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In utero exposure to radiation and haematological malignancies: pooled analysis of Southern Urals cohorts

Joachim Schüz*[,1], Isabelle Deltour[1], Lyudmila Y Krestinina[2], Yulia V Tsareva[3], Evgenia I Tolstykh[2], Mikhail E Sokolnikov[3] and Alexander V Akleyev[2,4]

[1]*International Agency for Research on Cancer (IARC), Section of Environment and Radiation, Lyon, France;* [2]*Urals Research Center for Radiation Medicine, Chelyabinsk, Russian Federation;* [3]*Southern Urals Biophysics Institute, Ozyorsk, Russian Federation and* [4]*Chelyabinsk State University, Chelyabinsk, Russian Federation*

Background: It is scientifically uncertain whether *in utero* exposure to low-dose ionising radiation increases the lifetime risk of haematological malignancies.

Methods: We pooled two cohorts from the Southern Urals comprising offspring of female workers of a large nuclear facility (the Mayak Production Association) and of women living in areas along the Techa River contaminated by nuclear accidents/waste from the same facility, with detailed dosimetry.

Results: The combined cohort totalled 19 536 subjects with 700 504 person-years at risk over the period of incidence follow-up, and slightly more over the period of mortality follow-up, yielding 58 incident cases and 36 deaths up to age 61 years. Risk was increased in subjects who received *in utero* doses of $\geqslant$80 mGy (excess relative risk (ERR): 1.27; 95% confidence interval (CI): −0.20 to 4.71), and the risk increased consistently per 100 mGy of continuous exposure *in utero* (ERR: 0.77; CI: 0.02 to 2.56). No association was apparent in mortality-based analyses. Results for leukaemia and lymphoma were similar. A very weak positive association was observed between incidence and postnatal exposure.

Conclusions: In summary, the results suggest a positive association between *in utero* exposure to ionising radiation and risk of haematological malignancies, but the small number of outcomes and inconsistent incidence and mortality findings preclude firm conclusions.

Ionising radiation and radioactive nuclides have long been established as carcinogens, associated with an increased risk of many cancers, including most haematological malignancies (International Agency for Research on Cancer (IARC), 2012). However, scientific uncertainty remains as to the magnitude of risk related to protracted low-dose exposure and various time windows of exposure (Kesminiene and Schüz, 2014). Data on cancer risks associated with *in utero* exposure are particularly sparse, providing inconclusive evidence, especially regarding adult-onset cancers (Doll and Wakeford, 1997; Boice and Miller, 1999; Streffer *et al*, 2003; International Agency for Research on Cancer (IARC), 2012). Few studies have provided informative data because of the long follow-up time required. Follow-up of the atomic bomb survivors in Japan revealed an excess risk of solid cancers in survivors exposed *in utero* (Preston *et al*, 2008), but there were too few haematological malignancies for a dose–response analysis (Delongchamp *et al*, 1997). The Oxford Survey of Childhood Cancers found an increased risk of childhood cancer associated with obstetric radiography, and particularly radiography during the first trimester (Stewart and Kneale, 1970; Bithell and Stewart, 1975), as well as other earlier studies (McMahon, 1962; Harvey *et al*, 1985). No associations between childhood haematological malignancies and maternal occupational exposures have been reported in the offspring of a cohort of US radiologic technologists

*Correspondence: Dr J Schüz; E-mail: schuzj@iarc.fr

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or in a nested case–control study of offspring of UK radiation workers (Johnson *et al*, 2008; Bunch *et al*, 2009). Several case–control studies of children with leukaemia and lymphoma have investigated maternal diagnostic radiation exposure during pregnancy, with inconsistent results, although one large case–control study in the United Kingdom, which used medical records to assess exposure, showed a small statistically non-significant increase in the risk of leukaemia and lymphoma (Rajaraman *et al*, 2011). Overall, the evidence from studies on childhood cancers after *in utero* exposure to ionising radiation suggests a non-zero increase in risk at doses as low as 10 mSv (Wakeford and Little, 2002, 2003; Schulze-Rath *et al*, 2008).

Two additional sizable cohorts of subjects exposed *in utero* originate from the operation of a large nuclear facility in the Southern Urals (Russian Federation) called the Mayak Production Association that was established in 1948 and was part of the former Soviet nuclear weapons programme (Akleyev *et al*, 1995). The facility houses several nuclear reactors, a radiochemical plant, and a plutonium-producing reactor. Two sources of exposure are associated with the facility. First, because of a lack of adequate radioprotection in the early days of operation, the workforce was exposed to considerable doses of external radiation. Depending on the worksite, there was also a risk of inhalation of plutonium aerosols. Therefore, the offspring of female Mayak workers may have received high doses *in utero* (Vasilenko *et al*, 2007; Vostrotin *et al*, 2014). Second, because of discharge of nuclear waste into the surrounding environment in the 1950s (particularly into the nearby Techa River) and a major nuclear accident in 1957, when a chemical explosion of a storage tank released as much as 100 tons of high-level radioactive waste, the offspring of women living along the Techa River or areas affected by the fallout during this time period were also exposed to substantial doses *in utero* (Degteva *et al*, 2006, 2012; Maynard *et al*, 2015a, b). The offspring of women exposed to each of these sources were identified and two cohorts established, with the oldest cohort members now in their early 60s. The two cohorts have been analysed separately for both incidence and mortality of haematological malignancies. Based on 32 incident cases, analysis of the Mayak female worker offspring cohort (MWOC) has revealed some weak indications of increased risk (Deltour *et al*, 2016), whereas analysis based on 26 incident cases in the Techa River *in utero* exposed cohort (TRCIU) has not shown an increase (Kharyuzov *et al*, 2015).

The objective of this study was to pool the data from these two cohorts to increase the statistical power of analyses to investigate the association between *in utero* exposure to ionising radiation and the risk of incidence and mortality of haematological malignancies.

MATERIALS AND METHODS

Study population. The TRCIU comprised all individuals born alive between January 1950 and September 1961 to mothers who have been permanent residents in the villages along the Techa River (41 villages) before and/or during their pregnancy between January 1950 and December 1960. The MWOC comprised all individuals born alive in the town of Ozyorsk between January 1948 and December 1988 to mothers who were members of the Mayak worker cohort that comprised workers employed by the Mayak Production Association (a large nuclear facility) for any period of time between January 1948 and December 1982 at one of the nuclear reactors, the plutonium production plant, the radiochemical plant, the water treatment plant, or the mechanical repair plant (Deltour *et al*, 2016). Because of the differences in inclusion criteria between the two cohorts, many members of the MWOC had an estimated zero radiation dose despite the potential of *in utero* exposure, whereas the TRCIU by definition comprised only individuals who had a non-zero dose (with few exceptions). There was no overlap of subjects between MWOC and TRCIU.

Data collection. The TRCIU members were followed up for incidence of haematological malignancies for as long as they lived within the Chelyabinsk *oblast* (administrative region) or the Kurgan *oblast* from January 1953 to December 2009. Until 2005, paper copies of information on cancer diagnoses were obtained from the Chelyabinsk and Kurgan *oblast* oncology dispensaries and from the clinical department of the Urals Research Center for Radiation Medicine (URCRM). From 2005 onwards, electronic information was obtained from the cancer registries of the *oblasts*. Mortality was followed up from January 1950 to December 2009, within the same catchment area as for the incidence analysis. This follow-up was conducted using records from the URCRM cause-of-death registry covering the entire time period (Winkelmann *et al*, 2002; Startsev *et al*, 2015). Subjects were followed up for incidence and mortality until their death, their emigration out of the catchment area, or the end of the follow-up period, or – for incidence analysis only – until their first cancer diagnosis. Until 2006, cohort members' residency and vital status were followed up through queries to the Chelyabinsk and Kurgan *oblast* address bureaus and civil registration offices. In 2006, the Russian legislation on data confidentiality changed, and informed consent became required for follow-up. As a result, a new follow-up procedure was established that relied on (1) searches in existing lists of Techa residents covered by free medical services and in the Ozyorsk database, (2) phone interviews with residents of the city of Chelyabinsk, (3) surveys mailed to relatives of cohort members, (4) interviews with cohort members visiting the URCRM clinic or receiving examinations by the URCRM mobile medical team, and (5) interviews with cohort members' relatives during such visits.

The MWOC members were followed up from January 1948 until December 2009, or until their death, their emigration out of the town of Ozyorsk, their loss to follow-up for another reason, or – for incidence analysis only – their first cancer diagnosis, whichever occurred first. The Epidemiology Laboratory at the Southern Urals Biophysics Institute established its own active follow-up process, with cause of death data obtained from the Ozyorsk cause-of-death registry and cross-checked against information from any other sources available, such as medical records, autopsy protocols, histological examination protocols, and communications with relatives (Azizova *et al*, 2012). The most reliable information available was then recorded in the database, with autopsy protocols considered to be the most reliable sources and communications with relatives the least reliable. The Southern Urals Biophysics Institute now maintains its own cancer registry of all incident cases occurring in cohort members, based on information obtained from local hospital records. Until 2006, vital status was followed up through queries to the local address bureau and civil registration office, and from then on with the requirement of obtaining informed consent before accessing these sources.

Information was anonymised before analysis. The study was approved by the Ethics committee of the URCRM, Chelyabinsk, Russia, and by the Ethics committee of the Southern Urals Biophysics Institute (SUBI), Ozyorsk, Russia.

Exposure assessment. To study the risk of haematological malignancies and the associated mortality, the estimated dose to red bone marrow was calculated for each member of the combined cohort.

For TRCIU members, *in utero* and annual postnatal doses were estimated using the Techa River Dosimetry System 2009 (Degteva *et al*, 2006) that includes a special algorithm for *in utero* dose estimations. Red bone marrow doses were calculated using a common protocol based on external dose rates in residential areas and village-average intake functions, then individualised according to age and history of residence in either the Techa River settlements or the East Urals Radioactive Trace (the area contaminated by

fallout from the nuclear accident). Accumulated fetal doses of strontium-89, strontium-90, and cesium-137 were assumed to be the sources of internal *in utero* exposure. Fetal biokinetic and dosimetric models for strontium adapted for the Techa River population were used for the calculation (Maynard *et al*, 2015a, b; Shagina *et al*, 2015a). The model published in the International Commission on Radiological Protection's Publication 88 was used to calculate the *in utero* doses from cesium (International Commission on Radiological Protection (ICRP), 2001). Estimates of dietary intake of strontium-90 and cesium-137 among adult Techa River residents (Tolstykh *et al*, 2011, 2013), adjusted for increased food consumption by pregnant women (Shagina *et al*, 2015a), were also used. External *in utero* exposure during pregnancy was estimated using the Techa River Dosimetry System 2009, using maternal uterine exposure as a surrogate measure. Postnatal exposure was estimated using the same system for individuals who continued to live in the contaminated areas or who were evacuated (as exposure because of bone-seeking strontium-90 continued long after intake regardless of place of residence). Breast milk, another source of radionuclides for infants, was also taken into account (Shagina *et al*, 2015b). Strontium-89 and strontium-90 exposure accounts for $\sim$90% of the total red bone marrow dose.

For MWOC members, fetal exposure to external radiation was estimated using the Mayak Worker Dosimetry System 2008 that incorporates estimates of each mother's annual uterine dose of γ-radiation based on film badge records and work history (Schonfeld *et al*, 2012). Pregnancies were assumed to have begun 280 days before childbirth. The period of no occupational exposure (because of maternity leave, other leave days, and the practice of transferring pregnant workers to worksites with no ionising radiation exposure) was assumed to be a total of 175 days for women who gave birth before 1960, and 265 days thereafter, as described elsewhere (Schonfeld *et al*, 2012). Dose rates were adjusted as appropriate for pregnancies that occurred very close together. The mothers of MWOC members may also have been exposed to plutonium; exposure to internal radiation was modelled for the MWOC-specific analysis but not used in the pooled analysis (Deltour *et al*, 2016). For MWOC members who later became Mayak workers themselves (and therefore members of the Mayak worker cohort), estimates of postnatal occupational exposure to γ-radiation (red bone marrow dose) were extracted from the Mayak Worker Dosimetry System 2008.

Statistical analysis. We used Poisson regression methods to quantify excess relative risk (ERR) and relative risk (RR) as functions of red bone marrow dose received *in utero* (d_{iu}) and postnatally (d_{pn}) for both incidence and mortality of haematological malignancies. The person-years table was stratified by population (Slavs, Tatars, and Bashkirs (part of the TRCIU) and Ozyorsk residents (part of the MWOC)), sex, 5-year age group, and birth period (before 1955, 1955–1959, 1960–1969, 1970–1979, and 1980–1988), as well as by *in utero* and postnatal dose (<1, 1–4, 5–9, 10–19, and further 10 mGy intervals up to the maximum dose) lagged by 1 year until age 15 years and by 2 years thereafter. Analyses were based on linear ERR models of the form $\lambda_0(a,s,p,r)(1+\beta d_{iu}+\delta d_{pn})$ and on log-linear RR models of the form $\lambda_0(a,s,p,r)\exp(\beta d_{iu}+\delta d_{pn})$, where $\lambda_0(\,)$ is the baseline hazard rate function, modelled as a function of log(age/45), $\log^2$(age/45) (a), sex (s), birth period (before 1955, 1955–1959, or after 1959) (p), and place of residence (r). Hypothesis tests and 95% confidence intervals (CIs) were based on likelihood ratio tests and direct evaluation of the profile likelihood.

Within the combined cohort, ERR and RR were calculated for all haematological malignancies combined (defined by diagnostic codes 200–208 in the International Classification of Diseases, 9th Revision) and for leukaemia (codes 204–208) and lymphoma (codes 200–202) separately (all subtypes combined). Additional analyses were conducted to investigate the risk of haematological malignancies occurring during childhood (i.e., before age 15 years).

RESULTS

The combined cohort totalled 19 536 subjects with 700 504 person-years at risk over the period of incidence follow-up, and slightly more (19 956 subjects with 706 269 person-years at risk) over the period of mortality follow-up (Tables 1A and B). In both individual cohorts, approximately half of the members were known to be alive and cancer free at the end of follow-up. The mean age of those alive and under follow-up was 51 years at the end of the follow-up (median age 52.3 years, maximum age 61 years); 32.4% were below and 67.6% above 50 years of age. The rate of loss to follow-up was somewhat higher in the MWOC. The proportion of deaths was somewhat higher in the TRCIU, and this was as expected because of this cohort's earlier average date of birth. The most frequent causes of deaths were injury and poisoning (29%), followed by circulatory system diseases (15%).

A total of 58 individuals were diagnosed with a haematological malignancy in the combined cohort: 28 with leukaemia, 28 with lymphoma, and 2 with multiple myeloma (Table 2). An equal number of males and females were affected, and 13 subjects were diagnosed before age 15 years. The numbers of individuals diagnosed were 7 (12.1%) in the 0–9-year-old age group, 9 (15.5%) in the 10–19-year-old group, 12 (20.7%) in the 20–29-year-old group, 6 (10.3%) in the 30–39-year-old group, 15 (25.9%) in the 40–49-year-old group, and 9 (15.5%) above age 50 years. There were no cases of chronic lymphoid leukaemia. The numbers of deaths were substantially smaller (totalling 36 in the combined cohort), with more deaths related to leukaemia than to lymphoma.

The maximum *in utero* dose received was 1.05 Gy, but most subjects (>55%) received doses of <2 mGy (Table 3). The *in utero* dose distributions in the MWOC and the TRCIU were similar, with both cohorts contributing equally to the lower and higher dose ranges. Nearly half (48.5%) of the combined cohort (with 339 539 person-years at risk) had received postnatal ionising radiation doses of <1 mGy, but 24.5% of the cohort (with 174 124 person-years at risk) had received accumulated doses of $\geqslant 20$ mGy. The main difference between the two cohorts was that there was no correlation between *in utero* and postnatal doses in the MWOC (Pearson's correlation coefficient: 0.02), whereas there was some correlation in the TRCIU (Pearson's correlation coefficient: 0.46); this finding was expected because postnatal dose in the MWOC comes from occupational exposure, whereas place of residence is the major determinant of dose in the TRCIU.

Table 4 shows the risk analyses of the combined cohorts for incidence and mortality of all haematological malignancies combined, modelled as ERR and RR as described in the Statistical Analysis section. With regard to incidence, categorical analyses showed considerable effect estimates in the two highest dose categories of *in utero* exposure, but only small increases with increasing postnatal dose. Analyses of continuous exposure showed some risk increase per 100 mGy of *in utero* dose, but no association between risk and postnatal dose. For mortality, the weak associations observed with incidence were further attenuated; no association was apparent with either *in utero* or postnatal exposure.

The results of separate analyses of leukaemia and lymphoma cases were similar to the overall results (Table 5). Although the ERRs of both lymphoma and leukaemia increased slightly per 100 mGy of exposure, this difference was only statistically significant for leukaemia. There was evidence of an association between *in utero* dose and incidence, but not mortality.

Restricting the analysis to outcomes occurring before the subjects reached the age of 15 years (to evaluate the risk of

Table 1A. Incidence of haematological malignancies; demographic characteristics and outcomes of the study population of the two Southern Urals cohorts – the Techa River *in utero* exposed cohort (TRCIU) and the Mayak female worker offspring cohort (MWOC) – exposed to ionising radiation *in utero*

	Combined cohort		TRCIU		MWOC	
	N (%)	PYAR	N (%)	PYAR	N (%)	PYAR
Total	19 536 (100)	700 504	11 070 (100)	423 502	8466 (100)	277 002
Demographic characteristics						
Sex						
Male	9949 (51)	352 325	5588 (50)	209 702	4361 (52)	142 623
Female	9587 (49)	348 179	5482 (50)	213 800	4105 (48)	134 379
Year of birth						
1948–54	7219 (37)	257 702	4073 (37)	163 161	3146 (37)	94 542
1955–59	7273 (37)	264 024	5263 (48)	195 256	2010 (24)	68 768
1960–69	3768 (19)	140 080	1734 (16)	65 085	2034 (24)	74 995
1970–79	921 (5)	30 173	0 (0)	0	921 (11)	30 173
After 1979	355 (2)	8526	0 (0)	0	355 (4)	8526
Outcomes						
Alive on 12/31/2009	9701 (50)		5648 (51)		4053 (48)	
Lost to follow-up						
Emigrated	5170 (26)		2208 (20)		2962 (35)	
Other reason	1395 (7)		1062 (10)		333 (4)	
Incident cancer	508 (3)		288 (3)		220 (3)	
Death	2762 (14)		1864 (17)		898 (11)	

Abbreviation: PYAR = person-years at risk over the period of cancer incidence follow-up.

Table 1B. Mortality of haematological malignancies; demographic characteristics and outcomes of the study population of the two Southern Urals cohorts – the Techa River *in utero* exposed cohort (TRCIU) and the Mayak female worker offspring cohort (MWOC) – exposed to ionising radiation *in utero*

	Combined cohort		TRCIU		MWOC	
	N (%)	PYAR	N (%)	PYAR	N (%)	PYAR
Total	19 956 (100)	706 269	11 490 (100)	427 979	8466 (100)	278 290
Demographic characteristics						
Sex						
Male	10 182 (51)	354 863	5821 (51)	211 862	4361 (52)	143 001
Female	9774 (49)	351 406	5669 (49)	216 117	4105 (48)	135 289
Year of birth						
1948–54	7639 (38)	262 178	4493 (39)	167 026	3146 (37)	95 152
1955–59	7273 (36)	264 840	5263 (46)	195 774	2010 (24)	69 066
1960–69	3768 (19)	140 469	1734 (15)	65 179	2034 (24)	75 290
1970–79	921 (5)	30 242	0 (0)	0	921 (11)	30 242
After 1979	355 (2)	8 540	0 (0)	0	355 (4)	8 540
Outcomes						
Alive on 12/31/2009	9927 (50)		5769 (50)		4158 (49)	
Lost to follow-up						
Emigrated	5187 (26)		2235 (19)		2952 (35)	
Other reason	1463 (7)		1127 (10)		336 (4)	
Death						
From neoplasms	248 (1)		145 (1)		103 (1)	
Of other causes	3131 (16)		2214 (19)		917 (11)	

Abbreviation: PYAR = person-years at risk over the period of cancer mortality follow-up.

developing a haematological malignancy specifically during childhood) reduced the number of incident cases to 13 (of which 9 were diagnosed with leukaemia), resulting in an ERR per 100 mGy of −0.09 (95% CI: (lower bound not defined) to 1.74) and an RR per 100 mGy of 0.78 (95% CI: 0.20 to 1.54) for *in utero* exposure (not shown in tables).

DISCUSSION

In this large study pooling data from two Southern Urals cohorts exposed *in utero* to ionising radiation, with a total of >700 000 person-years at risk, we observed 58 incident cases of haematological malignancies. Excess risk was increased by 77% (CI: 2 to 257%) per 100 mGy *in utero* dose. Some cohort members also had postnatal exposure to ionising radiation that was correlated with *in utero* exposure in one of the two cohorts, but adjustment for postnatal exposure did not alter the observed effect of *in utero* exposure. A total of 36 deaths from haematological malignancies occurred in the combined cohort, but mortality was not correlated with *in utero* exposure. For both incidence and mortality, the results were similar between leukaemia and lymphoma, and none of the incident cases of leukaemia were chronic lymphoid leukaemia. There is no straightforward explanation for the

Table 2. Incidence and mortality of haematological malignancies in the two Southern Urals cohorts – the Techa River *in utero* exposed cohort (TRCIU) and the Mayak female worker offspring cohort (MWOC) – exposed to ionising radiation *in utero*

	Combined cohort		TRCIU		MWOC	
	Incident, N	Deceased, N	Incident, N	Deceased, N	Incident, N	Deceased, N
Total	58	36	26	15	32	21
Leukaemia (subtotal)	28	23	15	11	13	12
Male	14	12	7	6	7	6
Age <15 years	9	8	2	2	7	6
Lymphoid[a]	7	7	1	1	6	6
Myeloid[b]	14	10	11	7	3	3
Other[c]	7	6	3	3	4	3
Lymphoma (subtotal)	28	11	11	4	17	7
Male	15	7	6	2	9	5
Age <15 years	4	2	3	2	1	0
Hodgkin[d]	14	5	3	1	11	4
Non-Hodgkin[e]	14	6	8	3	6	3
Myeloma[f] (subtotal)	2	2	0	0	2	2

International Classification of Diseases, 9th Revision (ICD-9) rubrics:
[a]204 (lymphoid leukaemia).
[b]205 (myeloid leukaemia).
[c]206–208 (other leukaemia).
[d]201 (Hodgkin lymphoma).
[e]200 and 202 (non-Hodgkin lymphoma).
[f]203 (multiple myeloma).

Table 3. Distribution of *in utero* red bone marrow doses (in Gy) within the two Southern Urals cohorts – from external radiation in the Mayak female worker offspring cohort (MWOC) and from external and internal radiation in the Techa River *in utero* exposed cohort (TRCIU) – followed up for incident cases of all haematological malignancies (International Classification of Diseases, 9th Revision (ICD-9) rubrics 200–208)

	Combined cohort		TRCIU		MWOC	
Dose percentile (Gy)	No malignancy (N = 19 478)	Malignancy (N = 58)	No malignancy (N = 11 044)	Malignancy (N = 26)	No malignancy (N = 8434)	Malignancy (N = 32)
50th (median dose)	0.001	0.002	0.002	0.003	0.000	0.000
75th	0.012	0.032	0.013	0.015	0.010	0.045
90th	0.076	0.159	0.079	0.203	0.072	0.153
95th	0.147	0.228	0.156	0.219	0.142	0.496
99th	0.369	0.534	0.387	0.228	0.321	0.534
Maximum dose	1.053	0.534	1.053	0.228	0.945	0.534

differences seen for incidence and mortality, as it was observed for all diagnostic subtypes; all of the 36 deaths were also among the 58 observed incidence cases. Hence, chance, with smaller numbers for mortality, is the most likely reason, especially with 9 incident compared with 3 deceased cases in the highest exposure category of $\geqslant$80 mGy. No associations were found between exposure and childhood haematological malignancies (i.e., those diagnosed before age 15 years), but the number of cases was small.

Overall, the available evidence suggests that there is a non-zero increase in the risk of childhood cancer (including leukaemia and lymphoma) associated with *in utero* exposure to ionising radiation doses of $\geqslant$10 mSv (Wakeford and Little, 2002, 2003). However, there remains doubt as to whether this constitutes a causal association (Tubiana *et al*, 2009), given that there have been large-scale studies on diagnostic radiation *in utero* that showed no association (Shu *et al*, 2002). We observed no association between risk and exposures to doses of <20 mGy, and a borderline statistically significant association with 100 mGy increases in exposure from log-linear models in the incidence follow-up. Virtually no data are available on lifetime cancer risk after *in utero* exposure, with too-small numbers in the *in utero* exposed cohort of the atomic bomb survivors in Japan (Delongchamp *et al*, 1997). Experimental animal studies and mechanistic data suggest that the fetus and embryo are indeed radiosensitive and that radiation-related effects, even those related to low doses, such as bystander effects and genomic instability, have detrimental effects on fetal development (Streffer, 2004). However, it is possible that the increase in cancer risk due to *in utero* exposure may be less than that due to postnatal early-life exposure, if defence mechanisms exist to destroy malignant cells during prenatal development (Pampfer and Streffer, 1989; Nakano *et al*, 2014).

Cohort studies have also been conducted on the populations exposed as adults in the same settings as our two *in utero* exposed cohorts. A study in the Techa River exposed population showed an excess risk of 0.22 per 100 mGy for leukaemia other than chronic lymphoid leukaemia, but no other haematological malignancies (Krestinina *et al*, 2013). A study in the Mayak workers showed an increased leukaemia mortality risk of $\sim$7 per gray of exposure in the 3–5 years before death, and 0.45 per gray of exposure in the 5–45 years before death, but no association with plutonium exposure (Shilnikova *et al*, 2003). We did not find an association with postnatal exposure, but the numbers of postnatally exposed cohort members were small, especially at higher dose ranges. Follow-up of our cohorts but restricted to individuals born in

Table 4. Excess relative risk (ERR) and relative risk (RR) of incidence and mortality of haematological malignancies related to *in utero*, postnatal, and continuous exposure to ionising radiation within the combined Southern Urals cohort

	N	PYAR	No. of cases	Mean exposure (Gy)[a]	ERR[b] (95% CI)	RR (95% CI)
Incidence						
In utero exposure (categorical)						
Reference (<1 mGy)	8 487	297 701	25	<0.001	0.00	1.00
1–4 mGy	4 737	178 593	9	0.002	−0.42 (−0.95 to 0.63)	0.73 (0.30 to 1.64)
5–19 mGy	2 278	81 517	6	0.011	−0.01 (−0.71 to 1.53)	1.00 (0.36 to 2.33)
20–79 mGy	2 145	74 037	9	0.042	0.79 (−0.28 to 3.22)	1.65 (0.69 to 3.66)
⩾80 mGy	1 889	68 656	9	0.200	1.27 (−0.20 to 4.71)	2.17 (0.87 to 5.09)
Postnatal exposure (categorical)						
Reference (<1 mGy)		339 539	30	<0.001	0.00	1.00
1–19 mGy		186 841	14	0.007	0.31 (−0.48 to 2.06)	1.17 (0.48 to 2.79)
⩾20 mGy		174 124	14	0.220	0.44 (−0.48 to 2.46)	1.10 (0.44 to 2.60)
Continuous exposure						
In utero (per 100 mGy)	19 536	700 504	58	0.026	0.77 (0.02 to 2.56)	1.30 (0.97 to 1.59)
Postnatal (per 100 mGy)	19 536	700 504	58	0.057	0.21 (−0.05 to 1.10)	1.10 (0.92 to 1.25)
Mortality						
In utero exposure (categorical)						
Reference (<1 mGy)	8550	299 575	16	<0.001	0.00	1.00
1–4 mGy	4791	179 480	6	0.002	−0.10 (−0.93 to 2.19)	1.02 (0.33 to 2.74)
5–19 mGy	2306	82 088	5	0.011	0.57 (−0.59 to 3.77)	1.37 (0.44 to 3.60)
20–79 mGy	2214	74 805	6	0.042	1.16 (−0.31 to 5.16)	1.69 (0.57 to 4.37)
⩾80 mGy	2095	70 320	3	0.201	−0.14 (−0.94 to 2.62)	0.95 (0.21 to 3.09)
Postnatal exposure (categorical)						
Reference (<1 mGy)		343 865	20	<0.001	0.00	1.00
1–19 mGy		187 285	7	0.007	0.58 (−0.62 to 4.29)	1.15 (0.35 to 3.54)
⩾20 mGy		175 119	9	0.221	0.94 (−4.30 to 4.98)	1.29 (0.40 to 3.83)
Continuous exposure						
In utero (per 100 mGy)	19 956	706 269	36	0.026	0.16 (−0.09 to 1.19)	1.11 (0.67 to 1.51)
Postnatal (per 100 mGy)	19 956	706 269	36	0.057	0.08 (−0.05 to 0.72)	1.05 (0.81 to 1.23)

Abbreviations: CI = confidence interval; PYAR = person-years at risk over the period of follow-up.
[a]Person-year-weighted mean.
[b]Model fit under constraint that estimated parameter is greater than −1.0 for categorical analysis or (−(maximum postnatal dose) − 1) for continuous analysis; lower bound of 95% CI may be estimated at boundary of parameter space.

Table 5. Excess relative risk (ERR) and relative risk (RR) of incidence and mortality of leukaemia and of lymphoma related to *in utero* and postnatal exposure to ionising radiation within the combined Southern Urals cohort

	N	PYAR	No. of cases	Mean exposure (Gy)[a]	ERR[b] (95% CI)	RR (95% CI)
Incidence						
Leukaemia						
In utero (per 100 mGy)	19 536	700 504	28	0.026	0.40 (0.07 to 2.41)	1.22 (0.78 to 1.62)
Postnatal (per 100 mGy)	19 536	700 504	28	0.057	0.17 (−0.05 to1.24)	1.09 (0.85 to 1.28)
Lymphoma						
In utero (per 100 mGy)	19 536	700 504	28	0.026	0.90 (−0.09 to 5.66)	1.16 (0.59 to 1.68)
Postnatal (per 100 mGy)	19 536	700 504	28	0.057	0.37 (−0.05 to 3.61)	1.14 (0.85 to 1.35)
Mortality						
Leukaemia						
In utero (per 100 mGy)	19 956	706 269	23	0.026	−0.09 (NA to 1.33)	0.90 (0.38 to 1.45)
Postnatal (per 100 mGy)	19 956	706 269	23	0.057	0.22 (−0.03 to 1.32)	1.13 (0.88 to 1.31)
Lymphoma						
In utero (per 100 mGy)	19 956	706 269	11	0.026	NA	0.47 (0.01 to 1.65)
Postnatal (per 100 mGy)	19 956	706 269	11	0.057	NA	0.85 (0.15 to 1.31)

Abbreviations: CI = confidence interval; NA = not estimated by the Epicure software; PYAR = person-years at risk over the period of follow-up.
[a]Person-year-weighted mean.
[b]Model fit under constraint that estimated parameter is greater than −1.0 for categorical analysis or (−(maximum postnatal dose) − 1) for continuous analysis; lower bound of 95% CI may be estimated at boundary of parameter space.

1950–1961 for solid cancers showed no association with *in utero* exposure but with postnatal exposure to ionising radiation (Akleyev *et al*, 2016).

The strengths of this study include the sizable cohort, the relatively long follow-up period, and the extensive work previously done on dosimetry that was adapted and put to use in the present study. In addition, the fact that some cohort members received relatively high doses *in utero* (especially during the earlier years) enabled investigation of risk across a wide exposure range in an otherwise locally restricted and relatively homogeneous population. Overall, because of this unique study setting, the Southern Urals combined cohort is exceptionally informative in addressing the lifelong cancer risk resulting from *in utero* exposure to ionising radiation, both on its own and through comparisons with the atomic

bomb survivors (a smaller cohort), medical exposure cohorts (a different type of exposure), and cohorts related to the Chernobyl accident (exposures that occurred at a date 30–40 years later).

The study's main limitation is the small number of cancers observed because of the relatively young age of the cohort, but this will change over the coming decade as many members reach their 70s. The small number observed thus far precludes firm conclusions at this point. That 26% of cohort subjects migrated out of the catchment area over the up to 60 years of follow-up period and were censored at their date of migration might be a concern, but as it is unlikely that moving away was associated with the level of *in utero* exposure it results rather in a loss of statistical power of the study than introducing any bias. Uncertainty in dose estimation is an inherent limitation when reconstructing exposures occurring several decades in the past, and the dosimetry developed in large-scale projects using dosimetry data for the evaluation of the external and internal doses include numerous radionuclide measurements in Techa riverside residents and measurements of γ-radiation fields in residential areas and on Techa riverbanks, and is considered the best data available. Another limitation is the strong correlation between *in utero* exposure and postnatal exposure in one of the two cohorts and the fact that preconceptional exposure of the parental gonads was not considered. The lack of information on exposure from radioactive iodine is assumed to be a minor issue in evaluating the risk of haematological malignancies, but an assessment of iodine-131 doses among Techa River cohort members has shown that individual thyroid doses can reach several grays, especially in individuals born in 1948–1950, the period of maximal airborne releases from the Mayak Production Association (Eslinger *et al*, 2014; Napier *et al*, 2015). This suggests that future research on thyroid cancer may be of interest. A model for estimating plutonium exposure among the female Mayak workers was developed for the purpose of the present study, but because this exposure was found to have no impact on the MWOC results and there was no plutonium exposure in the TRCIU, plutonium exposure was not included in the pooled analyses. Overall, we had no information on other potential confounding factors, but while natural radiation (because of the defined relatively small geographical area where the mothers lived during pregnancy) and smoking (being a modest risk factor for only myeloid leukaemia (Vineis *et al*, 2004)) are unlikely to have an impact, the lack of information on postnatal medical radiation is a limitation, although it is rather speculative of whether it may be correlated with *in utero* exposure.

Doses are lower compared with early studies of offspring of mothers who underwent diagnostic X-ray procedures, possibly explaining why we did not see the same association with childhood cancer; the majority of cases in our study however are adults for which there are little data in the literature. The *in utero* exposure in the atomic bomb survivor cohort was on average slightly higher ($\sim$14% with exposures $\geqslant$0.1 Gy; Preston *et al*, 2008) but, as said, risk of haematological malignancies was not analysed because of small numbers.

CONCLUSION

Our results suggest a positive association between *in utero* exposure to ionising radiation and risk of haematological malignancies, but the small number of observed cases, inconsistent incidence and mortality findings, and limited follow-up preclude firm conclusions. Half of the combined cohort was still alive at the end of 2009 and the oldest members had only reached age 61 years; a further 10 years of follow-up would increase the number of cases to the extent that higher statistical power and more robust results would be obtained. The lack of opportunities to address this research question in other settings makes this unique cohort extremely valuable for future research.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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