

<https://doi.org/10.47183/mes.2026-493>



CANCER INCIDENCE IN THE OFFSPRING OF MAYAK PRODUCTION ASSOCIATION WORKERS: CHARACTERISTICS AND ANALYSIS

Yulia V. Tsareva[✉], Svetlana F. Sosnina, Pavel V. Okatenko, Nailya R. Kabirova

Southern Urals Federal Research and Clinical Center for Medical Biophysics, Ozersk, Russia

Introduction. The study of the effects of preconceptive (before conception) and *in utero* radiation exposure, including the risk of malignant neoplasms (MNs) in the offspring of individuals exposed to occupational radiation, is a complex and ambiguous problem in radiation epidemiology.

Objective. Epidemiological analysis of carcinogenic effects among offspring whose parents were exposed to occupational preconceptive radiation and radiation during pregnancy at the Mayak Production Association.

Materials and methods. A retrospective analysis of outcomes in the form of oncopathology was conducted among 35,500 individuals, of whom 14,593 were offspring of workers at the Mayak Production Association (PA) — the first nuclear industry enterprise in Russia, operating since 1948. The comparison group included 20,872 individuals whose parents were not exposed to radiation at work and were not resettlers from radioactively contaminated territories. The study samples were drawn from individuals born in 1948–1988 in the closed administrative-territorial unit (CATU) of Ozersk, located near the nuclear facility. The follow-up period was 72 years (1949–2020). The data sources for the epidemiological analysis of cancer incidence among offspring whose parents were Mayak PA workers include: the Mayak PA personnel medical and dosimetric registry, the Children's Registry (includes the population exposed in childhood to technogenic impact due to Mayak PA activities), the Child Population Health Registry, the Cancer Registry, and the Cause of Death Registry of the CATU Ozersk population. Information on accumulated absorbed doses of external gamma radiation was extracted from the "Dosimetry System of Mayak PA Workers — 2013." Statistical analysis was performed using nonparametric statistics methods: frequency comparison was conducted using the χ^2 test (Pearson's chi-squared test).

Results. A comparative analysis of the structure and frequency of primary MNs showed that the incidence spectrum differs by sex across all study groups. Among male offspring, the main contribution came from MNs of the digestive tract; among female offspring — from MNs of the breast and female genital organs. A comparative analysis of "crude" cancer incidence rates showed a statistically significant excess of incidence rates in offspring of exposed mothers compared to similar rates in the offspring of exposed fathers. A significant excess of MN incidence rates was observed in offspring of exposed parents compared to the control group, both overall and for specific MN localizations. The highest proportion of MNs was observed in groups of Mayak PA workers with "zero" accumulated doses of external gamma radiation, both among offspring of exposed fathers and mothers and among individuals exposed *in utero*, which requires further detailed analysis.

Conclusions. The cohort of offspring of Mayak PA workers can be considered an important source of data for the epidemiological study of carcinogenic effects. Given the relatively young age of the cohort of Mayak PA offspring (47 years on average for offspring of exposed fathers, 51 years for offspring of exposed mothers, and 41 years for the control group), further epidemiological monitoring is necessary.

Keywords: offspring; malignant neoplasms; preconception exposure; *in utero* exposure; Mayak Production Association; cancer incidence; preconception doses; antenatal exposure doses

For citation: Tsareva Yu.V., Sosnina S.F., Okatenko P.V., Kabirova N.R. Cancer incidence in the offspring of Mayak Production Association workers: characteristics and analysis. *Extreme Medicine*. 2026. <https://doi.org/10.47183/mes.2026-493>

Funding: the work was carried out within the framework of applied scientific research "Technogenic exposure and its long-term medical consequences" (code "Consequences-25") based on the Federal Target Program "Ensuring Nuclear and Radiation Safety for 2016–2020 and for the period up to 2035".

Compliance with ethical principles: approval of the bioethics committee was not required, as the study was conducted based on anonymized archival materials.

Potential conflict of interest: the authors declare no conflict of interest.

✉ Yulia V. Tsareva ulichru2017@yandex.ru

Received: 26.03.2026 **Revised:** 13.05.2026 **Accepted:** 19.05.2026 **Online first:** 22 July 2026

УДК 613.648.4:616-006.04

КОГОРТА ПОТОМКОВ РАБОТНИКОВ ПО «МАЯК»: ХАРАКТЕРИСТИКА И АНАЛИЗ ОНКОЛОГИЧЕСКОЙ ЗАБОЛЕВАЕМОСТИ

Ю.В. Царева[✉], С.Ф. Соснина, П.В. Окатенко, Н.Р. Кабилова

Южно-Уральский федеральный научно-клинический центр медицинской биофизики Федерального медико-биологического агентства, Озерск, Россия

Введение. Изучение эффектов преконцептивного (до зачатия) и внутриутробного радиационного воздействия, в том числе риска возникновения злокачественных новообразований (ЗНО) у потомков лиц, подвергшихся профессиональному облучению, является неоднозначной проблемой радиационной эпидемиологии.

Цель. Эпидемиологический анализ канцерогенных эффектов среди потомков, чьи родители подвергались на ПО «Маяк» производственному преконцептивному облучению и облучению во время беременности.

Материалы и методы. Проведен ретроспективный анализ исходов в виде онкопатологии среди 35,5 тысячи человек, из которых 14 593 являлись потомками работников производственного объединения (ПО) «Маяк» — первого в России предприятия атомной промышленности, функционирующего с 1948 г. В группу сравнения вошли 20 872 человека, чьи родители не подвергались

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радиационному воздействию на производстве и не были переселенцами с радиоактивно загрязненных территорий. Исследуемые выборки сформированы из людей, рожденных в 1948–1988 гг. в закрытом административно-территориальном образовании (ЗАТО) г. Озерск, расположенном вблизи атомного объекта. Период наблюдения составил 72 года (1949–2020 гг.). Источниками данных для проведения эпидемиологического анализа онкологической заболеваемости у потомков, родители которых были работниками ПО «Маяк», являются: медико-дозиметрический регистр персонала ПО «Маяк», Детский регистр (включает население, подвергавшееся в детском возрасте техногенному воздействию за счет деятельности ПО «Маяк»), Регистр здоровья детского населения, Канцер-регистр и Регистр причин смерти населения ЗАТО г. Озерск. Информация о накопленных поглощенных дозах внешнего гамма-облучения извлечена из «Дозиметрической системы работников ПО «Маяк» — 2013». Статистический анализ проведен с использованием методов непараметрической статистики: сравнение частот проведено с использованием критерия χ^2 (Pearson's chi-squared test).

Результаты. Сравнительный анализ структуры и частоты первичных ЗНО показал, что спектр заболеваемости различается по полу во всех исследуемых группах. Среди мужчин-потомков основной вклад вносили ЗНО пищеварительного тракта, среди потомков женского пола — ЗНО молочной железы и женских половых органов. Сравнительный анализ «грубых» показателей онкозаболеваемости показал статистически значимое превышение уровня заболеваемости у потомков облученных матерей над аналогичными показателями в группе потомков облученных отцов. Отмечено значимое превышение уровня заболеваемости ЗНО у потомков облученных родителей по сравнению с контрольной группой как в целом, так и по отдельным локализациям ЗНО. Наибольший удельный вес ЗНО наблюдался в группах работников ПО «Маяк» с «нулевыми» накопленными дозами внешнего гамма-облучения как среди потомков облученных отцов и матерей, так и среди внутриутробно облученных людей, что требует последующего детального анализа.

Выводы. Когорту потомков работников ПО «Маяк» можно рассматривать в качестве важного источника данных для эпидемиологического изучения канцерогенных эффектов. Принимая во внимание относительно молодой возраст когорты потомков работников ПО «Маяк» (47 лет в среднем для потомков облученных отцов, 51 год для потомков облученных матерей и 41 год для контрольной группы), необходим дальнейший эпидемиологический мониторинг.

Ключевые слова: потомки; злокачественные новообразования; облучение до зачатия; внутриутробное облучение; производственное объединение «Маяк»; онкологическая заболеваемость; прекоцептивные дозы; дозы антенатального облучения

Для цитирования: Царева Ю.В., Соснина С.Ф., Окатенко П.В., Кабирова Н.Р. Когорта потомков работников ПО «Маяк»: характеристика и анализ онкологической заболеваемости. *Экстремальная биомедицина*. 2026. <https://doi.org/10.47183/mes.2026-493>

Финансирование: работа выполнена в рамках прикладной научно-исследовательской работы «Техногенное облучение и его отдаленные медицинские последствия» (шифр «Последствия-25») на основании Федеральной целевой программы «Обеспечение ядерной и радиационной безопасности на 2016–2020 гг. и на период до 2035 г.».

Соответствие принципам этики: не требовалось одобрение биоэтического комитета, поскольку исследование выполнено на основе обезличенных архивных материалов.

Потенциальный конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

✉ Царева Юлия Вячеславовна ulichru2017@yandex.ru

Статья поступила: 26.03.2026 **После доработки:** 13.05.2026 **Принята к публикации:** 19.05.2026 **Online first:** 22.07.2026

INTRODUCTION

Assessing the risk of malignant neoplasms (MNs) in the offspring of individuals exposed to radiation as a result of their occupational activities is a relevant but as yet unresolved problem in radiation epidemiology. Studies of the effects of parental exposure (preconception exposure of fathers and mothers and exposure of mothers during pregnancy) in different cohorts have not led to a unified understanding of the effects in the subsequent generation of offspring [1].

Extensive literature data are available on the results of animal experiments, in which the contribution of the radiation factor to adverse outcomes is beyond doubt [2–5]. However, it should be noted that the extrapolation of experimental data to humans must be performed with careful consideration of the characteristics of the biological systems being compared, the parameters of which are not always valid or permissible [6].

There is a large body of work reflecting the results of studies on the health consequences for offspring of parental radiation exposure for diagnostic or therapeutic

purposes [7, 8]. Such data should be treated critically, as these publications do not always provide actual radiation doses, but more often indicate the number of X-ray procedures performed. Furthermore, diagnostic exposure was usually prescribed for medical indications (multiple pregnancy, suspected abnormalities in mother and fetus, etc.), which could have initially influenced adverse reproductive outcomes.

A large body of work has focused on studying the health of offspring exposed to preconception/*in utero* radiation from the atomic bombings of Hiroshima and Nagasaki (Japan). These studies were conducted on a sufficiently large sample, involved long-term, multifaceted follow-up of the study population, and used modern tests [9, 10]. However, these studies have a number of limitations: there was a single acute exposure, doses were calculated, and there was a problem of selecting an adequate control group.

Some of the first studies on occupational exposure to radiation factors in people of reproductive age were conducted at the Southern Urals Federal Research and Clinical Center for Medical Biophysics

(SUFRCCMB). No significant evidence was found for the occurrence of malignant neoplasms in offspring depending on occupational preconception exposure of fathers and mothers, as well as exposure of mothers during pregnancy. This is most likely due to the small sample sizes, which did not allow for definitive conclusions regarding the presence or absence of a significant effect. Therefore, a decision was made to expand the observed cohort of offspring of workers at the Mayak Production Association (PA) — the country's first nuclear industry enterprise — and to conduct a comparative analysis of oncopathology in the expanded sample.

The study purpose is an epidemiological analysis of carcinogenic effects in the group of offspring whose parents were exposed to occupational preconception radiation and radiation during pregnancy.

MATERIALS AND METHODS

Sources of information

The data sources for conducting the epidemiological analysis of cancer incidence in offspring whose parents were Mayak PA workers are:

- Medical and dosimetric registry of personnel of the Federal State Unitary Enterprise “Mayak Production Association” (Mayak PA Registry) [11];
- Registry of the population of Ozersk exposed in childhood to technogenic impact due to the activities of Russia's first nuclear enterprise, Mayak PA (Children's Registry of Ozersk) [12];
- Child Population Health Registry of Ozersk [13];
- Population Cancer Registry of Ozersk [14];
- Registry of Causes of Death of the Population of the Closed Administrative-Territorial Unit (CATU) Ozersk [15];
- “Mayak Workers' Dosimetry System — 2013” [16].

Information on the date and place of birth of children and the vital status of offspring was obtained from the Children's Registry of Ozersk. Information on cases of primary MNs was obtained from the Population Cancer Registry of Ozersk. The Mayak PA Personnel Registry contains data on workers hired in 1948–1982 at the main (reactor, radiochemical, plutonium) production facilities and auxiliary (water treatment, repair and mechanical) plants. The registry includes 25,757 individuals (19,395 men — 75.3%; 6,362 women — 24.7%).

Information on accumulated absorbed doses of external gamma radiation was extracted from the “Dosimetry System of Mayak PA Workers — 2013.” The study used characteristics of accumulated absorbed doses of external gamma radiation to the gonads; preconception doses of parents were taken into account (the date of conception was considered to be 280 days before the birth of the child); doses to the

mothers' uterus were obtained using a developed algorithm for distributing annual doses across each period of pregnancy. A “zero dose” of occupational radiation exposure meant that the worker was part of the Mayak PA worker cohort, but during the preconception period / during pregnancy for female workers, occupational exposure doses were not recorded by an individual dosimeter.

Formation of study groups

The study was conducted along three main lines: examining effects among offspring of preconceptionally exposed fathers and mothers, as well as the consequences of *in utero* radiation exposure.

The list of selection criteria for offspring (for the main and control groups) includes the following conditions:

- years of birth of offspring: 1949–1988;
- offspring born in Ozersk — a closed administrative-territorial unit whose city-forming enterprise is Mayak PA;
- one of the parents began working at Mayak PA before the child's conception;
- child born alive;
- observation years: 1949–2020.

To analyze the effect of preconception exposure of fathers on MN incidence in their offspring, information was selected from the Children's Registry of Ozersk for children whose fathers could have been exposed to external gamma radiation during work at Mayak PA during the preconception period, while their mothers did not work at Mayak PA, were not cleanup workers of the 1957 accident at Mayak PA or the Chernobyl NPP, or members of the Ural cohort of accident-exposed population (UCAEP) [17], and were not exposed to occupational preconception radiation (Table 1).

To analyze the effect of preconception exposure of mothers and exposure during pregnancy on cancer incidence in their offspring, information was selected from the Children's Registry of Ozersk for children whose mothers could have been exposed to external gamma radiation during work at Mayak PA during the preconception period and during pregnancy, while information on the father was available for the children; fathers did not work at Mayak PA, were not cleanup workers of the 1957 accident at Mayak PA or the Chernobyl NPP, or members of the UCAEP cohort, and were not exposed to occupational preconception radiation (Table 1).

The control group included children whose parents did not work at Mayak PA before the child's conception, were not cleanup workers of the 1957 accident at Mayak PA or the Chernobyl NPP, were not members of the UCAEP cohort, and could not have received occupational exposure as they were not on the staff of Mayak PA (Table 1).

Table 1. Number of offspring included in the main and control groups

Sample parameters	Main group	Control group
Total offspring born 1949–1988 from the “Children’s Registry”	24,434	32,900
No information on the second parent	297	2854
Second parent worked at Mayak PA	8862	4476
Second parent is a cleanup worker, resettler, or member of the EURT cohort	277	2956
Second parent was exposed but was not on the staff of Mayak PA	405	1742
Number of offspring included in the study	14,593	20,872

Table compiled by the authors

Note. EURT — East Urals Radioactive Trace.

Table 2. Distribution of individuals and person-years of observation in the group of offspring born to fathers who may have been occupationally exposed at Mayak Production Association

Parameters	Males		Females		Total	
	abs. <i>n</i>	%	abs. <i>n</i>	%	abs. <i>n</i>	%
Offspring count	6694	51.4*	6342	48.6	13,036	100.0*
Person-years of observation	252,882		241,243		494,125	
Malignant neoplasm cases	209	3.1*	235	3.7*	444	3.4*
		47.1**		52.9**		100.0**
Offspring of fathers with non-zero preconception dose	5657	84.5*	5355	84.4*	11,012	84.5*
Offspring of fathers with zero preconception dose	1037	15.5*	987	15.6*	2024	15.5*

Table compiled by the authors

Note. * — % of the total number of offspring of that sex; ** — % of the total number of cases with malignant neoplasm.

The total follow-up period for the cohort of offspring was 72 years (01.01.1949–31.12.2020). The start of follow-up was considered the date of birth; the end of follow-up was the date of the event that occurred first: the date of MN diagnosis, the date of departure from the city, the date of last known vital status, the date of death, or the date of the end of cohort follow-up. The vital status as of 31.12.2020 is known for 95.8% of the cohort.

The creation of tabulated data began with the preparation of a text file containing the information required for the study on each member of the study cohort. After that, the resulting text file was processed by the Datab module of the Epicure software package [18] to obtain a file with tabulated data for further analysis.

Statistical analysis was performed using nonparametric statistics methods: frequency comparison was conducted using the χ^2 test (Pearson’s chi-squared test)

[19]. Differences were considered statistically significant at $p < 0.05$.

RESULTS

The group of offspring whose fathers were included in the Mayak PA worker registry and could have been exposed to occupational radiation comprised 13,036 individuals (Table 2). The number of children born to fathers with a “non-zero” dose of gonadal exposure at the time of the child’s conception was 11,012 (84.5% of the total offspring). There were no sex differences within this group. In total, 444 cases of primary malignant neoplasms were identified in this group, accounting for 3.4% of all offspring included in the group.

The size of the group of offspring whose mothers worked at Mayak PA and could have been exposed to preconception radiation is presented in Table 3. A total of

Table 3. Distribution of individuals and person-years of observation in the group of offspring born to mothers who may have been exposed to occupational radiation at the Mayak Production Association

Parameters	Males		Females		Total	
	abs. <i>n</i>	%	abs. <i>n</i>	%	abs. <i>n</i>	%
Offspring count	806	51.8*	751	48.2*	1557	100.0*
Person-years of observation	25,464		26,498		51,962	
Malignant neoplasm cases	38	4.7*	45	6.0*	83	5.3*
		45.8**		54.2**		100.0**
Offspring of mothers with non-zero preconception dose	564	70.0*	530	70.6*	1094	70.3*
Offspring of mothers with zero preconception dose	242	30.0*	221	29.4*	463	29.7*

Table compiled by the authors

Note. * — % of the total number of offspring of that sex; ** — % of the total number of cases with malignant neoplasm.

1,557 offspring were included in this group; 70.3% of the mothers had accumulated “non-zero” doses of ionizing radiation by the time of conception. In total, 83 cases of MNs were diagnosed in this group, accounting for 5.3% of all offspring.

The size of the group of individuals who could have been exposed *in utero* coincides with the size of the group of offspring of mothers who were part of the Mayak PA worker cohort (1557 individuals). However, in this group, the number of individuals exposed to gamma radiation during intrauterine development (59.8% of offspring with a “non-zero” *in utero* dose) is smaller compared to the group where mothers worked at Mayak PA and could have been exposed to preconception radiation (70.3% of offspring from mothers with a “non-zero” preconception dose).

The size of the control group was 20,872 individuals with a proportional sex ratio (50.9% male, 49.1% female, $p > 0.05$). In total, 559 primary cases of MNs were diagnosed in this group, accounting for 2.7% of all offspring included in this group.

Distribution of offspring according to dose characteristics of parental exposure

Tables 4–6 present the distribution of offspring depending on the accumulated preconception/*in utero* dose of external gamma radiation and the presence of a diagnosis of “Malignant neoplasm.” The distribution of offspring according to dose intervals of accumulated preconception doses of external gamma radiation for fathers who were Mayak PA workers (Table 4) was relatively uniform, ranging 11.2–19% in each dose category. “Zero” doses of preconception radiation exposure accounted for 15.5% of the group. Meanwhile, the highest proportions of offspring with MNs were recorded both

in the “zero” preconception dose category and in the category of maximum accumulated doses exceeding 500 mGy — 18.9% and 20%, respectively. Almost equal proportions (9.0–9.9% each) were observed in the dose categories 20–200 mGy.

The distribution of offspring of female workers at Mayak PA (Table 5) showed that one third of the offspring group were born to mothers whose accumulated preconception doses were characterized by a “zero” level, meaning that the female worker was part of the Mayak PA worker cohort, but in the period before the child’s conception, her occupational exposure doses were not recorded by an individual dosimeter. The dose range exceeding 500 mGy accounted for 16.6% of this offspring group. Among offspring with MNs, the same trend was observed: 30.1% of offspring had mothers with a “zero” exposure dose, while for one in ten offspring with MNs (9.6%), the mother was exposed to preconception external gamma radiation at a dose exceeding 500 mGy.

The distribution of offspring according to categories of accumulated antenatal doses of external gamma radiation (Table 6) as a result of the occupational activities of mothers at Mayak PA showed that more than 40% of this group were in the “zero” dose category for *in utero* exposure: during pregnancy, the mother was a Mayak PA worker, but during pregnancy, occupational exposure doses were not recorded by an individual dosimeter. The number of offspring exposed to ionizing radiation *in utero* at doses exceeding 100 mGy was 243 individuals (15.6% of the number of offspring with “non-zero” *in utero* exposure doses).

Analysis of the proportion of offspring depending on the categories of antenatal doses showed an inverse proportionality: as the dose characteristics increased,

Table 4. Distribution of offspring born to fathers who may have been exposed to occupational radiation at the Mayak Production Association, by sex, paternal radiation dose, and presence of malignant neoplasms

Dose*, mGy	Number of offspring, abs. <i>n</i> (%)			Number of offspring with MNs, abs. <i>n</i> (%)		
	males	females	total	males	females	total
=0	1037 (15.5)	987 (15.6)	2024 (15.5)	39 (18.7)	45 (19.1)	84 (18.9)
<20	1239 (18.5)	1232 (19.4)	2471 (19.0)	28 (13.4)	38 (16.2)	66 (14.9)
<50	947 (14.1)	873 (13.8)	1820 (14.0)	22 (10.5)	18 (7.7)	40 (9.0)
<100	827 (12.4)	784 (12.4)	1611 (12.4)	19 (9.1)	25 (10.6)	44 (9.9)
<200	776 (11.6)	679 (10.7)	1455 (11.2)	24 (11.5)	20 (8.5)	44 (9.9)
<500	888 (13.3)	877 (13.8)	1765 (13.5)	37 (17.7)	40 (17.0)	77 (17.3)
500+	980 (14.6)	910 (14.3)	1890 (14.5)	40 (19.1)	49 (20.9)	89 (20.0)
Total	6694	6342	13,036	209	235	444

Table compiled by the authors
Note. * — accumulated preconception external gamma radiation dose to paternal gonads; MNs — malignant neoplasms.

Table 5. Distribution of offspring born to mothers who may have been exposed to occupational radiation at the Mayak Production Association, by sex, maternal radiation dose, and presence of malignant neoplasms

Dose*, mGy	Number of offspring, abs. <i>n</i> (%)			Number of offspring with MNs, abs. <i>n</i> (%)		
	males	females	total	males	females	total
=0	242 (30.0)	221 (29.4)	463 (29.7)	8 (21.1)	17 (37.8)	25 (30.1)
<20	106 (13.2)	119 (15.8)	225 (14.5)	4 (10.5)	8 (17.8)	12 (14.5)
<50	79 (9.8)	55 (7.3)	134 (8.6)	5 (13.2)	3 (6.7)	8 (9.6)
<100	69 (8.6)	59 (7.9)	128 (8.2)	5 (13.2)	2 (4.4)	7 (8.4)
<200	56 (6.9)	73 (9.7)	129 (8.3)	3 (7.9)	6 (13.3)	9 (10.8)
<500	122 (15.1)	98 (13.0)	220 (14.1)	7 (18.4)	7 (15.6)	14 (16.9)
500+	132 (16.4)	126 (16.8)	258 (16.6)	6 (15.8)	2 (4.4)	8 (9.6)
Total	806	751	1557	38	45	83

Table compiled by the authors
Note. * — dose of external gamma radiation to the mother’s gonads accumulated before the child’s conception; MNs — malignant neoplasms.

the proportion of offspring decreased from 40.2% to 0.6%.

Among offspring with MNs, the distribution was similar: the highest contribution (39.8%) was observed among “zero” antenatal doses, with a subsequent progressive decrease as the accumulated doses of external gamma radiation increased.

Structure of primary malignant neoplasms

In the structure of MN incidence among individuals whose fathers could have been exposed to occupational radiation, the first place was occupied by MNs of the digestive organs (22.1%), mainly due to colon cancer; the second place was occupied by breast tumors

Table 6. Distribution of individuals in the offspring group exposed *in utero* to radiation, by sex, maternal radiation dose, and presence of malignant neoplasms

Dose*, mGy	Number of offspring, abs. n (%)			Number of offspring with MNs, abs. n (%)		
	males	females	total	males	females	total
=0	317 (39.3)	309 (41.1)	626 (40.2)	14 (36.8)	19 (42.2)	33 (39.8)
<20	196 (24.3)	172 (22.9)	368 (23.6)	11 (28.9)	10 (22.2)	21 (25.3)
<50	87 (10.8)	80 (10.7)	167 (10.7)	5 (13.2)	8 (17.8)	13 (15.7)
<100	83 (10.3)	70 (9.3)	153 (9.8)	2 (5.3)	2 (4.4)	4 (4.8)
<200	63 (7.8)	69 (9.2)	132 (8.5)	2 (5.3)	2 (4.4)	4 (4.8)
<500	53 (6.6)	48 (6.4)	101 (6.5)	4 (10.5)	4 (8.9)	8 (9.6)
500+	7 (0.9)	3 (0.4)	10 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Total	806	751	1557	38	45	83

Table compiled by the authors

Note. * — dose of external gamma radiation *in utero*; MNs — malignant neoplasms.

(17.8%) due to 78 cases — 33.2% of all MNs among female offspring; the third place was occupied by neoplasms of lymphoid and hematopoietic tissues (10.6%), of which 42.6% were represented by Hodgkin's lymphomas, 34.0% were leukemias, half of which were specified as lymphoid leukemias. Only among male offspring was a single case of monocytic leukemia diagnosed.

The structure of MNs by sex of the offspring differed significantly: among male offspring, the main proportion in the cancer incidence structure was occupied by MNs of the digestive organs (29.2%), the second place — by leukemias and hemolymphoblastoses (17.2%), the third place — by MNs of the respiratory organs (12.0%); whereas among female offspring, the leading place was occupied by breast tumors (33.2%),

the second place — by tumors of the female genital organs (23.4%), and only 15.7% were MNs of the digestive organs.

The cancer incidence spectrum of offspring whose mothers could have been exposed during work at Mayak PA, both preconceptionally and during pregnancy, is presented in the figure.

The main proportion in the entire group was accounted for by malignant tumors of the digestive system (33.7%), with breast MNs in second place, and female genital organ cancers in third (12.0%). Among both male and female offspring, the first place in the structure, as in the entire group, was occupied by MNs of the digestive organs (44.7% and 24.4%, respectively). However, while among female offspring the structure of cancer incidence did not differ from that of the overall

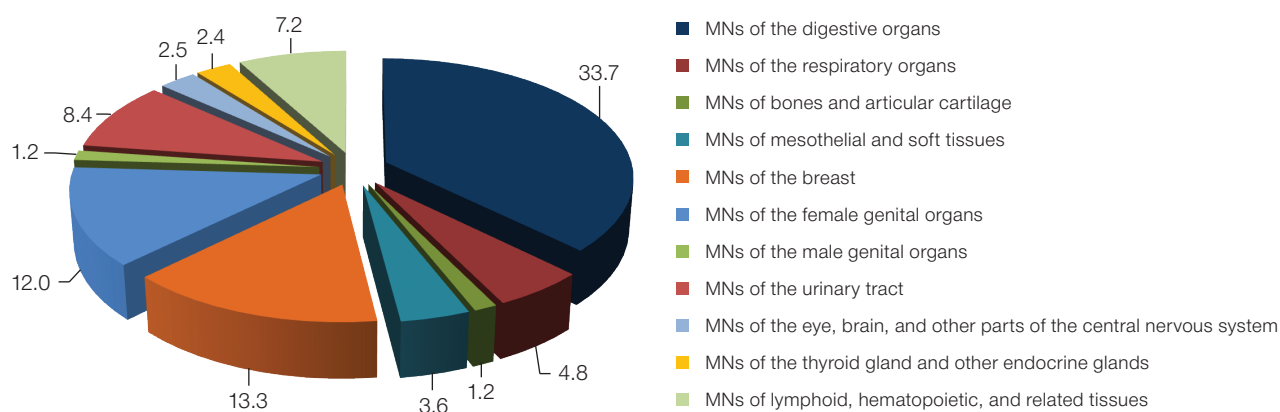


Figure prepared by the authors

Fig. Structure of cancer incidence among offspring whose mothers could have been exposed to occupational radiation at the Mayak Production Association (%). MNs — malignant neoplasms

Table 7. Cancer incidence rate among offspring whose fathers may have been exposed to occupational radiation at the Mayak Production Association

MNs localizations	Cancer incidence rate					
	mal., abs. n	× 10 ⁵	fem., abs. n	× 10 ⁵	total, abs. n	× 10 ⁵
MNs of lip, oral cavity and pharynx (C00–C14)	14	5.5 ^{1,2}	3	1.2 ²	17	3.4 ²
MNs of digestive organs (C15–C26)	61	24.1 ^{1,2,3}	37	15.3 ²	98	19.8 ^{2,3}
MNs of respiratory and intrathoracic organs (C30–C39)	25	9.9 ¹	8	3.3	33	6.7
MNs of bones and articular cartilage (C40–C41)	1	0.4	2	0.8	3	0.6
Melanoma and other MN of skin (C43–C44)	11	4.3	10	4.1	21	4.2
MNs of mesothelial and soft tissues (C45–C49)	3	1.2	9	3.7	12	2.4
MNs of breast (C50)	1	0.4	78	32.3 ^{1,3}	79	16.0 ³
MNs of female genital organs (C51–C58)	0	0.0	55	22.8	55	11.1
MNs of male genital organs (C60–C63)	20	7.9	0	0.0	20	4.0
MNs of urinary tract (C64–C68)	21	8.3 ¹	4	1.7 ²	25	5.1 ²
MNs of eye, brain and other parts of CNS (C69–C72)	6	2.4	8	3.3	14	2.8
MNs of thyroid gland and other endocrine glands (C73–C75)	6	2.4	9	3.7	15	3.0
Secondary, ill-defined and unspecified MNs (C76–C80)	4	1.6	1	0.4	5	1.0
MNs of lymphoid, hematopoietic and related tissues (C81–C96)	36	14.2 ^{1,3}	11	4.6 ³	47	9.5
Total	209	82.6 ^{2,3}	235	97.4 ^{2,3}	444	89.9 ^{2,3}

Table compiled by the authors

Note. MNs — malignant neoplasms; ¹ — statistically significant differences between males and females in the group; ² — statistically significant differences between the group of exposed fathers and the group of exposed mothers; ³ — statistically significant differences compared to the control group.

group, among males the second place was shared by tumors of the respiratory organs and urinary tract (10.5% each).

In the structure of MN incidence in the comparison group, as among offspring of Mayak PA workers, the first place was occupied by malignant tumors of the digestive organs (21.3%), the second place by tumors of the female genital organs (14.0%), and the third place by breast MNs (12.0%). The structure of cancer incidence among male offspring in the comparison group differed from that among male offspring of exposed parents. Thus, among male offspring, the leading positions were occupied by malignant neoplasms of the digestive system (26.9%), the second place by tumors of the respiratory system (16.7%), and the third place by MNs of lymphoid, hematopoietic, and related tissues (12.7%). The structure of MN incidence among female offspring in the comparison group differed from the structure among female offspring of exposed mothers in terms of the

percentage contribution of MNs: first place — tumors of the female genital organs (24.8%), second place — breast MNs (21.0%), third place — diseases of the digestive organs (16.9%).

Comparative analysis of cancer incidence in the groups

This study examined “crude” cancer incidence rates among offspring of occupationally exposed parents compared to controls.

In the group of offspring whose fathers could have been exposed to occupational radiation at Mayak PA, cancer incidence rates were 89.9×10^5 person-years overall, among male offspring — 82.6×10^5 , among female offspring — 97.4×10^5 (Table 7). The incidence level for different classes of malignant neoplasms varied by sex.

Among women, the first place was occupied by breast tumors (32.3×10^5). The incidence rate of MNs of

the digestive system in women was more than 1.5 times lower compared to men (15.3×10^5 vs. 24.1×10^5), and these differences were statistically significant ($\chi^2 = 4.69$; $p = 0.03$). At the same time, incidence rates in men were significantly higher than in women for such disease classes as MNs of the lip, oral cavity and pharynx ($\chi^2 = 6.55$; $p = 0.01$), MNs of the respiratory organs ($\chi^2 = 7.89$; $p = 0.005$), MNs of the urinary tract ($\chi^2 = 10.69$; $p = 0.001$), and MNs of lymphoid, hematopoietic and related tissues ($\chi^2 = 12.03$; $p = 0.001$).

The incidence rate of malignant neoplasms among offspring of exposed mothers was 159.7×10^5 overall in the group; cancer incidence rates in female offspring were somewhat higher than in male offspring (169.8×10^5 and 149.2×10^5 , respectively), but this excess was not statistically significant ($\chi^2 = 1.26$; $p > 0.05$).

The main contribution to the cancer incidence level in both men and women was made by tumors of the digestive organs (66.8×10^5 and 41.5×10^5 , respectively) without significant differences ($\chi^2 = 0.91$; $p > 0.05$). A significant role among male offspring was played by MNs of the respiratory and genitourinary organs (15.7×10^5 each); among female offspring — by breast and female genital organ tumors (41.5×10^5 and 37.7×10^5). For individual disease classes, no statistically significant differences were found, including for MNs of the respiratory organs, where the incidence rate among men was higher compared to women: $\chi^2 = 3.74$; $p > 0.05$. An exception was MNs of the genital organs, which were significantly more frequently diagnosed among female offspring (37.7×10^5) compared to men (3.9×10^5 ; $\chi^2 = 8.08$; $p = 0.004$).

The predominant cancer incidence rates in the group of offspring of unexposed parents were tumors of the digestive tract (18.8×10^5), mainly due to the contribution of male offspring (20.8×10^5 ; $\chi^2 = 0.99$; $p > 0.05$). They were followed by tumors of the genital organs (12.3×10^5) due to the contribution of female offspring rates (24.6×10^5), significantly exceeding the frequency of MNs of the genital organs among men (8.8×10^5 ; $\chi^2 = 25.6$; $p < 0.0001$). Third place was occupied by MNs of lymphoid, hematopoietic, and related tissues (10.4×10^5), with incidence rates among men and women in this group being almost identical (9.8×10^5 and 11.1×10^5 , respectively; $\chi^2 = 0.41$; $p = 0.50$).

It is important to note that in the group of offspring of unexposed parents, the overall MN incidence rate among female offspring was significantly higher than among males (99.2×10^5 vs. 77.3×10^5 ; $\chi^2 = 11.6$; $p = 0.001$). For individual disease classes, a significant excess among male offspring was recorded only for MNs of the respiratory organs ($\chi^2 = 24.86$; $p < 0.0001$). Among women, a significant excess over the analogous rates in men, in addition to the aforementioned MNs of the genital organs, was found in the class of skin MNs ($\chi^2 = 3.87$; $p = 0.049$), and tumors of the thyroid gland and other endocrine glands ($\chi^2 = 14.1$; $p < 0.001$).

When comparing cancer incidence rates between groups of offspring of exposed parents, a substantial (more than 1.5 times) excess of cancer incidence rates was observed in the group of offspring of exposed mothers (159.7×10^5) compared to the analogous rate in the group where only the father was exposed (89.9×10^5); and this excess was significant ($\chi^2 = 14.8$; $p < 0.0001$). The excess in MN incidence in the group of offspring whose mothers could have been exposed to occupational radiation mainly concerned tumors of the digestive tract, both in the overall group ($\chi^2 = 17.8$; $p < 0.001$), and among men ($\chi^2 = 10.3$; $p = 0.002$) and women ($\chi^2 = 7.8$; $p = 0.005$). This also concerned tumors of the lip, oral cavity and pharynx among offspring of exposed mothers overall ($\chi^2 = 11.95$; $p = 0.001$), among male offspring ($\chi^2 = 7.75$; $p = 0.005$) and female offspring ($\chi^2 = 4.57$; $p = 0.032$). Furthermore, a significant excess in incidence rates was observed for MNs of the urinary tract ($\chi^2 = 4.22$; $p = 0.04$) in the overall group, mainly due to incidence in women ($\chi^2 = 7.71$; $p = 0.006$).

When comparing cancer incidence rates between offspring whose fathers could have been exposed to occupational radiation and the comparison group, a statistically significant excess in the incidence rate of breast MNs was observed among female offspring of exposed fathers compared to the analogous rate in control offspring (32.3×10^5 and 20.8×10^5 , respectively; $\chi^2 = 15.2$; $p < 0.0001$), as well as for MNs of the digestive organs (19.8×10^5 and 18.8×10^5 , respectively; $\chi^2 = 4.16$; $p = 0.041$) due to the contribution of male offspring ($\chi^2 = 4.75$; $p = 0.029$). Furthermore, among offspring of exposed fathers, the frequency of MNs of lymphoid, hematopoietic, and related tissues significantly exceeded the control rates in both men ($\chi^2 = 6.46$; $p = 0.011$) and women ($\chi^2 = 4.01$; $p = 0.045$).

The MN incidence rate in the group of offspring of exposed mothers significantly exceeded the analogous rate in the control group, and this excess applied both to the overall cancer incidence rates in the group ($\chi^2 = 36.67$; $p < 0.0001$), and among male ($\chi^2 = 18.02$; $p < 0.0001$) and female offspring ($\chi^2 = 18.98$; $p < 0.0001$). Regarding the incidence of malignant neoplasms by individual classes, among offspring of exposed mothers, a statistically significant excess in incidence rate over the control was noted for the class of MNs of the digestive organs ($\chi^2 = 33.57$; $p < 0.0001$), MNs of the lip, oral cavity and pharynx ($\chi^2 = 18.09$; $p < 0.0001$), breast cancer ($\chi^2 = 6.21$; $p = 0.013$), and urinary tract ($\chi^2 = 6.91$; $p = 0.009$).

DISCUSSION

The likelihood of developing oncological pathology among offspring of individuals exposed to radiation as a result of occupational activity remains a subject of scientific inquiry, as the results obtained in numerous studies across different cohorts of exposed individuals are quite

contradictory. The results of experimental studies confirm that radiation exposure can induce various types of tumors in the next generation [2, 5]. However, the contribution of parental radiation exposure to carcinogenesis in the offspring of exposed individuals remains an open problem [1].

Considering the pathophysiological prerequisites for the risk of long-term consequences, including malignant neoplasms, in exposed individuals and their offspring, it is important to note that radiation exposure results in damage that causes genetic and epigenetic shifts, leading to changes in protein expression levels due to methylation of cytosine residues in DNA, histone modifications, and regulation of microRNA expression, thereby contributing to oncogenesis [20].

In this regard, studies of health indicators of offspring of Mayak PA workers — the leader of the nuclear industry in Russia, operating since 1948 — are of particular interest. The unique features of the Mayak PA worker cohort compared to other cohorts of nuclear energy professionals worldwide include: a long follow-up period comparable to the data from the Radiation Effects Research Foundation (RERF) on atomic bombing victims and their offspring, but characterized by prolonged radiation exposure from both external and internal irradiation (incorporated Pu-239); measured individual doses for personnel and detailed information on the occupational history of each worker; a high proportion of female workers (25%) who were exposed to ionizing radiation sources at work during their reproductive years; unified medical care for Mayak PA workers and the population of the CATU Ozersk, whose main enterprise is Mayak PA.

A retrospective analysis of MNs followed over a 72-year observation period not only revealed significant differences in the spectrum and frequency of MNs when compared to the group of offspring of unexposed parents but also noted differences between offspring of occupationally exposed fathers and mothers. For example, when compared with the control, among offspring of exposed parents, a statistically significant excess of certain classes of MNs was observed, in particular: of the digestive system, most often represented by MNs of the colon; breast MNs; hemolymphoblastoses (in offspring of exposed fathers). A significantly higher frequency of all primary MNs (of the digestive system, lip, oral cavity and pharynx, and urinary tract) was observed among offspring of exposed mothers compared to the group of offspring of exposed fathers. In each studied group, differences in the MN spectrum depending on the sex of the offspring were noted, which is consistent with national [21, 22] and international data [23, 24].

The distribution of offspring by categories of accumulated preconception and *in utero* doses indicated a significant percentage of parent workers with

so-called “zero” doses, where during work at Mayak PA in the preconception or antenatal period, no doses of external gamma radiation were recorded by individual dosimeters. On one hand, this may reflect occupational safety of female workers, who were promptly transferred to radiation-safe areas of the enterprise when pregnancy was established. On the other hand, this fact requires special attention and study, as it relates to the period of the establishment of the production facility and the dosimetry service, and indicates the importance of further analysis of other types of occupational exposure and the combined effects of various occupational factors.

It is important to note that the formed groups of offspring of female Mayak PA workers who were exposed to preconception occupational radiation exposure and radiation during pregnancy coincided in quantitative characteristics, including MNs, which did not allow a comparative analysis of the spectrum and frequency of oncopathology between these groups. From a pathogenetic point of view, it is also impossible to separate the effects of preconception and *in utero* exposure, since each female worker could have been exposed to preconception occupational radiation before the establishment of pregnancy. However, a planned future statistical analysis of carcinogenic risk depending on accumulated doses, separately for preconceptionally exposed and *in utero* exposed offspring, is quite feasible.

Another limitation of the study was the relatively small number of outcomes in the form of MNs of certain localizations, which reduced the statistical power of the analysis by nosological forms. It should be noted that despite the long follow-up period of the offspring cohort (72 years), its average age is quite young (47 years on average for offspring of exposed fathers, 51 years for offspring of exposed mothers, and 41 years for individuals included in the control group) for the manifestation of possible effects in the form of oncopathology; therefore, subsequent epidemiological monitoring is required. Similar information is reported by researchers of the offspring cohort of atomic bombing victims in Japan, noting the absence of significant risk estimates for MN development and cancer death, and pointing to the “relative youth of the F1 offspring cohort” [9, 25].

CONCLUSIONS

As a result of a retrospective study of cancer incidence in the group of offspring of workers exposed to external gamma radiation during work at Mayak PA ($n = 14,593$), compared to a control group of offspring whose parents were not exposed to radiation before the child's conception ($n = 20,872$), the following conclusions were drawn:

- the leading position in the structure of cancer incidence in all groups was occupied by MNs of the digestive organs;

- the structure of malignant neoplasm incidence in the groups differs by sex: among male offspring, the main contribution to the incidence structure is made by MNs of the digestive organs; among women — by MNs of the breast and genital organs;
- a comparative analysis of “crude” cancer incidence rates showed a statistically significant excess in the incidence level of offspring of exposed mothers compared to similar rates in the group of offspring of exposed fathers;
- a significant excess in MN incidence was noted in offspring of Mayak PA workers compared to the group of offspring of unexposed parents for

certain localizations: MNs of the digestive tract, breast (among all offspring of exposed parents); MNs of the lip, oral cavity and pharynx, female genital organs, and urinary tract (among offspring of exposed mothers), and hemolymphoblastoses (among male offspring of exposed fathers).

Given the relatively young age of the observed cohort (47 years on average for offspring of exposed fathers, 51 years for offspring of exposed mothers, and 41 years for individuals included in the control group), it is necessary to continue epidemiological monitoring with subsequent analysis of carcinogenic risk in offspring of exposed parents, taking into account radiation exposure doses.

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Authors' contributions. All authors confirm that their contributions meet the ICMJE criteria for authorship. The primary contributions are distributed as follows: Yulia V. Tsareva — conceptualization, formal analysis, manuscript drafting, writing and editing; Svetlana F. Sosnina — analysis, results interpretation, text editing, visualization; Pavel V. Okatenko — software, statistical data processing, visualization; Nailya R. Kabirova — analysis, results interpretation, text editing.

Authors:

Yulia V. Tsareva, Cand. Sci. (Med.), ORCID: <https://orcid.org/0000-0001-5559-4457>
Svetlana F. Sosnina, Dr. Sci. (Med.), ORCID: <https://orcid.org/0000-0003-1553-0963>
Pavel V. Okatenko, ORCID: <https://orcid.org/0000-0002-8260-1808>
Nailya R. Kabirova, ORCID: <https://orcid.org/0000-0001-7724-6103>