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THYROID PATHOLOGY AS LATE RADIATION EFFECT CAUSED BY EXPOSURE TO RADIATION DURING EMERGENCIES

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Several emergencies at "Mayak" Production Association (PA Mayak) led to radioactive contamination of some territories in the Urals; the territories were contaminated with radionuclides mixture and it caused consequent external and internal irradiation of population living there. Our research goal was to examine thyroid state 50–60 years after exposure to radiation in childhood. Our research objects to study thyroid gland structure and functioning were people who lived on territories contaminated with radionuclides in their childhood (The Techa river banks and the Eastern Urals radioactive track territory) and who then moved to Ozersk. The group was made of 256 people who accounted for 70 % of all such migrants who were available to us. Thyroid gland diseases were examined allowing for all the available data of subjective and objective clinical and laboratory screening examination, namely complaints, thyroid gland and neck area examination, ultrasound examination of thyroid gland structure, laboratory tests of thyroid gland functions.

Our research results revealed that all thyroid gland diseases prevailed in people who lived on radioactively contaminated territories in their early childhood 50–60 years after they moved to other places. Thus, such morbidity amounted to 64 % among women and to 32 % among men which was 1.6 times higher against people who were not exposed to any technogenic radiation during their lives. We detected statistically significant 2–2.6 times higher risks of thyroid pathology in migrants at P-value 0.012 and <0.001 for men and women correspondingly. Besides, migrants ran higher thyroid pathology risks than people irradiated in their childhood due to exposure to ^{131}I, which accumulated in the thyroid gland: odds relation amounted to 2.8 and 2.4 (90 % confidence interval being 2.08–3.83 and 1.45–4.06 for women and men correspondingly).

Key words: *thyroid gland, nodular goiter, radioactive contamination, the Techa river, the Eastern Urals radioactive track (EURT), irradiation in childhood, long-lived radionuclides, ^{131}I*

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In the middle of the 20th century atomic industry was just emerging and there wasn't enough technical experience in dealing with sources of ionizing radiation. It caused a number of radiation accidents all over the world and resulted in environmental contamination with radiation and population exposure to it. Large-scale contamination of vast territories in the Urals was related to activities by "Mayak" Production Association. Due to several accidents which happened there territories in Chelyabinsk, Sverdlovsk, Tyumen, and Kurgan regions were contaminated with radionuclides haing different half-decay; consequently, a large population group were irradiated externally and internally [1, 2]. Thus, people who lived in settlements located on the banks of the Techa river were exposed to radiation due to regulated and emergency discharges of liquid radioactive wastes from "Mayak" PA into the river in 1949-1956. Another population cohort was exposed to radiation due to their living on the territory of the so called Eastern Urals Radiation Track (the EURT) which occurred in 1957 after an emergency at "Mayak" PA when a tank with highly radioactive solid wastes exploded. Radiation doses in people living on contaminated territories occurred due to combined effects exerted by external and internal irradiation, mostly because of ^{90}Sr and ^{137}Cs long-lived isotopes incorporation [1, 2]. A major part of such doses emerged in most people in their childhood, in other words, at an age when the thyroid gland (TG) was the most radio-sensitive [3, 4].

A lot of data have been accumulated by now on TG non-carcinogenic diseases emergence long after the atomic bombings in Japan [5, 6], as well as after exposure to ^{131}I-containing regulated gas-aerosol emissions from "Mayak" PA [7, 8]. However, we couldn't find any data on remote thyroid effects caused by exposure to combined external and internal irradiation with radionuclides which didn't deposit in the thyroid gland.

Our research goal was to perform screening examination of thyroid state and to diagnose thyroid gland diseases in people who lived on territories contaminated with radionuclides as a results of emergencies at "Mayak" PA in their childhood.

Data and methods. Our basic group for TG state screening was made up of people living in Ozersk, Chelyabinsk region, who migrated there themselves or were made to do so (hereinafter called "migrants") in 50-60ties last century from territories contaminated with radionuclides (The Techa river banks and the EURT territories). They moved to Ozersk mostly at an age younger than 15. We didn't contemplate any limitations as per sex, nationality, or socio-economic peculiarities. Simultaneously we created a reference group with the following criteria of inclusion into it: a person moved to Ozersk at an age older than 15 from territories without any contamination with radionuclides and similar in terms of provision with iodine; he or she lived in social and communal conditions which were similar to those of migrants for not less than 20 years; he or she was at an age comparable to that of migrants at the moment of examination. The examination was voluntary; patients' rights were observed as they all gave their informative written consent to participation in our project. Physical examination included neck area checking and the thyroid gland palpation. Ultra-sound examination was performed with "SonoScape SSI-600" (China) with a linear sensor at a working frequency being 7.5 MHz. We detected thyroid stimulating hormone (TSH), free thyroxin (thyroid gland hormone, CT4), and concentration of anti-bodies to thyroid peroxidase

(TP), in blood serum with test sets manufactured by "Chema" company (Russia). Thyroid gland diseases were diagnosed on the basis of medical records given by endocrinologists and specialists on the thyroid gland allowing for all the available data obtained via subjective and objective examinations.

Significance of discrepancies in distribution of an effect among examined people was statistically assessed with "case-base" technique which is the most simple two-sample variant of cohort epidemiologic research. We assessed odds relations (OR) in samples which were different from each other because they had/lacked this or that factor which could supposedly influence observed morbidity levels. We applied two techniques to statistically assess significance of discrepancies; they were so called “1-tail exact Fisher test” [9] and “1-tail exact Altham test” [10]. The first one is based on a conventional frequency approach and allows to assess odds relation together with confidence interval (CI) and probability of an observed distribution occurrence and its more remote variants (P-value). The second one is based on strictly probabilistic Bayesian approach without any reliance on a zero hypothesis. As opposed to any classic statistic significance test, Altham test allows to establish a correlation between a marker of an effect (OR < 1 or OR > 1) and estimated probability of its occurrence. It is also important to note that odds relation value during Altham test application is an adequate measure of relative risk (RR) when we compare two groups with rare specific events due to the following: $R\{OR < 1\} = R\{RR < 1\}$, where RR is a relative risk in cohort examination. We applied a typical decision making level $\alpha = 0.05$ for both statistic tests as a one-side significance level; 90% CI matches it; CI was numerically assessed as per a technique [11], which is the most similar analogue to Altham test.

Results and discussion. 265 people took part in our examination and it accounts for approximately 70% of all the migrants who were irradiated in their childhood and who now live in Ozersk. As we can see from the Table 1, women prevailed among them (75%), most were Slavs (67%), 93% participants were irradiated in their childhood, and more than a half migrants (62%) were older than 60 at the moment they were examined by us. Our research results revealed thyroid gland pathology in 149 migrants from territories contaminated with radionuclides; 54% cases were diseases diagnosed for the first time.

Table 1

Migrants group: characteristic

Parameters	*n*	% from *n*
OVERALL	265	100
Sex		
Men	65	24,5
Women	200	75,5
Nationality		
Slavs (Russians, Ukrainians)	177	67,0
Tatars and Bashkir	88	33,0
Living on contaminated territories		
The Techa river banks	121	45,7
EURT	144	54,3
Age at which exposure to radiation occurred for the first time		
≤ 15	246	93,0
> 15	19	7,0
Age at the moment of examination		
50–59	100	38,0
60 years and older	165	62,0
Hereditary predisposition		
Yes	65	24,5
No	198	74,7
Not known	2	0,8

Thyroid pathology structure mostly included nodular goiter (Table 2). As per data taken from medical documentation, all the three cases of thyroid gland cancer were diagnosed long before our screening examination started.

Table 2

Thyroid gland diseases in the examined group

Diagnoses	Women		Men	
	n	%	n	%
Overall	136	100	23	100
Non-nodal forms, including:	50	36,8	6	26,1
diffuse goiter	7	5,2	4	17,4
Autoimmune thyroiditis (AIT)	43	31,6	2	8,7
Nodal forms, including:	86	63,2	17	73,9
one-nodular goiter	46	33,8	15	65,2
multi-nodular goiter	37	27,2	2	8,7
thyroid gland cancer	3	2,2	–	–

Overall, 149 people had 159 cases of thyroid gland diseases due to 10 of them having two diseases each; these diseases were, as a rule, nodular goiter combined with AIT. Prevalence of thyroid gland diseases as per most specific nosologic forms was statistically significantly higher among women than among men (Table 3), and it is well in line with data obtained in other research [6, 12].

Age is one of the most important non-radiation factors which cause thyroid pathology emergence. Our previous screening research performed on Chernobyl disaster liquidators revealed that nodular goiter was detected more frequently in people older than 60 than in people who were younger: OR amounted to 1.7 and 1.9 (at 95% CI 1.0–3.0 and 1.1–3.2) for women and men correspondingly [13]. Data on one-nodular goiter prevalence among men older than 60 in comparison with younger people can also be found in the work [14]. More than a half migrants examined by us were older than 60 (Table 1). And yet, we didn't detect any statistically significant discrepancies between different age groups (<60 years and ≥ 60 years) as per any nosologic form. Thus, OR as per all the nosologies amounted to 0.85 and 0.83 (90% CI 0.52–1.4 and 0.34–1.96) for women and men correspondingly; P-value was 0.35 and 0.45 (as per Fischer's test), and 0.70 and 0.64 (as per Altham test) correspondingly.

Table 3

Prevalence of thyroid gland diseases among migrants depending on their sex

Nosologic forms of thyroid pathology	Groups				OR median value (90% CI)	*P-value* (Fischer's test)	*P* { OR < 1} (Altham test)
	Women *n*=200		Men *n* = 65				
	n	%	n	%			
All patients	128	64,0	21	32,3	3,66 (2,25–6,05)	< 0,001*	< 0,001*
Non-nodal forms	42	21,0	4	6,1	3,55 (1,65–8,95)	0,003*	0,002*
Nodal forms:	86	43,0	17	26,1	2,08 (1,26–3,53)	0,011*	0,008*
Nodular goiter	83	41,5	17	26,1	1,96 (1,19–3,32)	0,018*	0,013*
One-nodular goiter	46	23,0	15	23,1	0,98 (0,57–1,71)	0,556	0,529
Multi-nodular goiter	37	18,5	2	3,1	5,48 (2,14–18,7)	0,001*	< 0,001*
Thyroid gland cancer	3	1,5	–	–	1,76 (0,29–25,9)	0,428	0,319

Note: * – means discrepancies are statistically significant at $p < 0,05$.

Our own data as well as those taken from literature prove that people who have thyroid pathology in their family case histories tend to suffer from various thyroid pathologies more frequently [8,12,15]. 25% migrants stated their closest blood relatives had thyroid gland diseases. And indeed, people from a subgroup with hereditary predisposition tended to have thyroid pathology diseases more frequently, both overall and as per specific nosologic forms. The only one statistically significant parameter was an increase in multi-nodular pathology prevalence among women with hereditary predisposition: OR amounted to 2.30 (90% CI 1.24 – 4.26); P-value as per Fischer's test was 0.023; as per Altham test, 0.014.

Medical-biological research revealed that people who lived on territories contaminated with radionuclides accumulated significant radiation doses in their bodies, including up to 1 Gy on soft tissues [1, 16]. And here irradiation scenarios were different for people who lived on the Techa river banks and on the EURT territories in terms of such parameters as types of radionuclides, exposure power, and ways of radiation exposure; these differences led to intensity of post-irradiation consequences. However, as our examined group was not big, we don't think it possible to assess remote thyroid effects depending on different irradiation scenarios.

Table 4 contains the results of thyroid pathology prevalence among people from our focus group and risk assessment in comparison with the reference group. We reveled 2-2.6 times higher risks of thyroid gland pathologies in migrant men and women correspondingly; this increase was statistically significant. The only exclusion were non-nodal thyroid gland pathologies, such as AIT and diffuse goiter. Despite these pathologies having the lesser share in thyroid pathologies structure, they are more serious in terms of their clinical course and quality of patients' life.

Table 4

Prevalence of thyroid gland pathology depending on irradiation status

Nosologic forms of thyroid pathology	Migrants		Reference group		OR median value (90% CI)	*P-value* (Fischer's test)	*P* { OR < 1} (Altham test)
	n	%	n	%			
Women							
Overall	200		248				
All patients	128	64	101	40,7	2,57 (1,87–3,56)	< 0,001*	< 0,001*
Non-nodal forms	42	21	42	16,9	1,30 (0,88–1,94)	0,165	0,136
Nodal forms:	86	43	59	23,8	2,40 (1,72–3,38)	< 0,001*	< 0,001*
Nodular goiter	83	41,5	57	23,0	2,36 (1,68–3,33)	< 0,001*	< 0,001*
One-nodular goiter	46	23	35	14,1	1,81 (1,21–2,72)	0,011*	0,008*
Multi-nodular goiter	37	18,5	22	8,9	2,30 (1,45–3,71)	0,002*	0,001*
Thyroid gland pathology	3	1,5	1	0,4	2,74 (0,65–15,2)	0,236	0,127
Benign tumors	–	–	1	0,4	0,51 (0,03–4,31)	0,554	0,694
Men							
Overall	65		304				
All patients	21	32,3	59	19,4	2,00 (1,21–3,25)	0,019*	0,012*
Non-nodal forms	4	6,1	13	4,3	1,62 (0,61–3,83)	0,350	0,200
Nodal forms:	17	26,1	46	15,1	2,01 (1,18–3,38)	0,028*	0,017*
Nodular goiter	17	26,1	43	14,1	2,18 (1,27–3,67)	0,017*	0,010*
One-nodular goiter	15	23,1	28	9,2	2,99 (1,66–5,27)	0,003*	0,001*
Multi-nodular goiter	2	3,1	15	4,9	0,78 (0,22–2,11)	0,398	0,651
Thyroid gland pathology	–	–	3	1,0	0,87 (0,06–5,21)	0,558	0,545

Note: * – means discrepancies are statistically significant at $p < 0,05$.

It is proved by the fact that 58% patients suffering from AIT have thyroid dysfunction, but as for those who have nodal forms it is detected only in 2.2% of them.

We should note that statistical estimates obtained as per all the applied criteria (OR, Fischer's test, and Altham test) are well in line with each other.

By now a lot of data have been accumulated on non-carcinogenic effects in the thyroid gland under various radiation exposure scenarios. Research performed on a Japanese cohort of people 60 years after they had suffered the atomic bombing in Hiroshima and Nagasaki revealed a statistically significant positive correlation between an irradiation dose in childhood (doses range was 0.0–4.0 Gy) and prevalence of one-nodular goiter ($p<0.001$) [5, 6]. Earlier we came to a conclusion that a relative risk of benign nodal diseases in the thyroid gland for people living in Ozersk increased 40–50 years after they were exposed to technogenic irradiation caused by ^{131}I-containing gas-aerosol emissions from "Mayak" PA: OR against a reference group amounted to 1.56 (95% CI 1.1–2.2) and 1.52 (95% CI 0.92–2.5) for women and men correspondingly [12]. As per various estimates, reconstructed doses of ^{131}I which the city population got on their thyroid gland varied from 2.3 to 4 Gy [1, 17]. It is interesting to compare thyroid pathology prevalence among people who moved to Ozersk and who were exposed to a set of radionuclides from "Mayak" PA emergency emissions in their childhood with all the earlier obtained data on prevalence of thyroid gland diseases among the city population irradiated as a result of exposure to ^{131}I-containing regulated emissions from this enterprise [8]. It is well known that the skeleton and soft tissues are the organs where long-lived radionuclides (^{90}Sr, ^{137}Cs) are deposited, and it is these nuclides that basically determine radiation exposure on contaminated territories; the thyroid gland is known to accumulate radioactive iodine.

Data given in Table 5 prove that migrants run statistically significantly higher relative risks of various thyroid gland pathologies (women, 1.9-4 times higher; men, 2.4-2.7 times higher) than Ozersk population who were irradiated with radioactive iodine contained in gas-aerosol emissions in their childhood. And a question naturally arises: what are the reasons for greater thyroid pathology prevalence among people who were exposed to irradiation by long-lived radionuclides? An answer to it is likely to be obtained via comparison of radiation doses, doses rates, exposure duration, combination of radiation and non-radiation factors; such comparison is an issue for further research.

Apart from increased risks of thyroid gland pathologies, we noted some peculiarities in thyroid pathology structure in the migrants group. A very interesting fact is that one-nodular goiter prevalence among men grew to the same extent as among women (Table 4), and it contradicts another commonly known fact that there are hormones-based and genetically-based sex differences in thyroid pathology emergence [6, 8, 18]. A phenomenon of these sex difference being "wiped off" became even more apparent when we applied an index which we tentatively called "inter-gender". This index is a ratio of this or that thyroid gland disease prevalence among men to that among women. As we can see in the Figure, one-nodular goiter prevalence among men from the reference group and men from the group of people irradiated with ^{131}I was 2 times lower than among women. And on the contrary, as this pathology prevalence was the same among male and female migrants, "inter-gender" index becomes equal to 1 as per "one-

Table 5

Prevalence of thyroid gland pathology (%) depending on an irradiation scenario

Nosologic form of thyroid pathology	Ionizing radiation sources: Radionuclides from emergency emissions	Ionizing radiation sources: ^{131}I from gas-aerosol emissions [cited as per 8]	OR median value (90% CI)	*P-value* (Fischer's test)	*P* { OR < 1} (Altham test)
Women					
Overall	*n* = 200	*n* = 332			
All patients	64,0	38,5	2,82 (2,08–3,83)	< 0,001*	< 0,001*
Non-nodal forms	21,0	12,0	1,94 (1,30–2,88)	0,004*	0,003*
Nodular goiter	41,5	25,6	2,06 (1,50–2,81)	< 0,001*	< 0,001*
One-nodular goiter	23,0	20,5	1,16 (0,82–1,66)	0,281	0,242
Multi-nodular goiter	18,5	5,1	4,12 (2,52–6,88)	< 0,001*	<0,001*
Thyroid gland cancer + benign tumors	1,5	0,9	1,67 (0,48–5,79)	0,406	0,244
Men					
Overall	*n* = 65	*n* = 249			
All patients	32,3	16,4	2,43 (1,45–4,05)	0,005*	0,003*
Non-nodal forms	6,1	3,6	1,89 (0,69–4,74)	0,272	0,145
Nodular goiter	26,1	12,0	2,60 (1,48–4,52)	0,006*	0,003*
One-nodular goiter	23,1	10,0	2,71 (1,49–4,84)	0,007*	0,003*
Multi-nodular goiter	3,1	2,0	1,81 (0,47–5,91)	0,444	0,221
Thyroid gland cancer	–	0,8	0,98 (0,06–6,57)	0,628	0,506

Note: * – means discrepancies are statistically significant at $p < 0{,}05$.

nodular goiter" criterion. Besides, multi-nodular goiter prevalence increased substantially among female migrants while this parameter remained at the same level among men as in the reference group (Table 4); as a result, the index decreased to 0.2 (Figure).

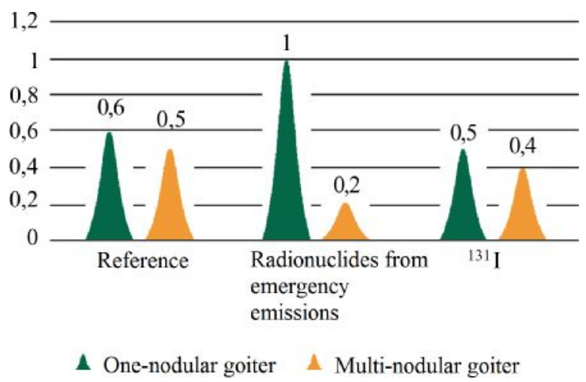

Figure. "Inter-gender" index depending on an irradiation scenario. Y-axis shows P_m: P_f (arbitrary units), where P_m is a disease prevalence among men (%); P_f is a disease prevalence among women (%). X axis shows the reference group and groups irradiated by various ionizing radiation sources

Pathological value of various nodular goiter types is being discussed now. Solitary nodes, especially those with big diameter, are thought to be highly risky in terms of malignant transformation [19]. There are data that multi-nodular goiter is combined with functional disorders and emergence of functional autonomy in the thyroid gland more frequently than one-nodular goiter [20, 21]. Combined irradiation with a set of radionuclides which formed due to emergencies can possibly change hypothalamo-pituitary-thyroid system regulation; it, in its turn, combined with non-radiation factors (hormonal or genetic ones), can lead to activation of various nodular goiter pathomorphism both in men and women.

Conclusion. Our research revealed that people who lived on territories contaminated with radiation (such areas in the

Urals as the Techa river bank and EURT) in their childhood suffered from thyroid gland diseases 50-60 years later; prevalence of such diseases amounted to 64% among women and 32% among men which was 1.6 times higher than among people who weren't exposed to radiation. These deviations are determined by statistically significant increase in risks of nodular goiter emergence; OR amounted to 2.2 for men (90% CI 1.27-3.67), P-value 0.01; 2.4, for women (90% CI 1.68-3.33), P-value <0.001. Post-radiation responses from the thyroid system in migrants irradiated by a set of radionuclides turned out to be even more apparent than in people who were exposed to ^{131}I in their early childhood, despite of the fact that only iodine out of all the existing radionuclides tends to concentrate in the thyroid gland. OR for nodular goiter amounted to 2.06 and 2.6 (90% CI 1.50–2.81 and 1.48–4.52) for women and men correspondingly. One-nodular goiter prevalence increased statistically significantly in male migrants as opposed to men exposed to ^{131}I.

We can't clearly define the reasons for these shifts in thyroid pathologies prevalence in migrants after exposure to combined irradiation in their childhood, caused mostly by long-lived radionuclides which are basically deposited in the skeleton and soft tissues. Obviously, it is necessary to perform further examination of remote effects occurring in the thyroid gland in order to assess risks of pathology under various scenarios of radiation exposure for population who lived on the Teach river bank and the EUTR territory in their childhood. It is also vital to examine and compare radiation doses, doses rates, and duration of exposure, as well as to make allowance for contribution made by external irradiation, radionuclide distribution, and non-radiation factors occurrence.

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