

POLYMORPHISM OF INTERLEUKIN CONTROL GENES AND RISK OF NEOPLASMS IN EXPOSED INDIVIDUALS

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Factors of the immune system, including secreted pro-inflammatory interleukins, enable tumor control. However, against the background of prolonged chronic inflammation, they can trigger oncogenesis. Polymorphic variants in the coding and regulatory regions of cytokine genes can affect gene expression, mRNA stability, structure and activity of the protein product, with consequences on the levels of cells and body as a whole. This study aimed to search for the relation between polymorphic variants of interleukin genes *IL1b* (rs1143634), *IL2* (rs2069762), *IL4* (rs2070874), *IL6* (rs1800795), *IL8* (rs4073), *IL10* (rs1800871) and risk of cancer, and to analyze the effect of polymorphic loci on concentration of serum interleukins. The study involved 585 persons chronically exposed to radiation. We established association of polymorphic *IL4* site (rs2070874) with concentration of serum *IL4* in individuals with chronic low dose-rate exposure of the red bone marrow 1.17 to 3507 mGy (mean value — 566 mGy). The content of serum *IL4* in people with C/T and T/T genotypes (as per the dominant model) was significantly lower than in those with C/C genotype ($p = 0.02$). Polymorphic sites rs1143634, rs2069762, rs2070874, rs1800795, rs4073, rs1800871 were not found to be associated with the risk of malignant neoplasms in exposed individuals.

Keywords: SNP, immune system, malignant neoplasms, chronic radiation exposure, long-term effects.

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Compliance with the ethical standards: the study was approved by the Ethics Committee of the Urals Research Center for Radiation Medicine of the FMBA of Russia (Minutes #4 of June 8, 2023). All procedures on humans performed in the context of the study conform to the requirements of the 1964 Helsinki Declaration and its subsequent amendments or comparable ethical standards. Each participant of the study signed the voluntary informed consent form.

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ПОЛИМОРФИЗМ ГЕНОВ КОНТРОЛЯ ИНТЕРЛЕЙКИНОВ И РИСК РАЗВИТИЯ ОПУХОЛЕВЫХ ЗАБОЛЕВАНИЙ У ОБЛУЧЕННЫХ ЛИЦ

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Факторы иммунной системы, в том числе секретируемые провоспалительные интерлейкины, обеспечивают противоопухолевый надзор, однако в случае длительного хронического воспаления могут приводить к активации онкогенеза. Полиморфные варианты, располагающиеся в кодирующих и регуляторных областях генов цитокинов, могут влиять на экспрессию гена, стабильность мРНК, структуру и активность белкового продукта, что в свою очередь отражается на клеточном и организменном уровнях. Целью работы было провести поиск связи полиморфных вариантов генов интерлейкинов *IL1b* (rs1143634), *IL2* (rs2069762), *IL4* (rs2070874), *IL6* (rs1800795), *IL8* (rs4073), *IL10* (rs1800871) с риском развития онкологических заболеваний, а также проанализировать влияние полиморфных локусов на концентрацию сывороточных интерлейкинов. В исследовании приняли участие 585 человек, подвергшихся хроническому радиационному воздействию. Была выявлена связь полиморфного участка *IL4* (rs2070874) с концентрацией сывороточного *IL4* у лиц, подвергшихся хроническому низкоинтенсивному радиационному воздействию в диапазоне доз на красный костный мозг (ККМ) от 1,17 до 3507 мГр. Содержание сывороточного *IL4* у носителей генотипов C/T и T/T в соответствии с доминантной моделью было статистически значимо ниже, чем у носителей генотипа C/C ($p = 0,02$). Не выявлено связи полиморфных участков rs1143634, rs2069762, rs2070874, rs1800795, rs4073, rs1800871 с риском развития злокачественных новообразований у облученных лиц.

Ключевые слова: SNP, иммунная система, злокачественные новообразования, хроническое радиационное воздействие, отдаленные последствия

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Interleukins play an important regulatory role in antitumor immunity. They enable mediator interaction of the immune system cells and regulate various processes, such as activation of immunocompetent cells, apoptosis, cell cycle and differentiation of immunocompetent cells. For example, *IL1* boosts proliferation of CD4⁺ cells and binding of natural killer cells (NK cells) to tumor cells; it also induces production of *IL2*, which, in turn, supports proliferation of dendritic cells, and infiltration of the tumor by dendritic cells correlates with the effectiveness of antitumor immunity [1]. In addition, the antitumor response regulated by Th1 through secretion of proinflammatory cytokines *IL2*, TNF α , and IFN γ , promotes not only priming and activation of cytotoxic T cells but also antitumor activity of macrophages and NK cells [2]. *IL4* is instrumental to the development of pro-inflammatory reactions. It enables proliferation of NK cells and activated T cells, enhances their antitumor effect, regulates activated anti-inflammatory macrophages that help eliminate cancer cells [3]. It is also believed to be directly capable of suppressing tumor growth by arresting the cell cycle [1]. At the same time, macrophages themselves can secrete *IL10*, which improves immune suppression by disrupting the activity of effector T cells and inhibiting maturation of dendritic cells [2]. *IL6* possesses a strong pro-inflammatory capability and it can suppress tumor growth, but in some cases it is produced by tumor cells, and then it promotes growth of myelomas and some types of tumor cells [4]. There is little data on the antitumor activity of *IL8*, however, it is known to attract and functionally modulate neutrophils and macrophages into tumor foci, and high levels of *IL8*, on the contrary, contribute to cancer progression and metastasis through various mechanisms, including proangiogenesis and maintenance of conditions for development of cancer stem cells [5].

Pro-inflammatory factors, including secreted pro-inflammatory cytokines, help suppress tumor, but with a prolonged chronic inflammation in the background, they can trigger oncogenesis [6].

Inflammation is known to play an important role in the development of cancer at different stages of carcinogenesis: it promotes genomic instability, epigenetic modifications, induction of proliferation of cancer cells, enhancement of anti-apoptotic signals, stimulation of angiogenesis [7]. At least 25% of cancer cases are associated with chronic inflammation [2, 8].

The possible causes of chronic inflammation are microbial infection, autoimmune disorders, obesity, immune dysfunction, as well as environmental factors. Several studies have shown that in the long run, radiation exposure promotes development of chronic inflammation [9]. In particular, the survivors of Hiroshima and Nagasaki bombings had the Th1/Th2 balance broken in the long term, which lead to chronic inflammation [10]. Moreover, among the exposed in Japan, greater dose meant higher level of such pro-inflammatory markers as C-reactive protein, *IL6*, INF γ , TNF α and *IL10* [11, 12]. Chernobyl accident liquidators had their cytokine profiles changing in the long run, with levels of INF γ and TNF α growing up [13]. Prolonged exposure to low and medium doses of radiation can also cause chronic inflammation. In particular, after 60–75 years, residents of the villages on the Techa River, which is contaminated with radioactive waste, exhibit changes in quantitative and functional indicators of systemic immunity [14] and pro-inflammatory changes in the cytokine profile [15].

Polymorphic variants in coding, regulatory and non-coding sites of genes, as well as in intergenic regions, can affect gene expression, mRNA stability, structure and activity of the protein product and, subsequently, alter the functional state at the levels of cells and body as a whole [16]. Some studies

have established the connection between polymorphic sites in interleukin genes and risk of oncogenesis. Polymorphism of rs2069762 (-330T>G) in the *IL2* gene's promoter site is associated with a predisposition to several types of cancer, such as bladder cancer [17], nasopharyngeal carcinoma [18], and non-Hodgkin's lymphoma [19]. A meta-analysis of studies has found that polymorphism of rs2070874 (-33T>C) in the *IL4* gene raises the risk of leukemia and oral cancer [20]. Polymorphism of rs1800795 in the *IL6* gene has been shown to play an important role in the pathogenesis of several types of cancer, including cervical cancer, colorectal cancer and breast cancer [21]. Polymorphism of rs4073 (-251A>T) in the *IL8* anti-inflammatory cytokine gene was found to increase the risk of gastric cancer [22]. All these data point to the modifying effect of polymorphic loci in interleukin genes manifesting during oncotransformation of the cell. However, despite the existing connection with the pathological condition, it is quite difficult to establish the functional significance of the identified polymorphism for the development of the disease, especially in the case of such a multifactorial pathology as cancer. One of the possible patterns of influence is alteration of the gene's expression activity, which affects concentration of the final product. In this connection, this study is a search for a relation between polymorphic variants of interleukin genes *IL1b* (rs1143634), *IL2* (rs2069762), *IL4* (rs2070874), *IL6* (rs1800795), *IL8* (rs4073), *IL10* (rs1800871) and the risk of cancer development, as well as an analysis of the effect polymorphic loci have on concentration of serum interleukins in people chronically exposed to radiation.

METHODS

Characteristics of the examined individuals

The study involved people chronically affected by low dose-rate exposure over the period from 1949 through 1960, the source being radioactive wastes discharged from Mayak Production Association to the Techa River (Southern Urals, Russia) [23]. We searched for an association between polymorphic alleles and genotypes *IL1b* (rs1143634), *IL2* (rs2069762), *IL4* (rs2070874), *IL6* (rs1800795), *IL8* (rs4073), *IL10* (rs1800871) and the risk of development of solid malignant neoplasms (SMN), as well as effect said alleles and genotypes have on the concentration of serum interleukins. The exposed individuals included in the study have had their state monitored at the clinical department of the Urals Research Center for Radiation Medicine (URCRM) for many years. The criteria for inclusion in the study were residence from January 1, 1950 to December 31, 1960 in one of the Techa riverside villages, and calculated individual doses to the red bone marrow (RBM), thymus and peripheral lymphoid organs. Applicants whose residence in radiation-contaminated areas could not be confirmed were excluded from the study. Additional exclusion criteria were applied to individuals without SMN that donated samples for the serum interleukins analysis: they were not supposed to have autoimmune, acute or chronic inflammatory diseases diagnosed at the time of examination, as well as hemoblastosis, renal or hepatic insufficiency, acute cerebral circulatory disorders during the last three months, oncological diseases, and take antibiotics, glucocorticoids, cytostatics. At the Biophysics laboratory of the URCRM, all study participants had their individual absorbed radiation doses calculated for RBM and soft tissues, the calculations enabled by the Techa River Dosimetry System (TRDS 2016) [24].

All in all, the study involved 585 individuals who were chronically exposed to radiation. They were divided into two

Table 1. Characteristics of participants of the study

Indicator		Exposed with MN (n = 207)	Exposed without MN (n = 378)
Gender, n (%)	male	81 (39,13)	127 (33,60)
	female	126 (60,87)	251 (66,40)
Ethnic group, n (%)	Slavs	98 (47,34)	153 (40,48)
	Turks	109 (52,66)	225 (59,52)
Age at the time of examination, years ¹ M ± SD (min–max)		75,71 ± 7,32 (55–95)	77,79 ± 7,33 (57–98)
Absorbed dose to RBM, mGy M ± SE (min–max) ²		566,27 ± 42,84 (1,17–3507,08)	700,39 ± 32,37 (0,70–3393,51)
Absorbed dose to soft tissues, mGy M ± SE (min–max) ²		97,35 ± 8,67 (0,13–740,78)	99,90 ± 5,68 (0,05–622,40)

Note: ¹ — mean value ± standard deviation (min–max); ² — mean value ± standard error (min–max).

groups: 207 people with a history of malignant neoplasms (MN) of various localizations made up the "Exposed with MN" group, and 378 practically healthy people formed the "Exposed without MN" (control) group. Table 1 presents the detailed characteristics of the examined individuals.

The solid MN diagnosed had the following localizations: digestive system — 70 persons (ICD-10 code C00.2, C02.1, C04.9, C06.9, C15.9, C16.9, C18.4, C19, C22.9, C25.9, Q15.9); female reproductive system — 66 people (ICD-10 C50, C53.9, C54.9, C57.4); respiratory system — 25 people (ICD-10 Z85.22, C32.9, C33, C34); urinary system — 16 man (ICD code-10 C67.9, C68.9); endocrine system — 10 people (ICD code-10 C73); male reproductive system — 9 people (ICD code-10 C61); integumentary system — 9 people (ICD code-10 C43.9, C44.90), vision system — 2 people (C69.90).

DNA isolation and genotyping

Genomic DNA (gDNA) was isolated from whole blood using the commercially available ExtractDNA Blood & Cells column system (Eurogen; Russia) following the standard protocol based on the manufacturer's recommendations. To assess the purity of the gDNA preparations, we used the NanoDrop 2000 spectrophotometer (Thermo Scientific; USA); the control value was the ratio of 260 and 280 nm (A260/280) wavelengths.

For amplification, we used the StepOnePlus™ Real-Time PCR System (Applied Biosystems; USA) and a set for genotyping polymorphic markers for *IL1b* (rs1143634), *IL2* (rs2069762), *IL4* (rs2070874), *IL6* (rs1800795), *IL8* (rs4073), *IL10* (rs1800871) (TestGen; Russia). The 10 µl of reaction mixture contained 4 µl of the PCR mixture, 3 µl of deionized water, 2 µl of Taq polymerase and 1 µl of the studied gDNA sample. StepOne Software v2.1 (Applied Biosystems; USA) was used to analyze the genotyping data.

Assessment of the serum interleukin concentration

We employed EIA and used the Lazurite automatic analyzer (DYNEX Technologies; USA) and corresponding test systems (Vector-Best; Russia) to assess the concentration of serum interleukins (IL1β, IL2, IL4, IL6, IL8, IL10). Participants donated blood samples fasting, through a puncture in the median cubital vein; samples were collected into a vacuum tube with a coagulation activator (SiO₂), in the amount of 9 ml. The serum was separated after 45–60 minutes of blood incubation at 20–25 °C and subsequent 10-minute centrifugation at 1500 rpm. Then the serum was frozen once at –20 °C and kept frozen until analyzed. The concentration of cytokines in serum was expressed in pg/ml.

Statistical data processing

For statistical processing, we used the STATISTICA v.12.0 software package (IBM, USA), as well as online calculators Medstatistics (<https://medstatistic.ru/>) and GeneCalc (<https://gene-calc.pl/hardy-weinberg-page>). The significance of differences in the frequency of distribution of alleles and genotypes in the study groups was established with the help of the chi-squared test with Yates's correction for multiple comparisons. Intergroup differences in serum interleukin concentrations were assessed using the nonparametric Mann–Whitney U test. We searched for links between the studied polymorphisms and the risk of MN development in two genetic models: dominant (combined comparison of heterozygous and variant homozygous genotypes with a reference homozygous genotype) and recessive (combined comparison of heterozygous and reference homozygous genotypes with a variant homozygous genotype). To assess the relation between polymorphic gene sites and the risk of MN development, we calculated the odds ratio (OR) and the 95% confidence interval (95% CI) as per the formula suggested in the literature [25]. Associations with $p < 0.05$ were considered statistically significant.

RESULTS

Table 2 presents genotype distribution for polymorphic loci rs1143634, rs2069762, rs2070874, rs1800795, rs4073, rs1800871. Hardy–Weinberg law held true for all the polymorphic loci studied.

Seeking to determine the possible effect of polymorphic sites of *IL1b* (rs1143634), *IL2* (rs2069762), *IL4* (rs2070874), *IL6* (rs1800795), *IL8* (rs4073), *IL10* (rs1800871) on the concentration of interleukins in the "Exposed without MN" group, we investigated concentration of the corresponding serum interleukins in people with different genotypes (Table 3). We found that, by polymorphic site rs2070874 in the *IL4* gene, those carrying minor allele rs2070874*T (genotypes C/T and T/T) had significantly less *IL4* in blood serum compared to the carriers dominant genotype C/C ($p = 0.02$). At 90% significance (registrable trend), carriers of minor allele rs1143634*T (genotypes C/T and T/T) of the *IL1* gene had smaller concentration of serum *IL1* compared with carriers of the C/C genotype ($p = 0.054$). For the remaining polymorphic loci, we discovered no significant changes in the concentration of serum interleukins in carriers of different genotypes.

In the context of this study, we found the remaining polymorphic sites of interleukin genes do not influence serum interleukin concentrations, but our previous research revealed the effect rs2069762 in the *IL2* gene has on the number

Table 2. Occurrence of genotypes of the studied SNPs in exposed individuals with and without MN

Gene/SNP	Genotype	Groups								Compared models (dominant/recessive)	OR (95% CI)	p ⁴		
		Exposed with MN				Exposed without MN								
		Frequency of genotypes, %												
		Quantity (%)	Ho ¹	He ²	pHWE3	Quantity (%)	Ho	He	pHWE					
<i>IL1b</i> rs1143634	C/C	95 (59.75)	0.35	0.35	0.96	203 (61.52)	0.34	0.34	0.94	C/C vs C/T+T/T	1.08 (0.73–1.59)	0.71		
	C/T	55 (34.59)				113 (34.24)				C/T+C/C vs T/T			1.35 (0.57–3.20)	0.49
	T/T	9 (5.66)				14 (4.24)								
<i>IL2</i> rs2069762	A/A	37 (44.05)	0.46	0.44	0.88	131 (39.94)	0.47	0.46	0.98	A/A vs A/C+C/C	0.84 (0.52–1.37)	0.5		
	A/C	39 (46.43)				154 (46.95)				A/C+A/A vs C/C			0.70 (0.31–1.55)	0.36
	C/C	8 (9.52)				43 (13.11)								
<i>IL4</i> rs2070874	C/C	74 (47.44)	0.46	0.42	0.55	164 (50.00)	0.41	0.42	0.87	C/C vs C/T+T/T	1.11 (0.76–1.62)	0.6		
	C/T	71 (45.51)				133 (40.55)				C/T+C/C vs T/T			0.73 (0.36–1.49)	0.37
	T/T	11 (7.05)				31 (9.45)								
<i>IL6</i> rs1800795	G/G	34 (34.69)	0.48	0.48	0.99	106 (35.22)	0.48	0.48	0.99	G/G vs G/C+C/C	1.02 (0.63–1.65)	0.92		
	G/C	47 (47.96)				145 (48.17)				G/C+G/G vs C/C			1.05 (0.58–1.93)	0.87
	C/C	17 (17.35)				50 (16.61)								
<i>IL8</i> rs4073	T/T	36 (29.03)	0.51	0.49	0.96	101 (32.27)	0.47	0.49	0.67	T/T vs T/A+A/A	1.16 (0.74–1.83)	0.51		
	T/A	63 (50.81)				147 (46.96)				T/A+T/T vs A/A			0.96 (0.57–1.62)	0.89
	A/A	25 (20.16)				65 (20.77)								
<i>IL10</i> rs1800871	C/C	70 (47.95)	0.45	0.42	0.74	108 (52.43)	0.39	0.4	0.85	C/C vs C/T+T/T	1.20 (0.78–1.83)	0.41		
	C/T	65 (44.52)				80 (38.83)				C/T+C/C vs T/T			0.85 (0.39–1.86)	0.68
	T/T	11 (7.53)				18 (8.74)								

Note: ¹ — observed heterozygosity; ² — expected heterozygosity; ³ — significance of deviation from the Hardy-Weinberg law (at $p > 0.05$); ⁴ — significance of the odds ratio indicator (OR).

of T lymphocytes and T NK cells (CD3⁺CD16⁺56⁺ phenotype) in exposed individuals, as well as the effect of rs1800795 in the *IL6* gene on the number of T helpers [26]. Therefore, we looked into the relationship of the studied polymorphic loci and the risk of cancer in the exposed individuals. For this substudy we considered two genetic models, recessive and dominant. However, as shown in Table 2, we found no association with oncological diseases for any of the studied polymorphic loci.

DISCUSSION

A possible link between a particular polymorphic site and cancer risk may be the effect this polymorphism has on the structure of the protein, if located in the coding region of the gene, or its concentration, if located in the intron and promoter regions of the gene. For example, rs2069762 polymorphism is located in the site of binding of transcription factor and promoter region of the *IL2* gene, and it affects expression of *IL2* [27].

In our studies involving individuals affected by chronic low dose-rate exposure (dose to RBM from 1.17 to 3507 mGr, mean value — 566 mGr), we identified a significant drop of serum content of *IL4* in carriers of the C/T and T/T genotypes compared with carriers of the dominant C/C genotype by polymorphic site of rs2070874.

Polymorphic site of rs2070874 is located in the 5'-untranslated region (5'UTR) of the *IL4* gene. This region is involved in control of efficiency of protein translation, since it manages binding of the transcription factor, RNA polymerase, and formation of the initiating ribosomal complex [28, 29]. It is possible that substitution in this region can affect the efficiency of the translation process and the final concentration of *IL4*.

In addition, carriers of minor allele rs1143634*T (genotypes C/T and T/T) of the *IL1* gene had smaller serum *IL1* concentration than carriers of the C/C genotype (90% significance). The rs1143634 polymorphic site is a synonymous variant, it can cause disturbance of mRNA splicing, which probably manifests as a change in the concentration of the protein product [30]. No published papers available describe any effect of the identified polymorphic sites on the concentration of serum products.

Several studies have found a link between polymorphic loci of *IL2* (rs2069762), *IL4* (rs2070874), *IL6* (rs1800795), *IL8* (rs4073) and the risk of development of MN of various localizations. Thus, rs2069762 is associated with a predisposition to bladder cancer [17], nasopharyngeal carcinoma [18] and non-Hodgkin's lymphoma [19]; rs2070874 — with risk of leukemia and oral cancer [20]; rs1800795 — with cervical cancer, colorectal cancer and breast cancer [21]; rs4073 — with increased risk of stomach cancer [22]. Moreover, polymorphism and oncogenic

Table 3. Indicators of systemic immunity in carriers of various genotypes of the studied SNPs, "Exposed without MN" group

Indicator	Model	Genotype1	Mean value of the indicator (SE)	p^2
IL1b rs1143634 (n = 246)				
IL1 content, pg/ml	Dominant	C/C (160) C/T+T/T (86)	41,05 (8,88) 30,21 (8,61)	0,054
	Recessive	C/C+C/T (239) T/T (7)	38,00 (6,69) 12,06 (5,64)	0,39
IL2 rs2069762 (n = 234)				
IL2 content, pg/ml	Dominant	A/A (98) A/C+C/C (136)	10,52 (1,07) 10,11 (1,09)	0,56
	Recessive	A/A+A/C (205) C/C (29)	10,38 (0,85) 9,58 (1,74)	0,92
IL4 rs2070874 (n = 240)				
IL4 content, pg/ml	Dominant	C/C (130) C/T+T/T (110)	5,16 (0,50) 4,13 (0,56)	0,02*
	Recessive	C/T+C/C (217) T/T (23)	4,56 (0,37) 4,99 (1,74)	0,64
IL6 rs1800795 (n = 114)				
IL6 content, pg/ml	Dominant	G/G (42) G/C+C/C (72)	24,00 (11,37) 16,24 (5,79)	0,84
	Recessive	G/C+G/G (93) C/C (21)	22,12 (6,73) 5,76 (2,89)	0,13
IL8 rs4073 (n = 231)				
IL8 content, pg/ml	Dominant	T/T (79) T/A+A/A (152)	6,36 (1,45) 7,94 (1,55)	0,58
	Recessive	T/A+T/T (189) A/A (42)	7,82 (1,34) 5,53 (1,56)	0,67
IL10 rs1800871 (n = 166)				
IL10 content, pg/ml	Dominant	C/C (88) C/T+T/T (78)	17,52 (2,02) 16,83 (2,61)	0,5
	Recessive	C/T+C/C (151) T/T (15)	16,50 (1,65) 24,23 (6,81)	0,4

Note: 1 — number in parentheses after name of the genotype is the number of its carriers among the participants; 2 — significance by Mann–Whitney U test; * — significance at $p > 0.05$, Mann–Whitney U test, IL content (pg/ml), between carriers of different genotypes.

factors were found to produce a joint effect. For example, rs1800795*G allele in the *IL6* gene was an additional squamous cell lung cancer risk factor in men who had been smoking for less than 35 years [16]. However, in our studies, we have not established the relationship between loci of *IL1b* (rs1143634), *IL2* (rs2069762), *IL4* (rs2070874), *IL6* (rs1800795), *IL8* (rs4073), *IL10* (rs1800871) and the MN development risk in persons chronically exposed to radiation. Likely, the reason therefor is heterogeneity of the MN considered in the study. It is important to remember that carcinogenesis is a multi-stage process involving various signaling pathways and protective systems of the body regulated by a large number of genes and gene networks, and therefore it is necessary to continue searching for genetic markers of MN development.

CONCLUSIONS

Our study revealed the link between polymorphic site of *IL4* (rs2070874) and concentration of serum *IL4*. Carriers of the C/T and T/T genotypes, dominant model, had significantly smaller *IL4* content than carriers of the C/C genotype. At the same time, we established no relation between polymorphic loci of *IL1b* (rs1143634), *IL2* (rs2069762), *IL4* (rs2070874), *IL6* (rs1800795), *IL8* (rs4073), *IL10* (rs1800871) and MN development risk in chronically exposed people with the dose to RBM ranging from 0.70 to 3,393 mGy (mean value — 700 mGy). However, as we have shown, presence of polymorphic sites in interleukin genes can affect individual indicators of the immune system and thereby modify the response to radiation exposure.

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