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Cancer Mortality Following *In Utero* Exposure Among Offspring of Female Mayak Worker Cohort Members

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Abstract

Little is known about long-term cancer risks following *in utero* radiation exposure. We evaluated the association between *in utero* radiation exposure and risk of solid cancer and leukemia mortality among 8,000 offspring, born from 1948–1988, of female workers at the Mayak Nuclear Facility in Ozyorsk, Russia. Mother's cumulative gamma radiation uterine dose during pregnancy served as a surrogate for fetal dose. We used Poisson regression methods to estimate relative risks (RRs) and 95% confidence intervals (CIs) of solid cancer and leukemia mortality associated with *in utero* radiation exposure and to quantify excess relative risks (ERRs) as a function of dose. Using currently available dosimetry information, 3,226 (40%) offspring were exposed *in utero* (mean dose = 54.5 mGy). Based on 75 deaths from solid cancers (28 exposed) and 12 (6 exposed) deaths from leukemia, *in utero* exposure status was not significantly associated with solid cancer: RR = 0.94, 95% CI 0.58 to 1.49; ERR/Gy = −0.1 (95% CI < −0.1 to 4.1), or leukemia mortality; RR = 1.65, 95% CI 0.52 to 5.27; ERR/Gy = −0.8 (95% CI < −0.8 to 46.9). These initial results provide no evidence that low-dose gamma *in utero* radiation exposure increases solid cancer or leukemia mortality risk, but the data are not inconsistent with such an increase. As the offspring cohort is relatively young, subsequent analyses based on larger case numbers are expected to provide more precise estimates of adult cancer mortality risk following *in utero* exposure to ionizing radiation.

INTRODUCTION

Age at exposure is an important determinant of the association between ionizing radiation exposure and cancer risk with the highest risks observed among individuals exposed at the youngest ages (1). The nature of risk following *in utero* radiation exposure is less clear. Case-control studies have reported associations between *in utero* radiation exposure from diagnostic X rays and childhood leukemia (2–5). In the large Oxford Survey of Childhood Cancers (6), there was also an increased risk for solid cancer mortality, but summary estimates from other studies are generally lower and not statistically significant (2, 5). Prospective epidemiological data regarding risk of childhood cancer from medical radiation exposure *in utero* (2, 5, 7), as well as studies of offspring of occupationally exposed mothers (8, 9), are limited and have not found strong evidence for an increased risk of either

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childhood leukemia or solid cancer. To date, the only published prospective data of adult-onset cancer following *in utero* exposure come from atomic bomb survivors. Analyses of that cohort suggest a significant dose-related increased risk of solid cancer incidence and mortality at attained age ≥12 years following *in utero* exposure (10, 11).

The study of offspring of female workers at the Mayak Nuclear Facility in Ozyorsk, Russia, presents a unique opportunity to examine both childhood and adult cancer risk following *in utero* radiation. In this report, we present preliminary risks estimates for mortality from solid cancers and leukemia in the offspring cohort and evaluate whether offspring's gender and attained age modify the radiation effect.

MATERIALS AND METHODS

Study Population

The Mayak nuclear facility in Ozyorsk, Russia, opened in 1948 as the first and largest nuclear weapons facility in the former Soviet Union. The Mayak Worker Cohort is a study of nearly 30,000 workers, first employed at the Mayak facility in the years 1948–1982. Detailed descriptions of the Mayak Worker Cohort study population and follow-up methods (12–14) and dose reconstruction methods (15–17) have been previously published. The main plants of the facility consisted of nuclear reactors, a radiochemical plant and a plutonium production plant (16). Workers at each of the plants were exposed to external γ radiation, while radiochemical and plutonium plant workers also received internal plutonium exposures due to inhalation of plutonium aerosols. Workers employed at auxiliary plants at Mayak had much lower potential for external radiation exposure than workers at the main plants and virtually no internal exposure. The highest external and internal exposures occurred during the earliest years of operation (1948 to mid 1950s).

In addition to the Mayak Worker Cohort, in the mid 1990s, the Southern Urals Biophysics Institute created a registry of approximately 72,000 individuals born between 1934 and 1988 who lived in Ozyorsk for at least 1 year before their 15th birthday. This registry, which is known as the Ozyorsk Offspring Cohort [referred to as the Mayak Children's Cohort (18)], includes offspring of Mayak workers and other children meeting the above mentioned age and residential history criteria. For both the Ozyorsk Offspring Cohort and Mayak Worker Cohort, vital status follow-up and cause of death are actively ascertained using address bureau records and vital statistics data (including death certificates and autopsy reports) (18).

In recent years, efforts have been made to create a common roster with unique individual IDs for the Ozyorsk Offspring Cohort and Mayak Worker Cohort. This roster makes it possible to determine whether or not an Ozyorsk Offspring Cohort member or his or her parents are members of the Mayak Worker Cohort. As we were specifically interested in the effects of *in utero* exposure, we restricted the analysis to Ozyorsk Offspring Cohort members born in Ozyorsk in the years 1948 to 1988 whose mothers were in the Mayak Worker Cohort (n = 8,562). After excluding 562 individuals with less than 1 year of follow-up, the analytic cohort included 8,000 Ozyorsk Offspring Cohort members. This study was record-based and did not involve contact with the cohort members. The project was reviewed and approved by the Institutional Review Board of the Southern Urals Biophysics Institute.

Dosimetry

All organ dose estimates used in these analyses were based on Mayak film badge records, individual work history information and the recently updated Mayak worker dosimetry system (MWDS-08), a refined version of MWDS-2005 (16). For each mother, annual

uterine doses for each year worked had been calculated. If no dose was provided for a given year, the mother was assumed to be unexposed in that year. Monthly film badge measurements were available for mothers of 1,513 offspring exposed *in utero*.

In Utero Exposure

We used mother's cumulative γ radiation uterine dose during pregnancy as a surrogate for fetal dose. This approach was also used to estimate *in utero* dose in the atomic bomb survivor cohort (10, 11). As we did not have individual data on length of gestation, the pregnancy was assumed to begin 280 days before the child's birth date. The dose during pregnancy was then calculated using monthly doses.

In the absence of monthly doses, we developed an algorithm to apportion the annual uterine dose to the months of the pregnancy. To do this, it was first necessary to determine which months a woman was likely to have worked in a given year. We randomly selected 25 medical records for female Mayak employees in each of 4 time periods (1948–1954, 1955–1959, 1960–1969, ≥1970) to investigate the changing distributions of pre- and postnatal maternity leave and to ascertain patterns of pregnant women being moved to "clean" (no radiation exposure) workplaces in the latter months of pregnancy. Although equal numbers of medical records were selected for each time period, maternity leave and related data were most complete for the pre-1960s. Our review of occupational medical records suggested that women had longer maternity leave after 1960 than before.

We divided the annual dose by the months worked in a given year (i.e., assuming that none of the exposure occurred during the pre- and post-birth maternity leave period). Doses from the months during pregnancy were then summed to estimate the *in utero* dose. For children born before 1960, the algorithm assumed that none of the mother's annual dose occurred between the 60 days before the child's birth date or the 115 days after the child's birth. For children born after 1960, the numbers of pre- and post-birth exclusion periods were 115 and 150 days, respectively. Sensitivity analyses were carried out to examine the impact of modifying these assumptions on the excess relative risk estimate. We did this by adjusting the number of days worked before and after the child's birth and apportioning annual dose over those days.

Additional Radiation Exposures

Mothers of approximately 40% of cohort members had some potential for occupational plutonium exposure during or prior to the pregnancy, although <5% would have had potential for substantial plutonium exposure based on their work histories. Efforts are currently underway to estimate fetal plutonium doses, expected to be small given previous studies of placental transfer of plutonium (19), are not yet available. For purposes of adjusting for potential plutonium exposure in our evaluation of γ radiation exposure, we used a categorical surrogate for mother's plutonium exposure defined by work location and calendar year of hire that was developed for Mayak Worker Cohort cancer analyses (12, 13). Since plutonium, unlike γ radiation, can remain in the body and continue to expose organs of interest, we used the maximum surrogate value for any time up to 1 year before the child's birth. We also examined father's maximum plutonium surrogate up to 1 year before the child's birth. Maternal (ovarian) and paternal (testicular) preconception doses were also evaluated as covariates and based on cumulative dose up to 2 years before the child's birth year. We also considered offspring's own occupational exposure as approximately 15% of the offspring subsequently worked at Mayak and are part of the Mayak Worker Cohort.

Statistical Methods

Participants were followed from age 1 year until death (n = 698), migration out of Ozyorsk (n = 2,762), or December 31, 2008 (n = 4,540), whichever occurred first. Cancer deaths were ascertained from the underlying cause of death on death certificates. We censored offspring at the time of migration from Ozyorsk as the proportion of deaths with unknown cause was substantially higher for migrants (19%) than for non-migrants (4%).

We used Poisson regression methods [Epicure, AMFIT module, (20)] to quantify the excess relative risk (ERR) as a function of dose for solid cancer mortality and leukemia mortality separately. The person-year table was stratified on gender and mother's plant of employment during pregnancy (none, other, reactor, radiochemical, plutonium, as reported in the Mayak work history data used in the computation of MWDS-08 doses), 5-year categories of attained age and calendar year, birth year (<1954, 1954–1959, 1960–1964, 1965–1969, ≥1970), *in utero* dose (none, <10, 10–<20, 20–<50, 50–<100 and ≥100 mGy), mother's age at birth (<15, 15–<20, 20–<25, 25–<30, 30–<40, ≥40), mother's and father's plutonium surrogate, father in the Mayak Worker Cohort (no, yes), maternal and paternal preconception doses (none, 10, 10–<20, 20–<50, 50–<100, 100–<250, and ≥250 mGy), and offspring's own inclusion in the Mayak Worker Cohort (no, yes). The person-year table used for the primary analyses has 81,653 cells with non-zero person-years.

These analyses were based on linear excess relative risk models of the form $\lambda_0(a,s,z)[1 + \beta d_{iu})]$, where $\lambda_0()$ is the baseline hazard (rate) function, stratified on attained age (<15, 15–<25, 25–<35, 35–<45, 45–<55, ≥55) (a) and gender (s). For some analyses, the baseline was allowed to depend on other factors (z) such as *in utero* exposure status, birth year, mother's age at birth, mother's work place (plant), father in the Mayak Worker Cohort, or offspring's own inclusion in the Mayak Worker Cohort. We adjusted for offspring's own employment at Mayak using a time-dependent variable in which an individual was considered potentially exposed as of the year first worked at Mayak. The ERR was generally modeled as linear *in utero* dose (d_{iu}) although, for some analyses we let the dose-response parameter vary with gender or attained age categories [childhood (<15 years) or adulthood (≥15 years)]. When looking at the effects of adjusting for preconception dose, the basic ERR model was expanded to include additional terms for the dose(s) of interest. The expanded model can be written as $\lambda_0(a, s, z) [1 + \beta d_{iu} + \Sigma_i \gamma_i d_{i(other)}]$, where the summation is over one or more terms involving maternal or paternal preconception dose. Hypothesis tests and confidence intervals were based on likelihood ratio tests and direct evaluation of the profile likelihood. Two-sided P values <0.05 were considered statistically significant.

RESULTS

Selected characteristics of the cohort are presented in Table 1. The distribution of males and females is similar. The cohort is relatively young with a mean birth year of 1959, although approximately 36% of the cohort was born in the earliest time period when the radiation dose was highest. Among 3,226 offspring exposed *in utero*, the mean estimated *in utero* dose was highest for those born before 1954 (mean 113.4 mGy) and lowest for offspring born after 1969 (mean 2.7 mGy). Dose also varied by mother's work place, with the highest mean dose estimated for offspring whose mothers worked at the radiochemical plant, followed by the plutonium, reactor and auxiliary plants.

During the follow-up period (January 1, 1949 to December 31, 2008), approximately 35% of the cohort migrated out of Ozyorsk. These migrants were censored at migration. The mean (median) age at migration was 13.7 (13.3) years. As of the end of follow-up, there were 698 deaths among non-migrants including 75 deaths due to solid cancers (28 among offspring exposed *in utero*) and 12 (6 among offspring exposed *in utero*) deaths due to leukemia. In a

model adjusted for age and gender, overall solid cancer and leukemia mortality rates were not significantly associated with birth year, mother's work place, father being in the Mayak Worker Cohort, offspring's own inclusion in the Mayak Worker Cohort (Table 2), or mother's age at birth (not shown).

The relative risks for any *in utero* exposure (versus none) and by dose category are shown in Table 3. *In utero* exposure status was not significantly associated with solid cancer (RR 0.94, 95% CI 0.58 to 1.49) or leukemia mortality (RR 1.65, 95% CI 0.52 to 5.27). Categorical examination of dose revealed no clear dose-response pattern for either solid cancer mortality or leukemia. Consistent with this, the ERRs/Gy were not statistically significant for solid cancer (−0.1, 95% CI < −0.1 to 4.1) or leukemia mortality (−0.8, 95% CI < −0.8 to 46.9) (Table 3).

We also carried out analyses of both outcomes in which we allowed for effects of maternal and paternal preconception γ radiation dose and plutonium surrogates. As the data are limited, and effects of these doses were not statistically significant and did not markedly alter the *in utero* exposure risk estimates, we only present the unadjusted risk estimates. Adjusting for personal employment at Mayak did not change the dose-response estimate from *in utero* exposure for either solid cancer or leukemia. Sensitivity analyses in which we altered maternity leave assumptions, showed no appreciable impact on the excess relative risk. For example, if we assumed that women began leave 56 days before the child's birth and returned to work 56 days after the child's birth, corresponding to reported maternity leave policies, the estimated ERR/Gy for solid cancer mortality remained −0.1.

We then examined whether offspring's attained age and gender modified the ERR/Gy. At attained age <15, the estimated ERR/Gy was 50 (95% CI −0.1 to 1334; $P = 0.05$). There were a total of three solid cancer deaths in this younger age group, including one due to eye cancer in the unexposed group, and one death each from liver and bone cancers within the exposed group. The estimated *in utero* exposures were 459.6 mGy and 19 mGy for the liver and bone cases, respectively. Consistent with the overall results, there was no suggestion of excess risk at older attained ages [age ≥15: ERR/Gy <0, 95% CI (<0–2.4)]. Based on 6 leukemia deaths (2 exposed) at attained age <15 years and 6 deaths (4 exposed) at older ages, there was no evidence of heterogeneity by age ($P_{\text{heterogeneity}}$ 0.45) nor was there any indication of heterogeneity by gender for either solid cancer or leukemia mortality ($P_{heterogeneity} > 0.5$). For both age and gender, power to detect heterogeneity was limited.

DISCUSSION

In its 2003 report on the health effects of prenatal irradiation, the International Committee on Radiation Protection highlighted the importance of studying lifetime cancer risk following *in utero* radiation exposure (2). This study of 8,000 males and females, including over 3,000 offspring whose mothers were exposed to radiation during pregnancy as a result of their work at the Mayak nuclear facility, offers the possibility to quantify the risk of long-term cancer mortality following radiation exposure *in utero*.

The atomic bomb survivor data provides the only other published prospective data of adult-onset cancer risk following *in utero* exposure. Overall, statistically significant excess relative risks (ERRs) per Sv of 2.4 (90% CI 0.3 to 6.7) (10) and 1.3 (95% CI 0.2 to 2.8) (11) were reported for solid cancer mortality (attained ages 15–46) and incidence (attained ages 12–54), respectively, in the atomic bomb survivor data. Although we did not observe an increased risk of solid cancer mortality at attained age ≥15 years in the Ozyorsk Offspring Cohort and the point estimate of the ERR was less than zero, the upper confidence limit of 2.4 is consistent with the results from the atomic survivor data and we cannot exclude the

possibility of an increased risk comparable to that seen among the atomic bomb survivors. Our results also suggest, however, that the increased risk of solid cancer mortality is greater at younger attained ages. This observation is consistent with the pattern of decreasing ERR with increasing attained age reported in the incidence analysis of atomic bomb survivors (11). In the atomic bomb survivor data, there were too few leukemia deaths to estimate the dose-response relationship (10). The two cases reported by Delongchamp *et al.* (10) were among individuals exposed to 0.023 Sv and 0.04 Sv. Interestingly, this is the same range for four of the six leukemia deaths that occurred among the exposed group in our study.

To date, most studies of *in utero* radiation exposure have focused on childhood cancer risk (2–9, 21). Similar odds ratios were obtained for solid cancer and leukemia in the large Oxford Survey Childhood Cancers (6), whereas smaller case-control studies provide more convincing evidence for an increased risk of childhood leukemia following *in utero* X-ray exposure than for childhood solid cancers (2–4). Our results, based on very few childhood cancer deaths, do not suggest a stronger risk of leukemia compared with solid cancer mortality at attained age <15 years. This is consistent with a study of childhood cancer risk among offspring of British nuclear workers that reported a weak association between *in utero* radiation exposure and childhood cancer risk that was largely driven by cancers other than leukemia and lymphoma (8). It is interesting to note that our estimated ERR for childhood solid cancer mortality (*50*) is very close to that estimated for the OSCC (51) (22).

A major advantage of this study is that external dose estimates for the mothers are based on personal dosimeters worn by the workers. Nevertheless, adjustments made to account for dosimeter limitations in measuring doses under all exposure conditions are subject to uncertainties, and the neutron dose received by some workers was not included in the uterine dose used for the present analysis (16). As in most occupational studies, we were unable to include non-occupational radiation exposure such as exposure for medical reasons.

There are recognized limitations of using annual doses supplemented with monthly film badge readings for only a portion of the mothers. The data preclude us from refining *in utero* dose that could be accomplished from finer (e.g., weekly or daily) dose measurements. For women without a monthly film badge dose, it was necessary to make assumptions to apportion annual dose to the pregnancy. It is reassuring, however, that our inferences were unchanged through a series of sensitivity analyses in which the algorithm to apportion dose varied. The nature of the exposure data also precluded us from investigating potential differences by the timing (e.g., gestational age) of *in utero* exposure. Review of data for mothers with monthly doses indicated that exposure dropped off substantially after month 6 and thus this study is largely one of *in utero* radiation exposure during the first two trimesters. It is not clear from previous studies whether gestational age modifies *in utero* radiation related risks. While the ERR/Gy did not vary by trimester of exposure in the atomic survivor data (11), the OSCC data suggested that risk may be highest for exposures incurred during the first trimester (21).

The small case numbers cause a greater limitation. Since there were only 28 solid cancer deaths and 6 leukemia deaths among the exposed, we were not able to quantify the risk from *in utero* exposure with great precision and we were unable look at site-specific risks. In part, the overall small numbers of cancer deaths reflects the relatively young age of this cohort (the maximum age at the end of follow-up was 60 years). The large number of migrants (and the need to censor individuals at migration) is a recognized limitation of our study. Exclusion of person-years and deaths after migration reduced statistical power, but would bias results only if the effect of a given dose of *in utero* radiation exposure was different for migrants than for non-migrants. While we did not have information about non-radiation risk

factors (such as smoking), it seems unlikely that post-natal risk factor exposure would be associated with *in utero* radiation exposure.

Despite limited case numbers, this is one of the few prospective studies of its kind and is therefore uniquely suited to address the unresolved questions related to cancer mortality throughout life following *in utero* radiation exposure. Additional strengths include the wide range of doses (up to ~800 mGy), long period of follow-up, and good ascertainment of cause of death for non-migrants.

In summary, these preliminary results do not suggest that low-dose gamma *in utero* radiation exposure is a strong determinant of subsequent mortality from solid cancers or leukemia. Nonetheless, data are consistent with risk estimates from atomic bomb survivors and do not preclude the possibility of an increased risk of cancer mortality following *in utero* exposure. As the cohort ages, cancer mortality rates are expected to increase. It will be important to continue follow-up of this cohort and to reanalyze the data with larger case numbers to obtain more precise estimates of the risk of cancer mortality from *in utero* radiation exposure.

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TABLE 1

Selected Characteristics of 8,000 Offspring of Female Mayak Worker Cohort Members with at Least 1 Year of Follow-Up

	N offspring (%)	Exposed (%)	Mean *in utero* dose, among exposed (mGy)
Gender			
Male	4113 (51.4%)	41.3%	54.5
Female	3887 (48.6%)	39.3%	54.4
Birth year			
1948–1954	2377 (29.7%)	43.1%	113.4
1954–1959	2394 (29.9%)	52.8%	42.7
1960–1964	1221 (15.3%)	26.3%	10.6
1965–1969	763 (9.5%)	28.4%	5.1
≥1970	1245 (15.6%)	32.1%	2.7
In utero dose			
None	4774 (59.7%)		
<10 mGy	1285 (16.1%)		3.9
10–<20 mGy	428 (5.4%)		14.3
20–<50 mGy	569 (7.1%)		32.4
50–<100 mGy	363 (4.5%)		71.1
≥100 mGy	581 (7.3%)		207.0
Mother's workplace during pregnancy			
None[a]	2964 (37.1%)	1.1%	2.4
Other/auxiliary	1192 (14.9%)	34.4%	16.0
Reactor	1030 (12.9%)	72.0%	16.5
Radiochemical	1553 (19.4%)	90.9%	92.2
Plutonium	1261 (15.8%)	50.0%	42.3
Offspring part of the Mayak Worker Cohort			
No	6815 (85.2%)	40.2%	52.9
Yes	1185 (14.8%)	41.3%	63.1

[a]Includes 31 offspring whose mothers have a dose during the year of and/or prior to child's birth, but work history file indicates not working at Mayak at that time.

TABLE 2

Relative Risks of Cancer Mortality from Factors Other Than *In Utero* Radiation Exposure among 8,000 Offspring of Female Mayak Worker Cohort Members with at Least 1 Year of Follow-Up

		Solid cancer mortality		Leukemia mortality	
	Person years	**Cases**	**RR (95% CI)[a]**	**Cases**	**RR (95% CI)[a]**
Birth year					
1948–1953	75,361.6	40	1.00 (REF)	4	1.00 (REF)
1954+	190,177	35	0.68 (0.42–1.11)	8	0.85 (0.26–3.26)
P value[b]			*0.12*		*>0.5*
Mother's workplace during pregnancy					
None	108,587	30	1.00 (REF)	4	1.00 (REF)
Auxiliary	39,046.2	5	0.52 (0.18–1.24)	0	NA
Reactor	32,527.2	13	1.38 (0.69–2.59)	2	1.63 (0.23–8.35)
Radiochemical	49,102.8	15	0.91 (0.48–1.66)	4	2.13 (0.50–9.03)
Plutonium	36,275.3	12	1.20 (0.59–2.28)	2	1.45 (0.20–7.41)
P value[b]			*0.36*		*0.30*
Father in the Mayak Worker Cohort					
No	85,748.4	28	1.00 (REF)	2	1.00 (REF)
Yes	179,790	47	0.78 (0.49–1.25)	10	2.37 (0.62–15.39)
P value[b]			*0.29*		*0.22*
Offspring in the Mayak Worker Cohort					
No	230,553	47	1.00 (REF)	11	1.00 (REF)
Yes	34,985.2	28	1.23 (0.72–2.06)	1	0.47 (0.02–3.45)
P value[b]			*0.44*		*0.49*

[a]Relative risk (RRs) and 95% Confidence Intervals (CIs) estimated from Poisson regression, adjusted for age and gender.

[b]*P* values based on likelihood ratio test.

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TABLE 3

Relative Risks and Excess Relative Risks Per Gray of Cancer Mortality from *In Utero* Radiation Exposure among 8,000 Offspring of Female Mayak Worker Cohort Members with at Least 1 Year of Follow-Up

		Solid cancer mortality		Leukemia mortality	
	Person years	**Cases**	**RR (95% CI)[a]**	**Cases**	**RR (95% CI)[a]**
In utero exposure status					
No	167,119	47	1.00 (REF)	6	1.00 (REF)
Yes	98,419.1	28	0.94 (0.58–1.49)	6	1.65 (0.52–5.27)
P value[b]			*>0.5*		*0.39*
In utero dose category					
None	167,119	47	1.00 (REF)	6	1.00 (REF)
>0–10 mGy	40,065.9	8	0.94 (0.41–1.88)	0	NA
10 mGy–<20 mGy	13,475.1	7	1.79 (0.74–3.72)	1	2.05 (0.11–11.98)
20 mGy–<50 mGy	18,223.3	3	0.45 (0.11–1.23)	4	5.91 (1.51–20.79)
50 mGy–<100 mGy	10,185.1	4	1.06 (0.32–2.60)	1	2.58 (0.14–15.15)
≥ 00 mGy	16,469.6	6	0.86 (0.33–1.86)	0	NA
P value[b]			*0.46*		*0.03*
ERR/Gy			−0.1 (<−0.1–4.1)		−0.8 (<−0.8–46.9)
P value[b]			*>0.5*		*>0.5*

[a]Relative risk (RR), excess relative risk per gray (ERR/Gy), and 95% Confidence Intervals (CIs) estimated from Poisson regression, adjusted for age and gender.

[b]*P* values based on likelihood ratio test.