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Research article

THE RISK OF COLORECTAL CANCER INCIDENCE IN A COHORT OF INDIVIDUALS OCCUPATIONALLY EXPOSED TO IONIZING RADIATION

G.V. Zhuntova, M.V. Bannikova, T.V. Azizova

Southern Urals Biophysics Institute, 19 Ozerskoe shosse, Ozersk, 456780, Russian Federation

The increased risk of colorectal cancer following ionizing radiation exposure was demonstrated in a number of epidemiological studies. Earlier, no impact of occupational radiation exposure on colorectal cancer incidence or mortality was observed in a cohort of workers of the nuclear industrial facility, Mayak Production Association (PA). Extension of the follow-up of the cohort and improvement of dose estimates for personnel made it possible to update the earlier findings.

The study objective is to assess the risk of colorectal cancer incidence associated with chronic occupational radiation exposure taking into account non-radiation factor effects.

The study cohort included 22,377 workers employed at the reactor, plutonium-producing and radiochemical plants of Mayak PA (hiring period 1948–1982; follow-up period ended on December 31, 2018). Using the Poisson regression (EPICURE software), the relative risks (RRs with 95 % confidence intervals, (95 % CI)) of colorectal cancer incidence were estimated depending on the most significant non-radiation factors (sex, age, smoking, alcohol consumption, excessive body mass and obesity, intestinal polyps, chronic colitis). These values were also calculated for certain ranges of occupational exposure doses relying on data provided by 'The Mayak Worker Dosimetry System – 2013'. The linear model was used to analyze the dose-response relationship.

In the study cohort, the RR of colorectal cancer incidence was lower in females than in males: 0.72 (95 % CI: 0.55; 0.96) for colon and 0.48 (95 % CI: 0.34; 0.67) for rectum. The increased RR of the rectum cancer incidence was observed for cases with intestinal polyps: 3.42 (95 % CI: 1.68; 6.19). The colon cancer incidence risk increased with increasing age of workers, but other non-radiation factors were not shown to affect the results. This study supported the earlier results: no association was observed between the risk of colorectal cancer incidence and doses of occupational external gamma-ray or internal alpha-particle exposures.

Keywords: *colon cancer, rectum cancer, external gamma-ray exposure, internal alpha-particle exposure, risk factors, nuclear workers, Poisson regression, analysis of dose-response relationship.*

Colorectal cancer (colon and rectum cancer) occupies a significant place in incidence and mortality caused by malignant tumors (MTs) [1]. Over the last decades, incidence of colorectal cancer has been growing in most countries, Russia included [1, 2]. Given that, etiology of colorectal cancer has been given a lot of expert attention.

Age older than 50 years, male sex, specific lifestyles (dietary patterns, smoking, alcohol consumption, and low physical activity), and obesity are the most significant risk factors of colorectal cancer [3–7]. Approximately 25–30 % of patients with colorectal cancer (CRC) have a family history of the disease attributed to genetically-determined high sensitivity to environmental exposures as well as habitual behaviors [8], and about 5 % of all colorectal cancer cases are caused by hereditary mutations [9].

The International Agency for Research on Cancer (IARC) lists colon and rectum MTs as cancer sites with evidenced associations between tumor progression and exposure to ion-

Galina V. Zhuntova – Candidate of Medical Sciences, Leading Researcher of Clinical Department (e-mail: clinic@subi.su; tel.: +7 (35130) 2-93-30; ORCID: https://orcid.org/0000-0003-4407-3749).

Maria V. Bannikova – Researcher of Clinical Department (e-mail: clinic@subi.su; tel.: +7 (35130) 2-93-30; ORCID: https://orcid.org/0000-0002-2755-6282).

Tamara V. Azizova – Candidate of Medical Sciences, Deputy Director for Science, Head of Clinical Department, Chief Researcher (e-mail: clinic@subi.su; tel.: +7 (35130) 2-93-30; ORCID: https://orcid.org/0000-0001-6954-2674).

izing radiation [10]. An elevated risk of colorectal cancer was reported for atomic bomb survivors exposed to acute gamma-neutron radiation in Japan (an LLS cohort) as well as for patients who had once been prescribed radiotherapy to treat MTs in organs of the pelvis minor [11–16].

Some growth in the excess relative risk of colorectal cancer was identified for nuclear workers in France, Great Britain and the USA (INWORKS); however, a significant relationship with an occupational exposure dose was established only for rectum cancer [17]. No relationships between exposure doses and incidence (in 1948–2004) or mortality (1948–2008) caused by colorectal cancer were established in the cohort made of workers employed at Mayak Production Association (Mayak PA), the first nuclear enterprise in Russia [18–19]. Extension of the follow-up of the cohort and improvement of dose estimates for Mayak PA personnel made it possible to update the earlier findings by conducting the present study [20].

The aim of this study was to assess effects of chronic occupational radiation exposure and non-radiation factors on the colorectal cancer risk in a cohort of nuclear workers.

Materials and methods. The analyzed cohort includes workers employed at reactor, radiochemical and plutonium-producing plants of Mayak PA (the hiring date is within 1948–1982) and covers the period up to December 31, 2018. The analyzed period was limited to the date of the last medical entries for workers who dropped out of observation or a date of death for deceased workers. The total number of people in the cohort is 22,377; women account for 25 % in it. Previous studies [21] describe in detail how the medical follow-up of the Mayak PA personnel is organized, sources and methods for obtaining data on incidence and non-radiation factors as well as the 'Clinic" database, which is a valuable resource for conducting epidemiological studies. Complete data on incidence were collected for 21,679 (97 %) of the cohort members. Forty-three workers were excluded from analysis of the colorectal cancer risk related to chronic radiation exposure; in the first years of the Mayak PA operation, they had been exposed to acute gamma radiation at high doses, which had led to acute radiation sickness (Table 1).

Table 1

The description of the analyzed cohort

The cohort structure	**Number of workers (%)**
Number of people in the cohort	22,377
Dropped out of observation	698
Suffered from acute radiation sickness	43
Are included in the study	21,636 (100 %)
Occupational exposure	***Me*** **($Q_{25\%}$–$Q_{75\%}$)**
A dose of external gamma-ray exposure absorbed in the colon wall, Gy	0.163 (0.047–0.527)
A dose of internal alpha-particle exposure absorbed in the colon wall, Gy	0.00018 (0.00005–0.0007)

N o t e: *Me* is median, $Q_{25\%}$–$Q_{75\%}$ is interquartile range.

By the end of the observation period, 43 % of the people in the analyzed cohort were older than 60 years. Sixty-three percent of the workers were hired at the nuclear enterprise in 1948–1960 when the production was in the process of formation and occupational exposure doses were the highest [20]. Duration of occupational radiation exposure exceeded 20 years for 33 % of the analyzed workers.

Workers employed at the reactor plant (24 % of the cohort members) experienced only external gamma-ray exposure whereas workers of the radiochemical (42 % of the cohort members) and plutonium-producing (35 % of the cohort members) plants were additionally exposed to alpha-active plutonium-239 aerosols. Individual doses of external gamma-ray exposure are known for all cohort members whereas doses of internal alpha-particle exposure are available only for 36 % of workers exposed to plutonium-239. This is due to peculiarities related to implementation of occupational radiation exposure monitoring at Mayak PA [20].

Total doses of external gamma-ray exposure and internal alpha-particle exposure (hereinafter gamma- and alpha-doses) absorbed in the colon wall were provided by the Mayak Worker Dosimetry System – 2013 [20] as of the date when colorectal cancer was diagnosed (the end of the observation period for workers without cancer in the cohort), a lag period was 0 years. In addition to that, a lag-period of 10 years was used to estimate the excess relative risk per unit dose (ERR/Gy). In this case, doses accumulated over the first 10 years of employment at Mayak PA were included into the zero-dose category. Characteristics of exposure doses (the lag period is 0 years) for the workers are provided in Table 1.

Risks were analyzed separately for colon and rectum cancer. We calculated relative risks (RR) of colorectal cancer incidence associated with non-radiation factors as well as for certain categories of occupational radiation exposure doses. The following non-radiation factors were taken into account: sex, age, smoking status, alcohol consumption, body mass index (BMI = weight (kg) / height (m^2)), chronic colitis as well as intestinal polyps in medical history.

Comprehensive data on non-radiation factors were available for most cohort members: smoking status, 99 %; alcohol consumption, 96 %; BMI values, 82 % of the analyzed workers. Smoking status was estimated as of the end of the follow-up period. Alcohol consumption was classified as follows: 'rarely' and 'moderately', if the workers used the same definitions when describing their drinking habits; 'alcohol abuse', if 'binge drinking' or 'chronic alcoholism' were diagnosed in a worker by an addiction specialist within the follow-up period. Two BMI categories were considered, namely BMI < 25 kg/m^2 (normal weight) and ≥ 25 kg/m^2 (overweight or obesity).

At early stages, a tumor can develop either under disguise of another disease or without any clinical manifestations; therefore, data on chronic colitis as well as intestinal polyps were taken into account if an interval between these diagnoses and diagnosed colorectal cancer (the end of the follow-up for workers without it) was not shorter than 2 years. A similar approach (a 2-year lag) was used in BMI calculation. Workers without available information on any analyzed factor were included into a separate category ('unknown').

Risks of colorectal cancer incidence were estimated based on the Poisson regression using the AMFIT module; to group the data and calculate person-years at risk, the DATAB module of the EPICURE software[1] was used. While estimating RR, the stratification by age and sex was applied.

The following model was used to estimate ERR/Gy for colorectal cancer incidence:

$$\lambda = \lambda_0 (s, a, x_1 \ldots .x_n) \times (1 + \beta D),$$

where λ_0 is the background risk, β is excess relative risk per dose unit (ERR/Gy), and D is gamma dose or alpha dose.

When calculating the background risk (λ_0), we applied stratification to take into account the impact of sex, s; age, a; and other factors mentioned above, $x_1 \ldots .x_n$. This includes an adjustment for an alpha dose in the analysis of the incidence risk due to gamma dose and vice versa. The maximum likelihood technique was used to calculate 95 % confidence intervals (95 % CI) for *RR* and ERR/Gy. In case CI boundaries were not identified, the abbreviation 'n/a' was used. The obtained estimates were considered statistically significant at $p < 0.05$.

Results and discussion. As of December 31, 2018, colorectal cancer was diagnosed in 409 members of the analyzed cohort; several colorectal MTs of different sites were identified in 19 of them during the follow-up period. For these workers, the earliest diagnosed cancer case was considered within risk analysis. Therefore, risk analysis included 225 colon cancer cases (66 % males and 34 % females) and 184 rectum cancer cases (74 % males and 26 % females). Diag-

[1] Preston D.L., Lubin J.H., Pierce D.A., McConney M.E. Epicure Users Guide. Seattle, WA, Hirosoft International Corporation, 1993.

nosed colorectal cancer was histologically verified in 89 % of workers.

The colorectal cancer risk was lower for women than men in the analyzed cohort; the *RR* = 0.72 (95 % CI: 0.55–0.96) was estimated for colon cancer and the *RR* = 0.48 (95 % CI: 0.34–0.67) was estimated for rectum cancer (Table 2). The colorectal cancer risk increased with age and reached its maximum in the age group of 70–79 years. We established a significant increase in the rectum cancer risk, *RR* = 3.42 (95 % CI: 1.68–6.19) for workers who had intestinal polyps. We did not establish any significant relationships between the colorectal cancer risk and smoking status, alcohol consumption, chronic colitis, or BMI values in the analyzed cohort (Table 2).

Table 2

Relative colorectal cancer risk (*RR*)

Factor	Colon cancer			Rectum cancer		
	Cases	Person-years	*RR* (95 % CI)	Cases	Person-years	*RR* (95 % CI)
Sex:						
men	148	413,534	1	136	414,023	1
women	77	176,022	0.72 (0.55–0.96)	48	176,398	0.48 (0.34–0.67)
Age:						
< 50	13	360,317	0.02 (0.01–0.03)	12	360,584	0.02 (0.01–0.04)
50–59	45	108,115	0.20 (0.14–0.30)	36	108,260	0.21 (0.14–0.33)
60–69	74	73,273	0.51 (0.37–0.70)	63	73,496	0.57 (0.40–0.83)
70–79	73	37,678	1	53	37,873	1
≥ 80	20	10,173	1.05 (0.62–1.69)	20	10,207	1.52 (0.89–2.51)
Smoking status:						
never	105	253,806	1	68	254,393	1
quit smoking	62	123,324	1.1 (0.74–1.64)	60	123,482	1.46 (0.95–2.30)
smoke	55	205,044	1.06 (0.70–1.60)	54	205,135	1.46 (0.93–2.32)
unknown	3	7382	1.55 (0.38–4.14)	2	7410	1.51 (0.25–4.83)
Alcohol consumption:						
rarely	68	154,229	1	46	154,554	1
moderately	107	268,936	0.88 (0.61–1.28)	95	269,168	0.92 (0.6–1.43)
abused	43	144,720	0.78 (0.49–1.24)	38	145,013	0.78 (0.46–1.3)
unknown	7	21,669	1.08 (0.44–2.26)	5	21,684	0.94 (0.32–2.21)
Body mass index:						
normal	32	99,242	1	21	99,338	1
above normal	98	268,849	0.95 (0.64–1.44)	83	268,972	1.30 (0.82–2.16)
unknown	95	221,465	1.03 (0.70–1.56)	80	222,110	1.38 (0.87–2.30)
Intestinal polyps:						
no	221	586,679	1	174	587,421	1
yes	4	2876	1.13 (0.35–2.68)	10	2999	3.42 (1.68–6.19)
Colitis:						
no	162	501,668	1	141	502,026	1
yes	63	87,888	0.95 (0.69–1.28)	43	88,394	0.8 (0.55–1.13)
Gamma-dose, Gy:						
0–0.2	103	316,989	1	71	317,455	1
> 0.2–0.5	53	109,360	1.08 (0.77–1.51)	45	109,621	1.25 (0.85–1.82)
> 0.5–1.0	36	72,710	1.02 (0.69–1.48)	34	72,737	1.32 (0.86–1.99)
> 1.0	33	72,337	0.89 (0.59–1.32)	34	72,444	1.24 (0.81–1.86)
Alpha-dose, Gy:						
0–0.0001	46	178,043	1	31	178,259	1
> 0.0001–0.0005	62	89,208	1.30 (0.89–1.93)	29	89,538	0.87 (0.52–1.46)
> 0.0005–0.001	16	26,647	0.96 (0.53–1.67)	21	26,692	1.80 (1.01–3.13)
> 0.001	27	38,494	0.93 (0.57–1.50)	29	38,546	1.46 (0.87–2.45)
unknown	74	249,465	1.03 (0.71–1.50)	74	249,687	1.46 (0.97–2.25)

Categorical analysis did not reveal any impacts of gamma- and alpha-doses on the colorectal cancer risk for workers in the analyzed cohort. A significant increase in the rectum cancer, *RR* = 1.80 (95 % CI: 1.01–3.13), was detected only for internal alpha-particle exposure at a dose within 0.0005–0.001 Gy (against 0.0–0.0001 Gy) but the reasons for that need further clarification (Table 2).

The dose-response relationship was analyzed based on a linear model and this analysis confirmed the results obtained by categorical analysis (Tables 3 and 4). ERR/Gy estimates varied between -0.03/Gy and 0.04/Gy (colon cancer) and between 0.17/Gy and 0.29/Gy (rectum cancer) for the lag period of 0 years and with the use of background risk models with sets of different non-radiation factors. The results were not significant (Table 3).

ERR/Gy of alpha-dose varied within -5.73/Gy and -4.78/Gy (colon cancer) and between -5.69/Gy and -4.80/Gy (rectum cancer) for the 0-year lag period but it did not reach statistical significance either (Table 4). Analysis based on occupational exposure doses, which considered the 10-year lag period, did not demonstrate any relationship between occupational radiation exposure and the colorectal cancer risk (Tables 3 и 4).

Table 3

Excess relative risk (*ERR*/Gy) of colorectal cancer: external gamma-ray exposure

Factors considered in the background risk model	*ERR*/Gy (95 % CI)	
	Colon cancer	Rectum cancer
0-year lag period		
Age, sex	0.01 (-0.13–0.21)	0.17 (-0.08–0.55)
Age, sex, smoking	0.01 (-0.14–0.20)	0.17 (-0.08–0.56)
Age, sex, smoking, alcohol consumption	0.03 (-0.13–0.24)	0.22 (-0.06–0.65)
Age, sex, smoking, alcohol consumption, body mass index	0.04 (-0.12–0.25)	0.20 (-0.07–0.62)
Age, sex, smoking, alcohol consumption, body mass index, intestinal polyps, colitis	0.02 (-0.14–0.23)	0.18 (-0.09–0.62)
Age, sex, smoking, alcohol consumption, body mass index, intestinal polyps, colitis, alpha-dose	-0.03 (-0.20–0.21)	0.29 (-0.06–0.93)
10-year lag period		
Age, sex	0.02 (-0.13–0.23)	0.16 (-0.09–0.54)

Table 4

Excess relative risk (*ERR*/Gy) of colorectal cancer: internal alpha-particle exposure

Factors considered in the background risk model	*ERR*/Gy (95 % CI)	
	Colon cancer	Colon cancer
0-year lag period		
Age, sex	-5.73 (n/a–37.61)	-4.80 (n/a–76.58)
Age, sex, smoking	-4.97 (n/a–33.06)	-5.25 (n/a–72.78)
Age, sex, smoking, alcohol consumption	-4.92 (n/a–34.82)	-5.34 (n/a–79.45)
Age, sex, smoking, alcohol consumption, body mass index	-5.69 (n/a–38.41)	-5.30 (n/a–85.37)
Age, sex, smoking, alcohol consumption, body mass index, intestinal polyps, colitis	-5.16 (n/a–32.61)	-5.28 (n/a–87.76)
Age, sex, smoking, alcohol consumption, body mass index, intestinal polyps, colitis, gamma-dose	-4.78 (n/a–46.65)	-5.69 (n/a–79.55)
10-year lag period		
Age, sex	-9.05 (n/a–64.79)	-9.24 (n/a–125.7)

N o t e: n/a means limits of the CI interval were not identified.

We observed elevated colorectal cancer risks for older age groups as well as for men compared to women in the analyzed cohort. Our findings are consistent with results of other epidemiological studies where 90 % of malignant tumors of this localization were reported in patients older than 50 years [1, 5]. Men have 1.4–1.5 times higher risks of colorectal cancer than women; this fact is explained by differences in the prevalence of lifestyle factors in male and female populations [5, 6].

Smoking plays a significant role in colorectal cancer etiology, which is especially relevant for tumors in the proximal colon and the rectum. Levels of risk depend on smoking intensity and duration and are different for specific molecular subtypes of colorectal cancer [22, 23]. Some epidemiological studies suggest that even moderate regular drinking increases the colorectal cancer risk by 20–40 % against people who drink rarely or even do not drink alcohol at all [24].

Chronic inflammatory bowel diseases (CIBD) are a significant risk factor of colorectal cancer and approximately 10–15 % of CIBD patients die due to malignant tumors of this localization [25]. An elevated colorectal cancer risk in obese people is also explained by inflammatory changes in intestinal epithelium due to metabolic disorders [26]. Changes in organization and structure of intestinal epithelium induced by inflammation promote growth of adenomatous polyps which can undergo malignant transformation in 10–20 % cases [27].

In this study, we established an elevated rectum cancer risk in patients with intestinal polyposis but did not reveal any impacts of such factors as smoking, alcohol consumption, chronic colitis, overweight and obesity on colorectal cancer incidence among the analyzed cohort of nuclear workers. It is noteworthy that according to accumulated research data, microbiota in the large intestine has considerable influence on metabolism of ethanol and tobacco smoking products as well as on development and outcome of inflammatory reactions. This microbiota is considered a carcinogenesis mediator [28]. Byproducts of gut microbiota can have either carcinogenic or anti-tumor properties and this can modify effects produced by carcinogenic factors in some individuals. State of gut microbiota largely depends on nutrition [29].

Large-scale epidemiological studies observed effects of ionizing radiation on colorectal cancer incidence and mortality; however, estimated risk levels differ for MTs of the colon and rectum. In the LSS cohort, a positive significant relationship was demonstrated between doses of acute gamma-neutron exposure and the colon cancer risk in atomic bomb survivors [11–13]. *ERR*/Gy estimates adjusted for smoking, alcohol and meat consumption, and body mass index were calculated for 70-year old people who had been exposed at the age of 30 years (both sexes). The results were as follows: colon cancer (all sections), *ERR*/Gy = 0.63 (95 % CI: 0.34–0.98); the proximal colon, *ERR*/Gy = 0.80 (95 % CI: 0.32–1.44); the distal colon, *ERR*/Gy = 0.50 (95 % CI: 0.04–0.97). These estimates were not significant for rectum cancer: *ERR*/Gy = 0.023 (95 % CI: -0.081–0.13) [11].

Previously, no effects of acute gamma-neutron exposure were observed in the LSS cohort for rectum cancer incidence (1958–1998) and mortality (1950–2003) [12, 13]. Estimates of radiation-related colon cancer risks adjusted for sex, age and age of exposure (without taking into account other non-radiation factors) were the same: *ERR*/Gy = 0.54 (90 % CI: 0.30–0.81) for incidence and *ERR*/Gy = 0.54 (90 % CI: 0.23–0.93) for mortality [12, 13].

Meta-analysis of findings reported in studies of patients who were treated with radiotherapy for prostate cancer revealed an increase in relative risk (*RR*) of rectum cancer, *RR* = 1.64 (95 % CI: 1.39–1.94) and colon cancer, *RR* = 1.33 (95 % CI: 1.02–1.76) compared to those patients who had never received the radiotherapy [14]. Elevated colon cancer risks were established 8 years after and rectum cancer risks 15 years after radiotherapy for cervical cancer [15]. The colon cancer risk was *RR* = 2.00 (95 % CI: 1.43–2.80) in these female patients; the rectum cancer risk was

RR = 4.04 (95 % CI: 2.08–7.86). The observed *RR* values remained the same during the next 20 years of the follow-up [15]. An elevated colorectal cancer risk was also observed for patients who had undergone the radiotherapy at doses between 20 Gy and 29.99 Gy for whom odds ratio was 7.8 (95 % CI: 1.3–56.0) compared to those who had never received the radiotherapy [16].

Elevated risks of rectum cancer mortality were reported for nuclear workers of the United Kingdom (the UK) as well as in the joint INWORKS study, which included cohorts of occupationally radiation-exposed workers from France, the UK and the USA [17, 30]. Cumulative exposure doses absorbed in the large intestine were 0.4–19.8 mGy in INWORKS workers and the risk of rectum cancer mortality calculated using maximum likelihood technique based on the Poisson regression was *ERR*/Gy = 1.87 (90 % CI: 0.04–4.52) [17]. When the analysis was performed by using hierarchical regression, *ERR*/Gy estimates for rectum cancer were not significant. The INWORKS did not reveal a relationship between radiation doses from occupational exposure and the risk of colon cancer mortality [17].

Epidemiological studies conducted in various countries did not report any findings indicating an association between internal alpha-particle exposure and the colorectal cancer risk in industrial workers exposed to plutonium or radium; in patients who had been treated with radium- or thorium-based medications, either diagnostic or therapeutic ones; as well as in individuals exposed to radon (miners and general population) [31–36]. It is noteworthy that doses of alpha-active nucleotides absorbed in the intestine were very low in all cases mentioned above [31–36].

Previously, incidence [18] and mortality [19] due to MTs of various localizations were analyzed in the cohort of Mayak PA workers. The analysis did not reveal any relationship between occupational exposure doses (gamma and alpha radiation) and colorectal cancer. A study of cancer incidence included workers hired at the reactor, plutonium-producing and radiochemical plants of Mayak PA in 1948–1982 and covered the follow-up period until December 31, 2004 [18]; a study of cancer mortality also included personnel hired at auxiliary production of Mayak PA and covered a longer follow-up period up to the end of 2008 [19]. Occupational exposure doses were provided by the 'Mayak Worker Dosimetry System – 2008'; sex, age, and smoking status were considered in the baseline risk calculations.

In this study, the follow-up period was extended up to 14 years for the same cohort; occupational exposure doses were provided by the improved 'Mayak Worker Dosimetry System – 2013' [20]; we used a wider set of non-radiation factors in the baseline risk modeling (alcohol consumption, intestinal polyps, chronic colitis, and BMI). This analysis, similarly to the previous one, did not reveal any significant relationship between occupational radiation exposure doses and the colorectal cancer risk.

It is noteworthy that the number of colorectal cancer cases included in this study was relatively small. In addition to that, we did not consider workers' dietary habits, physical activity, other individual peculiarities (genetic predisposition, state of gut microbiota), or interactions between specific risk factors. This might affect the study findings.

Conclusions:

1. This study did not find any impact of chronic occupational external gamma-ray exposure or internal alpha-particle exposure on the colorectal cancer risk in the cohort of Mayak PA workers.

2. We observed a significant increase in the colorectal cancer risk in older age groups as well as in males compared to females; in addition to that, the rectum cancer risk was higher in workers diagnosed with intestinal polyposis.

3. We did not establish any associations between the colorectal cancer risk in the study cohort and such factors as smoking, alcohol consumption, overweight and obesity, or chronic colitis.

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Competing interests. The authors declare no competing interests.

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