XX century. The exposure pattern is detailed in the book [10].

The inclusion criteria for the studied groups were as follows: permanent residence in one of 41 villages located along the Techa River between 1 January 1950 and 31 December 1960; availability of individual absorbed doses to red bone marrow (RBM), thymus and peripheral lymphoid organs calculated using the Techa River Dosimetry System-2016 (TRDS-2016) [11]. Exclusion criteria: no information about the residence on the territory of radioactive contamination; autoimmune, acute or chronic (period of exacerbation) inflammatory disorders, hematologic cancers, kidney or liver failure diagnosed at the time of examination, acute cerebrovascular accident in the last three months, cancer (for comparison group); taking drugs capable of affecting the studied parameters (antibiotics, glucocorticoids, cytostatics).

All the examined individuals were divided into two groups: the index group included 34 exposed people who were later diagnosed with neoplasms (immunology tests were performed once, 1–7 years before the onset of the disease in 2007–2014), the comparison group included exposed individuals with no oncology disorders (70 people). In the index group consisting of exposed people, small intestine and colorectal cancer (five cases), gastric cancer (two cases), bladder cancer (three cases), skin cancer (seven cases), cancer of the orbital connective tissue and retro-ocular space (one case), lip cancer (one case), breast cancer (two cases), cancer of female reproductive organs, including cervical cancer (three cases), cancer of male reproductive organs (three cases), bronchial and lung cancer (four cases), osteosarcoma of the skull (one case), and MTs of unspecified site (two cases) were diagnosed in 2009–2017.

The studied groups were comparable in gender, ethnicity, age at the time of examination, and radiation dose. Characteristics of the studied groups are provided in Table 1.

Venous blood of the individuals in the studied group (10 mL) was collected from the cubital vein into a syringe with heparin. The white blood cell, neutrophil granulocyte, basophil, and monocyte counts in peripheral blood were defined with the Pentra 120 DX automatic hematology analyzer (HORIBA ABX S.A.S.; France). NK cells ($CD16^+/CD56^+$ lymphocytes) were counted using the fluorochrome-labeled monoclonal antibodies to appropriate CD receptors (conjugated antibody $CD3^-$FITC/$CD16^+$CD56-PE, Beckman Coulter; USA). Cell number was assessed using the Navios flow cytometer (Beckman Coulter; USA).

Table 1. Characteristics of studied groups

Parameters of the groups		Index group	Comparison group	*p*
		n = 34	*n* = 70	
Age at the time of examination, years: M ± SE (min–max)		69.09 ± 0.78 (60–78)	68.96 ± 0.53 (58–79)	0.89
Gender, *n* (%)	Male	14 (41.2)	24 (34.2)	0.49
	Female	20 (58.8)	46 (66.8)	
Ethnicity, *n* (%)	Slavs	14 (41.2)	30 (42.9)	0.87
	Turks	20 (58.8)	40 (57.1)	
Accumulated dose to RBM, mGy: M ± SE (min–max)		852 ± 116 (5.37–3507)	826 ± 72.40 (6.03–3394)	0.92
Accumulated dose to thymus and peripheral lymphoid organs, mGy: M ± SE (min–max)		140 ± 20.7 (2.45–466)	127 ± 13.70 (0.55–460)	0.58

Note: *n* — number of surveyed people; M ± SE — mean ± standard error of the mean; *p* — significance levels for intergroup differences.

Table 2. Quantity of innate immune cells in blood of examined individuals

Parameter	Index group Me (Q_1–Q_2)	Comparison group Me (Q_1–Q_2)	Significance level
Basophils, %	0.85 (0–1)	0.60 (0–1)	0.9
Eosinophils, %	2.00 (1–4)	2.25 (1–3.75)	0.78
Band neutrophils, %	5 (2.50–6.50)	3 (2–5.50)	0.08
Segmented neutrophils, %	53 (43.25–61)	52 (43.20–57)	0.95
Leukocytes, 10^9/L	6.36 (5.26–7.38)	6.58 (5.29–7.76)	0.66
Lymphocytes, %	31 (26.65–39.25)	34 (29.10–40.75)	0.71
Lymphocytes, 10^9/L	1.83 (1.60–2.57)	2.14 (1.83–2.74)	0.22
Neutrophils, %	57.50 (52–63.50)	54 (48.25–59.95)	0.29
Neutrophils, 10^9/L	3.62 (2.81–4.76)	3.53 (2.76–4.37)	0.64
Monocytes, %	6 (3–7.25)	6.9 (4–9.15)	0.21
Monocytes, 10^9/L	0.35 (0.20–0.51)	0.38 (0.27–0.61)	0.35
Natural killers ($CD16^+/CD56^+$ lymphocytes), %	16.25 (12.08–23.90)	14.40 (9.20–19.70)	0.09
Natural killers ($CD16^+/CD56^+$ lymphocytes), 10^9/L	0.30 (0.23–0.53)	0.31 (0.17–0.46)	0.24

Note: Me (Q_1–Q_2) — median (25^{th}–75^{th} percentile range).

Phagocytic, lysosomal activity, as well as neutrophil and monocyte intracellular oxygen-dependent metabolism were determined by standard methods [12, 13]. The following parameters were assessed: phagocytic activity of neutrophils and monocytes (PAN, PAM), phagocytosis rate of neutrophils and monocytes (PRN, PRM), phagocytic numbers for neutrophils and monocytes (PNN, PNM), the levels of neutrophil and monocyte intracellular oxygen-dependent metabolism in both spontaneous and induced variants (NBT-test of neutrophils, NBT-test of monocytes), lysosomal activity and total lysosomal activity of neutrophils and monocytes (LAN, LAM, TLAN, TLAM). The details of the methods are provided in previously published articles [7]. In all cases the Axio Imager A2 light microscope (Carl Zeiss; Germany) was used for recording of reactions.

Statistical processing of primary data, that involved the use of Mann–Whitney U test to compare two data sets, was performed with the SigmaPlot software, ver. 12.5 (SYSTAT Software; USA). Pearson and Spearman correlation analysis, as well as linear regression analysis were performed. The results with the significance levels below 0.05 were considered significant.

RESULTS

Peripheral blood cell counts and parameters of neutrophil and monocyte functional activity in the studied groups were compared. The results are presented as median values (Me) and 25^{th}–75^{th} percentile ranges (Q_1–Q_2) (Tables 2, 3).

The study revealed no significant differences in the indicators of cellular immunity between exposed people, who subsequently developed cancer, and exposed people with no cancer.

Assessment of the neutrophil granulocyte and monocyte system functional characteristics revealed the significantly increased phagocytosis rate of neutrophils and lysosomal activity of monocytes in individuals who subsequently developed cancer compared to the group of people with no MTs.

Table 3. Functional characteristics of innate immune cells in the examined individuals

Parameter	Index group Me (Q_1–Q_2)	Comparison group Me (Q_1–Q_2)	Significance level
PAM, %	4.50 (2.25–10)	4 (2–5.50)	0.27
PRM, AU	10.50 (3.25–21.75)	6 (3–12)	0.05**
PNM, AU	1.88 (1.04–2.95)	1.50 (1–2)	0.11
NBT-test of monocytes, spontaneous, %	53 (39.25–60.75)	52 (42–58.50)	0.66
NBT-test of monocytes, induced, %	55.50 (42.25–63.75)	52 (42.50–58)	0.53
LAM, AU	292 (214.50–373)	306.50 (254.50–370.25)	0.45
TLAM, AU	1.06 (0.44–1.53)	1.19 (0.62–1.94)	0.11
PAN, %	5 (3–7)	4 (2–6.50)	0.42
PRN, AU	9 (5.25–18)	8 (4–11)	0.14
PNN, AU	1.78 (1.34–2.65)	1.80 (1.16–2.26)	0.48
NBT-test of neutropils, spontaneous, %	56 (40.25–62)	50 (40.50–55)	0.61
NBT-test of neutropils, induced, %	56 (40.25–62)	50 (40.50–55)	0.61
LAN, AU	482 (408.50–613.50)	435.50 (362–491)	0.03**
TLAN, AU	15.96 (11.27–25.28)	15.88 (11.19–19.51)	0.45

Note: Me (Q_1–Q_2) — median (25^{th}–75^{th} percentile range); ** — significant differences between the studied groups.

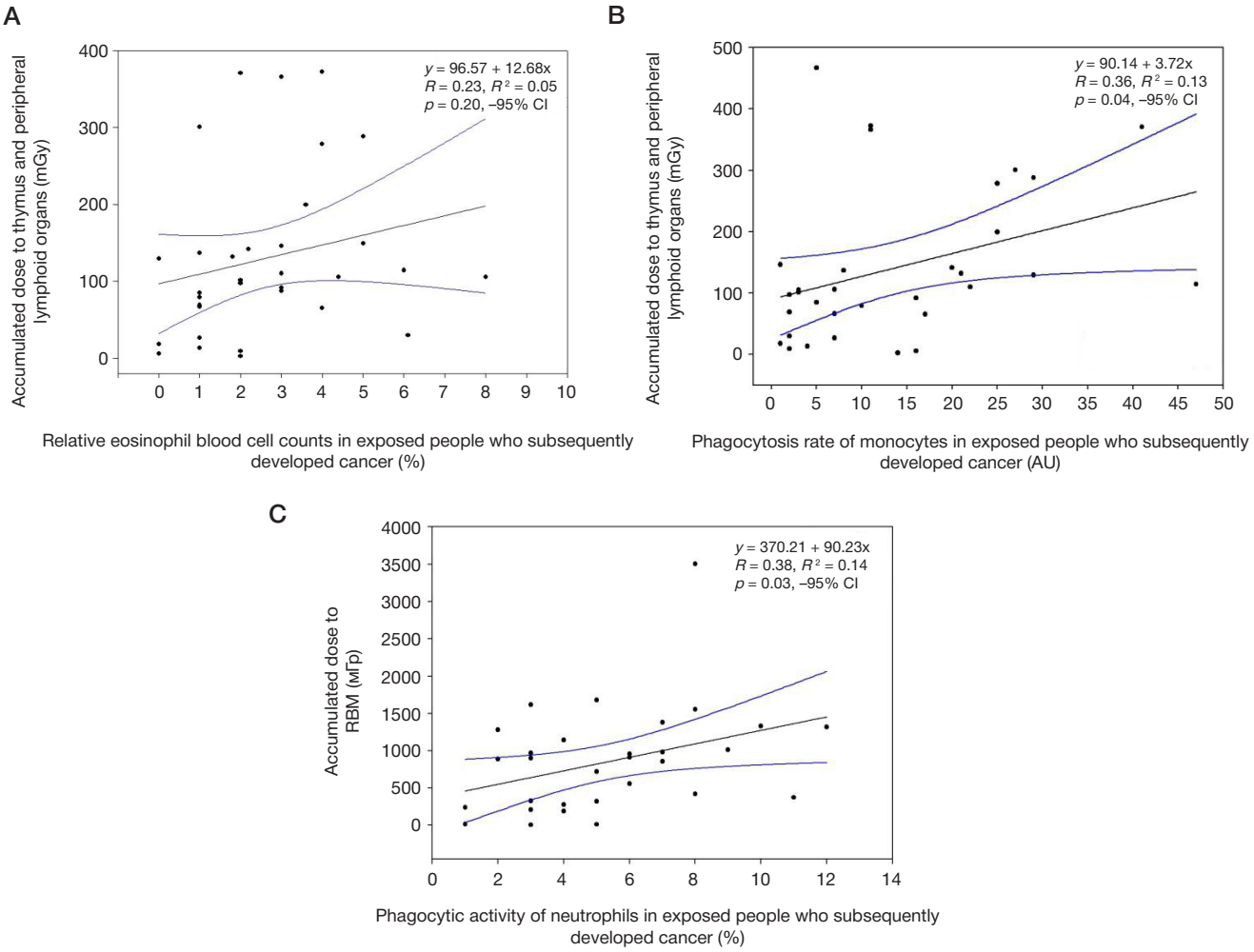

Fig. 1. Linear regression analysis of the dose–response relationships in the group of exposed people who subsequently developed cancer for the following indicators: **A** — relative eosinophil counts, **B** — phagocytosis rate of monocytes, **C** — phagocytic activity of neutrophils

When assessing the dose–response relationship in exposed people who subsequently developed cancer, a significant increase in the percentage of eosinophils in blood as a function of the dose to thymus and peripheral lymphoid organs was revealed (Spearman correlation analysis: ρ = 0.38, p = 0.03). However, linear regression analysis showed no reliable results (Fig. 1A). The dose-dependent increase in the phagocytosis rate of monocytes with the increase in the accumulated dose to thymus and peripheral lymphoid organs was also noted (Spearman correlation analysis: ρ = 0.45, p = 0.009; Pearson correlation analysis: r = 0.36, p = 0.04), along with the increase in phagocytic activity of neutrophils with the increase in the accumulated dose to RBM (Spearman correlation analysis: ρ = 0.44, p = 0.01; Pearson correlation analysis: r = 0.38, p = 0.03). The results of linear regression analysis for these indicators are provided in Fig. 1B, C.

Different relationships were found in the comparison group: there was a significant decrease in relative basophil counts with the increase in the accumulated dose to RBM (Spearman correlation analysis: ρ = –0.26, p = 0.03; Pearson correlation

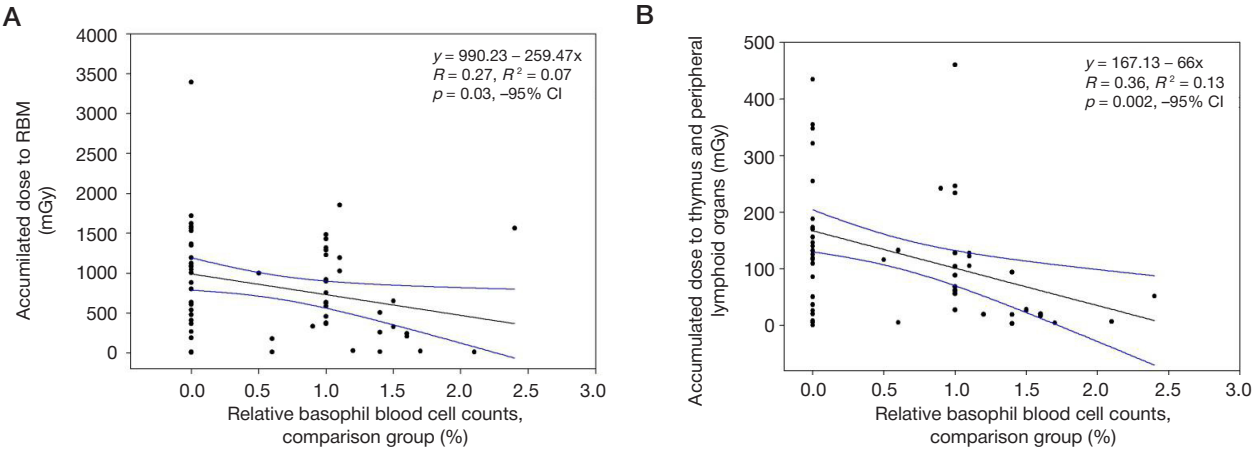

Fig. 2. Linear regression analysis of the dose-dependent decrease in basophil counts for: **A** — accumulated dose to RBM, **B** — accumulated dose to thymus and peripheral lymphoid organs

analysis: $r = –0.27$, $p = 0.03$) and the accumulated dose to thymus and peripheral lymphoid organs (Spearman correlation analysis: $\rho = –0.42$, $p = 0.0005$; Pearson correlation analysis: $r = –0.32$, $p = 0.009$). The results of linear regression analysis for these indicators are provided in Fig. 2.

There was also a significant increase in the phagocytic activity of monocytes with the increase in the accumulated dose to thymus and peripheral lymphoid organs (Spearman correlation analysis: $\rho = 0.27$, $p = 0.03$). However, linear regression analysis showed no reliable results (Fig. 3).

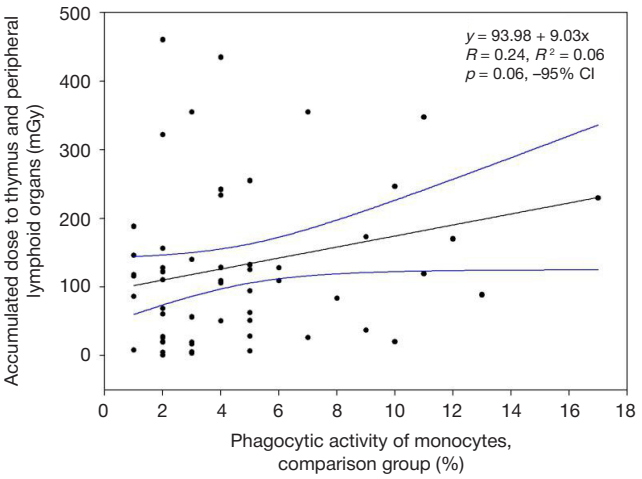

Fig. 3. Linear regression analysis of the dose-dependent increase in the monocyte phagocytic index, comparison group

DISCUSSION

The study has shown that more than 60 years after the beginning of chronic radiation exposure, years before the diagnosis of cancer, the significantly increased phagocytosis rate of neutrophils and lysosomal activity of monocytes are observed in exposed individuals compared to patients who have not developed MTs. Furthermore, the dose-dependent increase in the phagocytosis rate of monocytes as a function of the accumulated dose to thymus and peripheral lymphoid organs was revealed, along with the increase in phagocytic activity of neutrophils as a function of the accumulated dose to RBM.

Several studies provide evidence of the important role of neutrophils in antitumor immune response. Thus, experiments with SR/CR mice have shown that neutrophil granulocytes are the first immune cells to migrate into tumor tissue, and that these cells are involved in realization of the phenomenon of spontaneous regression of tumors of different histological types [14]. The mechanism underlying the neutrophil cytolytic effect on tumor cells is associated with the production of the reactive oxygen and nitrogen species by these cells, although necrosis plays a key part in the tumor cell death [14].

On the other hand, neutrophils and monocytes may promote invasive tumor growth, vascularization and metastasis [15, 16], while the selectin-mediated adhesion of atypical cells to the membrane of neutrophil granulocytes may result in their hematogenous dissemination [17]. Furthermore, the abundance of infiltrating innate immune cells, such as macrophages, mast cells and neutrophils, in the tumor stroma is related to both increased tumor angiogenesis and adverse outcome [18].

It is important to note that the previously conducted retrospective dynamic studies of the peripheral blood cellular composition in individuals exposed on the Techa River, who later developed chronic myeloid leukemia or acute leukemia, showed that neutrophil counts and composition were predictors that made it possible to predict the increased risk of radiation-induced leukaemia in the early period after the start of exposure [19]. Perhaps, the changes in neutrophil and monocyte functional activity observed in chronically exposed people a few years before the onset of the clinically diagnosed cancer could be considered the response to the increased number of transformed cells. However, it is worth noting that phagocytosis rate of monocytes and lysosomal activity of neutrophils may be also affected by non-radiation factors, such as harmful habits and lifestyle.

That is why it is currently impossible to draw definitive conclusions about the possibility of treating the indicators identified as candidate biomarkers of MTs in the long term after the start of exposure. To draw a conclusion about allocation of these indicators to predictors of MTs, further research focused on assessing sensitivity and specificity is required.

CONCLUSIONS

The study of people exposed over a wide dose range in the long term after chronic radiation exposure, years before the development of MTs (MTs diagnosed between 2009 and 2017), revealed a significant increase in the phagocytosis rate of monocytes and lysosomal activity of neutrophils compared to people with no MTs and comparable exposure doses. In the long-term period, the dose-dependent changes in the phagocytosis rate of monocytes and phagocytic activity of neutrophils were observed in chronically exposed individuals.

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