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RISK OF MORBIDITY WITH STOMACH CANCER AMONG WORKERS EMPLOYED AT RADIATION-HAZARDOUS ENTERPRISE

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We performed retrospective research among a cohort made up of workers employed at "Mayak" Production Association (Mayak PA), a state nuclear enterprise, who had been exposed to long-term external gamma-irradiation and internal alpha-irradiation caused by plutonium-239 under inhalation introduction. Our research goal was to assess impacts exerted by occupational irradiation and non-radiation factors on a risk of morbidity with stomach cancer (SC) in workers employed at Mayak PA.

We used individual data on occupational irradiation doses obtained from "Dosimetric system for Mayak PA workers – 2008" for external gamma-irradiation, and "Dosimetric system for Mayak PA workers – 2013" for internal alpha-irradiation. We applied Poisson regression to calculated odds ratio (OR) for morbidity with stomach cancer among the examined cohort both for radiation and non-radiation factors.

We detected statistically significant influence exerted on risk of morbidity with SC among workers employed at Mayak PA by the following factors: age, sex, attitudes towards to smoking and alcohol intake, stomach and duodenum ulcer, and external gamma-irradiation. Taking into account adjustments as per non-radiation factors, we detected a statistically significant increase in OR of morbidity with SC which was equal to 1.48 (95 % CI 1.10; 1.98), when a dose of external gamma-irradiation accumulated in the stomach walls was more than 1.0 Gy. We didn't detect any correlation between risk of morbidity with CS among the examined cohort and internal alpha-irradiation.

Given that data obtained in epidemiologic research concerning impacts exerted by occupational irradiation on SC risks are ambiguous, it is necessary to clarify the obtained results and to perform more profound analysis of dose – response relationship among a more extended cohort of workers employed at Mayak PA.

Key words: *morbidity risk, stomach cancer, gamma-irradiation, alpha-irradiation, smoking, alcohol, ulcer, dose – response relationship.*

Stomach cancer is among the most widely spread malignant neoplasms though over the last decades there has been a slight decrease in morbidity and mortality caused by it in most countries all over the world, including Russia [1, 2]. Stomach cancer is a polyetiologic disease that occurs due to complicated interaction between environmental factors, and impacts exerted by this interaction to a great extent depend on genetically determined peculiarities of a body [3].

Infection with *Helicobacterpylori (H. pylori)*, nutrition, and alcohol intake are considered to be the basic risk factors that cause stomach cancer [4–6]. About 10% of stomach cancer cases among population are caused by inherited susceptibility to the disease [7]. Certain industrial agents (asbestos, chromium, nickel, coal, aromatic hydrocarbons, etc.) were shown to also contribute into stomach cancer etiology [8–11].

Influence exerted by ionizing irradiation on morbidity and mortality caused by stomach cancer was revealed in epidemiologic research performed among people living in Hiroshima and Nagasaki who had survived the atomic bombing as well as among patients who had undergone radiation therapy [12–19]. Workers employed at the nuclear enterprise Mayak PA

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and exposed to long-term irradiation turned out to run elevated risks of malignant neoplasms; however, data related to stomach cancer are rather ambiguous [20–22]. Up to now, a period of observations performed on Mayak PA workers has been extended considerably and there are new improved techniques for assessing doses of occupational internal alpha-irradiation [23] and it creates better conditions for refining previously obtained results on influence exerted by ionizing irradiation on stomach cancer risk.

Our research goal was to assess influence exerted by occupational irradiation and non-radiation factors on stomach cancer morbidity over 1948-2013 among workers employed at basic enterprises belonging to Mayak PA.

Data and methods. We performed our research among workers who were first employed by basic Mayak PA works (reactor, radiochemical, and plutonium one) in 1948-1982; the cohort included 22,377 people, 25% of them were women. The observation period started on a day when a worker was employed and lasted till December 31, 2013 (or until a day when stomach cancer was diagnosed or a day of death if it happened before this date) or till the last date on which medical information about a person was available (for those who moved somewhere and ceased to be observed). As on December 31, 2013, life status was detected for 95% of cohort members; 62% of them were dead. Average age (± standard deviation) at the moment of death was equal to 61.5 ± 13.6 for men, and to 70.5 ± 12.4 for women; average age of those who were alive at the end of December 2013 amounted to 68.5 ± 10.4 for men; and to 76.6 ± 9.8, for women.

Personnel employed at all the basic works of Mayak PA were exposed to general external gamma-irradiation, and those who were employed at radiochemical and plutonium works were additionally exposed to alpha-active aerosols of plutonium-239. In our research we used estimations of occupational irradiation doses calculated on the basis of up-to-date dosimetric systems, "Dosimetric system for Mayak PA workers – 2008" for external gamma-irradiation doses and "Dosimetric system for Mayak PA workers – 2013" for doses of internal alpha-irradiation caused by incorporated plutonium [23, 24].

External irradiation has been monitored since PA Mayak started its operations and individual gamma-irradiation doses are known for each worker. Monitoring over internal irradiation has been introduced gradually since the late 1960ties; therefore, internal alpha-irradiation doses are detected for 31% workers exposed to plutonium-239 aerosol at their work places as the activity of this nuclide in their urine has been measured [23, 24]. 55% workers in the examined cohort were employed by Mayak PA in 1948-1958 when radiation exposure on personnel was the highest. Most workers (81%) started their work at the enterprise when they were younger than 30.

Data on diseases that workers had during the observation period were collected for 21,740 cohort members (97%); attitudes to smoking (93% workers) and its quantitative characteristics (71% workers) were known for most of them, as well as attitudes towards alcohol intake (85% workers).

To perform an integral assessment of how long and intense smoking was, we applied smoking index (SI) calculated as per the following formula: SI = number of cigarettes packs smoked a day × duration of smoking (pack × years). Workers who consumed alcohol in rather large doses every day or had chronic alcoholism in their case history as per data obtained from addiction clinics were ranked as those who abused alcohol.

Besides, we examined influences exerted on morbidity with stomach cancer by the following diseases in the digestive system: stomach ulcer, duodenum ulcer, gastritis, duodenitis, malignant neoplasms in the stomach (codes K25–K26, K29, D13.1 of the ICD-10). All the above-mentioned diseases were taken into account only if they had been detected not later than 2 years prior to stomach cancer was diagnosed (to the end of the observation over the cohort); it was done in order to exclude an already existing but not diagnosed tumor process which can have similar symptoms at its early stages.

Odds ratio (OR) for non-radiation factors was calculated on the basis of Poisson regression with corrections for attained age and sex. When calculating OR which was related to occupational irradiation, we took into account corrections for smoking status, alcohol intake, and occurrence of stomach and duodenum ulcer. Besides, when OR related to external gamma-irradiation was calculated, we made a correction for internal irradiation caused by incorporated plutonium; workers who weren't covered with monitoring over alpha-irradiation were attributed into a separate category. Analysis of stomach cancer risk caused by internal alpha-irradiation was performed only for workers who underwent procedures for control over plutonium contents in their bodies; the analysis was accomplished taking into account corrections for external gamma-irradiation doses.

All the calculations were made with AMFIT module of EPICURE software [25]. Discrepancies were considered to be statistically significant at $p < 0.05$. External gamma-irradiation doses and internal alpha-irradiation doses absorbed in the stomach walls as well as smoking index were considered to be time-dependent variables. Smoking status and smoking index value, as well as attitudes towards alcohol intake were taken at the moment when the observation over the cohort was over (or stomach cancer was diagnosed).

Results and discussion. Our research included 343 stomach cancer cases (280 men and 63 women) diagnosed in workers from the examined cohort during a period from the moment they had started working at basic Mayak PA plants to December 31, 2013. 248 workers (72%) had the stomach cancer diagnosis confirmed by histology results; in all other cases it was confirmed by clinical data.

Workers who suffered from stomach cancer had average total external irradiation dose absorbed in the stomach wall ± SD equal to 0.66 ± 0.83 Gy which was higher than among the examined cohort overall (0.46 ± 0.66 Gy). Discrepancies in internal alpha-irradiation doses absorbed in the stomach walls which were equal to 0.0012 ± 0.0026 Gy in patients with stomach cancer and 0.0014 ± 0.0064 Gy in the cohort overall were not so significant. Distribution of stomach cancer cases and workers in the examined cohort depending on occupational irradiation doses is shown on Figures 1 and 2.

OR for stomach cancer morbidity was lower for women than for men and amounted to 0.35 (95% CI 0.27; 0.46) (Table 1). Risk of stomach cancer in the examined cohort depended on an attained age. We revealed a statistically significant OR decrease among workers younger than 40 against those aged 40–45 and growing OR in older age categories (after 50). Maximum OR value for stomach cancer morbidity in the examined cohort was detected for people older than 70 and was equal to 7.53 (95% CI 4.84; 12.22) (Table 1).

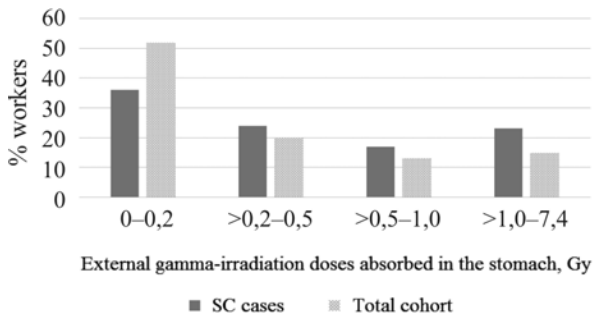

Figure 1. Distribution of workers in the examined cohort and stomach cancer cases depending on total external gamma-irradiation doses absorbed in the stomach walls

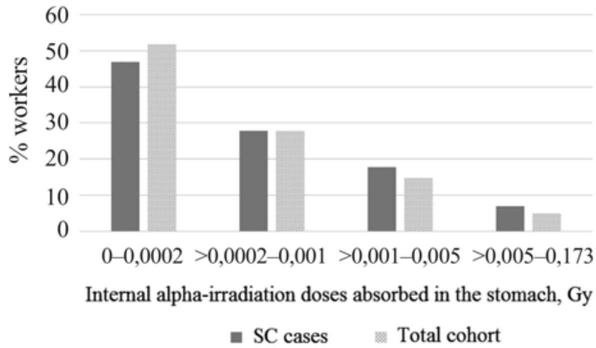

Figure 2. Distribution of workers in the examined cohort and stomach cancer cases depending on total internal alpha-irradiation doses absorbed in the stomach walls

Table 1

Influence exerted by sex, age and a calendar period when a tumor was diagnosed on stomach cancer risk in the examined cohort

Factor	Number of cases	Person-years of observation	OR (95% CI)
Sex:			
men	280	396,205	1
women	63	168,459	0.35 (0.27; 0.46)
Age at which stomach cancer was diagnosed, years:			
<20	0	9,616	–
[20 – 25)	0	44,885	–
[25 – 30)	5	59,589	0.22 (0.07; 0.53)
[30 – 35)	9	60,124	0.39 (0.17; 0.82)
[35 – 40)	11	61,104	0.48 (0.23; 0.96)
[40 – 45)	23	62,346	1
[45 – 50)	30	61,045	1.34 (0.78; 2.34)
[50 – 55)	41	55,271	2.06 (1.25; 3.48)
[55 – 60)	48	46,315	2.94 (1.81; 4.91)
[60 – 65)	53	37,395	4.12 (2.56; 6.85)
[65 – 70)	36	28,758	3.77 (2.25; 6.45)
[70+	87	38,216	7.53 (4.84; 12.22)
A calendar period during which stomach cancer was diagnosed:			
1948 – 1950	0	7,623	–
1951 – 1955	7	31,331	1.77 (0.71; 3.78)
1956 – 1960	9	38,722	1.46 (0.66; 2.91)
1961 – 1965	9	47,408	0.91 (0.41; 1.80)
1966 – 1970	20	48,183	1.34 (0.76; 2.26)
1971 – 1975	25	50,294	1.15 (0.69; 1.87)
1976 – 1980	28	56,778	0.89 (0.55; 1.42)
1981 – 1985	43	59,105	1
1986 – 1990	30	55,262	0.54 (0.34; 0.86)
1991 – 1995	34	50,110	0.51 (0.32; 0.80)
1996 – 2000	47	43,925	0.62 (0.41; 0.96)
2001 – 2005	35	37,201	0.44 (0.27; 0.69)
2006 – 2010	34	28,785	0.44 (0.27; 0.70)
2011 – 2013	22	9,937	0.66 (0.38; 1.12)

The obtained results are well in line with population data according to which stomach cancer is diagnosed 1.5-2.5 times more frequently in men than in women; experts think it can be due to different attitudes towards smoking, different nutrition, and different frequency of contacts with hazardous industrial factors [26]. It is also known that morbidity with stomach cancer taken for the overall population grows with age, especially among people older than 50, and reaches its peak among people aged 70–75 [2, 26].

We observed a statistically significant decrease in OR for stomach cancer morbidity in the examined cohort in 1986-2010 against 1981-1985 (Table 1). Morbidity with stomach cancer has decreased over last decades both in Russia and many other countries all over the world; in experts' opinion, it is due to changes in nutrition structure, lower frequency of infection with *H. pylori,* and lower prevalence of other risk factors that can cause stomach cancer, including improved working conditions [1, 2].

OR for stomach cancer morbidity was statistically significantly higher for smoking workers in the examined cohort and was equal to 1.57 (95% CI 1.17; 2.13) as compared to those who didn't smoke (Table 2). A statistically significant increase in OR which was equal to 1.40 (95% CI 1.03; 1.91) was also detected for smokers with SI greater than 20 pack × years. Besides, stomach cancer risk was statistically significantly higher for men who abused alcohol: OR = 2.00 (95% CI 1.22; 3.49) (Table 2).

Smoking is a well-known and well-proven risk factor that causes stomach cancer; according to meta-analysis data, it causes 1.5-1.6 times higher risk of the disease [27]. Alcohol abuse also contributes into stomach cancer etiology and it was revealed by meta-analysis and in large cohort research. There are data that intake of strong spirits in a dose higher than 60 g/day in terms of ethanol leads to 1.64 times higher stomach cancer risk [28]. Smoking, alcohol intake and *H. pylori* infection were shown to interact in a synergic manner causing greater inflammation and elevated probability of malignant transformations in the stomach mucous tunic [29].

Russia is among countries where there is high prevalence of *H. pylori,* as 78.5% population in the country is infected with it [30]. However we, within our retrospective research, could only indirectly take into account the role played by this factor in stomach cancer etiology among workers employed at Mayak PA.

Clinical effects produced by *H. pylori* depend on localization and peculiarities of inflammation processes in the stomach [31]. *H. pylori*–associated atrophic gastritis and stomach ulcer are known to cause elevated stomach cancer risks [26, 31]. But at the same

Table 2

Influence exerted by smoking, alcohol intake, and chronic diseases on stomach cancer risk in the examined cohort

Factor	Number of cases	Person-years of the observation	OR (95% CI)
Smoking, status:			
never smoked	111	241,531	1
gave up smoking	67	112,659	0.77 (0.54; 1.10)
smoked	159	201,964	1.57 (1.17; 2.13)
Smoking index, pack × years			
never smoked	111	241,531	1
≤ 10	15	76,748	0.60 (0.33; 1.04)
10 – 20	33	68,234	1.03 (0.66; 1.57)
> 20	143	109, 704	1.40 (1.03; 1.91)
Alcohol intake, status (men only):			
didn't drink or did it rarely	17	48,956	1
moderate drinkers	146	242,713	1.36 (0.85; 2.33)
abused alcohol	87	70,133	2.00 (1.22; 3.49)
Stomach ulcer:			
no	312	548,891	1
yes	31	15,773	1.69 (1.14; 2.42)
Duodenum ulcer:			
no	326	535,042	1
yes	17	29,623	0.49 (0.29; 0.78)
Gastritis and duodenitis:			
no	149	356,573	1
yes	194	208,091	1.23 (0.98; 1.54)
Stomach polyps:			
no	338	561,803	1
yes	5	2,861	1.18 (0.42; 2.58)

time, when a patient suffers from duodenum ulcer or chronic gastritis with the increased secretory function, he or she runs lower stomach cancer risks [26, 31].

We detected a statistically significant increase in stomach cancer risk which was equal to 1.69 (95% CI 1.14; 2.42) in the examined cohort for workers who suffered from stomach ulcer against those who didn't have this disease (Table 2). But in case a worker had duodenum ulcer, he or she, on the contrary, ran lower stomach cancer risk with OR = 0.49 (95% CI 0.29; 0.78). We revealed a slight increase in OR for workers who suffered from gastritis and duodenitis and its estimation was close to the statistical significance boundary ($p<0.1$). We didn't reveal any statistically significant correlation between stomach polyposis and stomach cancer among workers from the examined cohort but there were few cases of this disease (Table 2).

The performed analysis revealed a statistically significant increase in OR for stomach cancer morbidity when external gamma-irradiation doses absorbed in the stomach walls were higher than 1.0 Gy against those workers who had external irradiation doses not higher than 0.2 Gy (Table 3). Estimation of OR for stomach cancer morbidity calculated with corrections for sex, age, and alpha-irradiation, amounted to 1.37 (95% CI 1.02; 1.83). We introduced additional corrections for smoking status, attitudes towards alcohol, and occurrence of stomach and duodenum ulcer, and OR estimation went up slightly to 1.48 (95% CI 1.10; 1.98) (Table 3).

Table 3

Influence exerted by long-term total external gamma-irradiation on stomach cancer risk in the examined cohort

External gamma-irradiation dose absorbed in the stomach walls, Gy	Number of cases	Person-years of the observation	OR (95% CI)
Model with corrections for sex, age, and alpha-irradiation:			
[0.0 – 0.2)	123	284,928	1
[0.2 – 0.5)	83	107 ,64	1.26 (0.95; 1.66)
[0.5 – 1.0)	58	71,608	1.24 (0.89; 1.69)
[1.0+	79	82,125	1.37 (1.02; 1.83)
Model with corrections for sex, age, smoking status, and alpha-irradiation:			
[0.0 – 0.2)	123	284,928	1
[0.2 – 0.5)	83	107,464	1.27 (0.96; 1.68)
[0.5 – 1.0)	58	71,608	1.26 (0.91; 1.72)
[1.0+	79	82,125	1.44 (1.07; 1.93)
Model with corrections for sex, age, smoking status, alcohol intake, and alpha-irradiation:			
[0.0 – 0.2)	123	284,928	1
[0.2 – 0.5)	83	107,464	1.29 (0.97; 1.70)
[0.5 – 1.0)	58	71,608	1.29 (0.93; 1.76)
[1.0+	79	82,125	1.47 (1.09; 1.97)
Model with corrections for sex, age, smoking status, alcohol intake, stomach ulcer, and alpha-irradiation:			
[0.0 – 0.2)	123	284,928	1
[0.2 – 0.5)	83	107,464	1.28 (0.96; 1.70)
[0.5 – 1.0)	58	71,608	1.28 (0.93; 1.75)
[1.0+	79	82,125	1.47 (1.09; 1.96)
Model with corrections for sex, age, smoking status, alcohol intake, stomach ulcer, duodenum ulcer, and alpha-irradiation:			
[0.0 – 0.2)	123	284,928	1
[0.2 – 0.5)	83	107,464	1.29 (0.97; 1.71)
[0.5 – 1.0)	58	71,608	1.29 (0.93; 1.76)
[1.0+	79	82,125	1.48 (1.10; 1.98)

Table 4

Influence exerted by long-term total internal alpha-irradiation on stomach cancer risk in the examined cohort

Internal alpha-irradiation dose absorbed in the stomach walls, Gy	Number of cases	Person-years of the observation	OR (95% CI)
Model with corrections for sex, age, and gamma-irradiation:			
[0.0 – 0.2)	101	219,531	1
[0.2 – 0.5)	57	64,106	0.95 (0.66; 1.35)
[0.5 – 1.0)	35	27,361	1.04 (0.66; 1.61)
[1.0+	10	6,727	1.26 (0.59; 2.42)
Model with corrections for sex, age, smoking status, and gamma-irradiation:			
[0.0 – 0.2)	101	219,531	1
[0.2 – 0.5)	57	64,106	0.93 (0.65; 1.32)
[0.5 – 1.0)	35	27,361	1.03 (0.65; 1.60)
[1.0+	10	6,727	1.26 (0.59; 2.42)
Model with corrections for sex, age, smoking status, alcohol intake, and gamma-irradiation:			
[0.0 – 0.2)	101	219,531	1
[0.2 – 0.5)	57	64,106	0.93 (0.65; 1.32)
[0.5 – 1.0)	35	27,361	1.03 (0.65; 1.60)
[1.0+	10	6,727	1.24 (0.58; 2.39)
Model with corrections for sex, age, smoking status, alcohol intake, stomach ulcer, and gamma-irradiation:			
[0.0 – 0.2)	101	219,531	1
[0.2 – 0.5)	57	64,106	0.93 (0.65; 1.31)
[0.5 – 1.0)	35	27,361	1.03 (0.65; 1.60)
[1.0+	10	6,727	1.24 (0.58; 2.41)
Model with corrections for sex, age, smoking status, alcohol intake, stomach ulcer, duodenum ulcer, and gamma-irradiation:			
[0.0 – 0.2)	101	219,531	1
[0.2 – 0.5)	57	64,106	0.92 (0.64; 1.31)
[0.5 – 1.0)	35	27,361	1.02 (0.65; 1.59)
[1.0+	10	6,727	1.20 (0.56; 2.31)

We didn't detect any influence exerted by internal alpha-irradiation on stomach cancer risk in the examined cohort (Table 4) and the result is well in line with the previously obtained ones [20–22]. Other researchers also didn't reveal any carcinogenic effects in the stomach when alpha-irradiators (Ra, Th, Rn, Pu) were introduced in a body; it is most frequently explained by rather insignificant doses of such irradiation absorbed in this organ [32–34].

Previously experts who had conducted "case – control" research on workers employed at Mayak PA revealed an elevated stomach cancer risk when total external gamma-irradiation doses were higher than 3.0 Gy [20]. Cohort research performed on workers employed at basic Mayak PA plants revealed increased risks of morbidity (observation period 1948–2004) [21] and mortality (observation period 1948–2008) caused by stomach cancer when external gamma-irradiation doses grew [22]; however, estimations of excessive relative risks were only close to the statistical significance boundary ($p<0.07$ and < 0.06 accordingly).

We prolonged the observation period up to 2013 within the framework of our research; also, when assessing influence exerted by occupational irradiation on stomach cancer risk, we took into account a wider range of non-radiation factors including chronic stomach diseases that can be caused by infection with *H. pylori.*

Research performed on people who had survived the atomic bombing in Japan revealed a dependence between a dose of acute gammaneutron irradiation and risks of morbidity and mortality caused by stomach cancer [12, 13]. Elevated stomach cancer risks were also detected for patients who had undergone radiation therapy or had had ^{131}I introduced into their bodies when hyperthyrosis had been treated [14–19, 35].

But a lot of researchers who examined personnel employed at nuclear enterprises in foreign countries, people living on territories contaminated with radiation emissions and in zones where natural radiation background was a bit increased didn't obtain any convincing evidence that there was a correlation between long-term irradiation in small doses and stomach cancer risk [36–39]. However, an elevated stomach cancer risk caused by exposure to radiation was revealed for a combined cohort of workers employed at nuclear enterprises in France, Great Britain, and the USA, when average external gamma-irradiation doses absorbed in the stomach were equal to 20 mGy [40].

Conclusion. The research performed on workers employed at Mayak PA revealed an elevated stomach cancer risk under long-term external gamma-irradiation in total doses absorbed in the stomach walls equal to more than 1.0 Gy. Given the fact that data on influence exerted by occupational irradiation on stomach cancer risks that have been accumulated so far are rather ambiguous, it is necessary to analyze a dose-effect relationship in greater detail and on an extended cohort of workers employed at Mayak PA.

We didn't reveal any influence exerted by long-term internal alpha-irradiation on stomach cancer morbidity in workers employed at Mayak PA.

Stomach cancer risk for the examined cohort, just as for overall population, depended on an attained age, sex, attitudes towards smoking and alcohol intake, as well as on occurrence of stomach and duodenum ulcer.

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Conflict of interests. The authors state there is no any conflict of interests.

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