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Leukaemia incidence in the Techa River Cohort: 1953–2007

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Background: Little is known about leukaemia risk following chronic radiation exposures at low dose rates. The Techa River Cohort of individuals residing in riverside villages between 1950 and 1961 when releases from the Mayak plutonium production complex contaminated the river allows quantification of leukaemia risks associated with chronic low-dose-rate internal and external exposures.

Methods: Excess relative risk models described the dose–response relationship between radiation dose on the basis of updated dose estimates and the incidence of haematological malignancies ascertained between 1953 and 2007 among 28 223 cohort members, adjusted for attained age, sex, and other factors.

Results: Almost half of the 72 leukaemia cases (excluding chronic lymphocytic leukaemia (CLL)) were estimated to be associated with radiation exposure. These data are consistent with a linear dose response with no evidence of modification. The excess relative risk estimate was 0.22 per 100 mGy. There was no evidence of significant dose effect for CLL or other haematopoietic malignancies.

Conclusion: These analyses demonstrate that radiation exposures, similar to those received by populations exposed as a consequence of nuclear accidents, are associated with long-term dose-related increases in leukaemia risks. Using updated dose estimates, the leukaemia risk per unit dose is about half of that based on previous dosimetry.

Previous studies suggest that both acute and protracted radiation exposures are associated with an increased risk of leukaemia (Curtis *et al*, 1994; Preston *et al*, 1994; Gilbert, 2009; Daniels and Schubauer-Berigan, 2011). An estimate of the proportion of leukaemia cases associated with natural background exposures has been made using published risk models (Kendall *et al*, 2011) and variation in the risk of childhood leukaemia associated with variation in natural background radiation levels observed (Kendall *et al*, 2013). The challenge remains to quantify and describe the dose–response relationship from low dose (<100 mGy) and low-dose-rate exposures ($<5\,\mathrm{mGy\,h^{-1}}$) (Wakeford and Tawn, 2010).

The current analyses focus on characterising the radiation effects on the risk of leukaemia and other haematopoietic malignancies over more than 50 years in a population that received low-dose-rate radiation exposures as a consequence of environmental contamination arising from the production of plutonium for nuclear weapons in the Russian Southern Urals. The nature (i.e. protracted exposure to multiple radionuclides, including caesium and strontium) of the exposures is similar to those experienced as a consequence of nuclear accidents such as those in Chernobyl and Fukushima.

The Techa River Cohort (TRC), as described previously (Kossenko *et al*, 2005; Krestinina *et al*, 2005, 2007, 2010),

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is a unique resource for estimating cancer risks following chronic exposure to environmental radiation in a general population. It is one of few human populations protracted strontium exposure, a radionuclide which concentrates in the bone and is thus of great relevance for leukaemia studies. The TRC members were exposed to external γ-radiation exposure from contaminated river sediments and flood plain soil and internal exposure from radionuclides including strontium^{89}, strontium^{90}, and caesium^{137} from the consumption of contaminated water, milk, and food products following the release of radioactive waste into the River by the Mayak Radiochemical Plant between 1949 and 1956 (Akleyev *et al,* 1995; Degteva *et al,* 2006; Tolstykh *et al,* 2011).

We previously reported a statistically significant, dose–response relationship between the red bone marrow (RBM) dose and risk of leukaemia using an earlier dosimetry system (Techa River Dosimetry System (TRDS-2000)) (Krestinina *et al,* 2005; Ostroumova *et al,* 2006; Krestinina *et al,* 2010). The development of a better understanding of the nature of the releases, improved radiation transport and bio-kinetic models, and efforts to further individualise dose estimates led to the development of an updated dosimetry system (TRDS-2009) (Degtevea *et al*, 2012; Napier *et al,* 2013). Improvements to the strontium biokinetic model (Shagina *et al,* 2003) and the incorporation of previously unavailable information about the composition and timing of radionuclide releases into the river are of particular relevance to RBM dose estimates. Although the TRDS-2009 doses have been used for analyses of solid cancer mortality risks (Schonfeld *et al,* 2013), the work reported here is the first to make use of the improved doses in risk estimation for haematological malignancies. The primary focus in this work concerns estimating radiation risk for non-chronic lymphocytic leukaemia (non-CLL); however, we also describe the results for all leukaemias as a group, CLL, and other haematological malignances.

MATERIALS AND METHODS

Previous publications provide detailed information about the compilation, design, and follow-up of the TRC (Kossenko *et al,* 2005; Krestinina *et al,* 2010) briefly summarised below. This study was approved by the Institutional Review Boards of the Urals Research Center for Radiation Medicine (URCRM) and the University of Illinois at Chicago.

Cohort definition. The full TRC includes 29 730 individuals who were born before 1950 and lived in one of the riverside villages between 1950 and 1960. Cohort members ($n = 1119$) who died or were lost to follow-up prior to 1953 and not known to have lived in the study region (Chelyabinsk and Kurgan oblasts) between 1953 and the end of 2007 ($n = 388$) were excluded. This report includes the remaining 28 223 cohort members known to have lived for a period of time in the Chelyabinsk or Kurgan Oblasts between 1 January 1953 and 31 December 2007.

Cohort follow-up. The URCRM staff conducted regular, systematic follow-up to ascertain vital status, cancer incidence, and cause of death for cohort members (Krestinina *et al,* 2010).

Follow-up for individual cohort members began at the latest of 1 January 1953 or the date they first lived in a riverside village and continues until the earliest of the date of the first cancer diagnosis (including leukaemia), death, migration from Chelyabinsk or Kurgan oblasts, date of last-known vital status, or 31 December 2007. Individuals who moved in and out of the two Oblasts contributed follow-up time only during periods of residence in the Chelyabinsk or Kurgan oblasts. Follow-up for this analysis begins in 1953 because of concern about underascertainment prior to that time (Krestinina *et al,* 2010).

Case definition. Haematological malignancies (ICD-9 codes 200–208), including leukaemia (ICD-9 codes 204–208), lymphosarcoma, and reticulosarcoma (ICD-9 200), Hodgkin lymphoma (HL) (201), non-Hodgkin lymphoma (NHL) (202), multiple myeloma (MM) (203), other/unknown haematopoietic malignancies (206–207–208) were ascertained from the URCRM medical records, Oblast oncology dispensaries, regional oncology clinics and health centres, and death certificates (Ostroumova *et al,* 2006; Krestinina *et al,* 2010).

Eligible cases included all first primary haematological malignancies ascertained in the TRC between 1953 and 2007. Nine cohort members who were diagnosed with another cancer before leukaemia were censored at the first cancer diagnosis. The ascertainment of haematological malignancies is largely complete for cohort members residing in Chelyabinsk and Kurgan Oblasts.

Dosimetry. Radiation exposures to the TRC members included external γ-radiation exposure from river sediments and flood plain soil and internal exposure from the consumption of water and milk contaminated primarily by strontium^{89,90} and caesium^{137}.

The TRDS-2000 was developed in 2000 (Degteva *et al,* 2000b, 2006) and improved in 2009 (TRDS-2009). Recent improvements are described in (Shagina *et al,* 2003; Degteva *et al,* 2007, 2009; Tolstykh *et al,* 2011; Degteva *et al,* 2012; Shagina *et al,* 2012a,b).

TRDS-2000 (Degteva *et al,* 2000a) applied individual information about age and residence history to estimated village-level average intake functions and external dose rates to obtain annual site-specific dose estimates, including those for RBM. TRDS-2009 dose estimates make use of improved source term parameters describing the time-dependent rates of radioactive release and radionuclide composition (Degteva *et al,* 2009, 2012). TRDS 2009 also provided greater individualisation of internal dose estimates for 27% of the entire cohort based on a resident's or a co-inhabitant's measurements of strontium^{90} body burden, available for 7903 cohort members.

The mean cumulative RBM dose (0.42 Gy, range 0–9 Gy) is markedly higher and the range broader with TRDS-2009 estimates than the corresponding statistics based on the TRDS-2000 dose estimates (0.29 Gy; range 0–2 Gy). The change in mean doses is primarily due to the fact that the new dosimetry includes a greater contribution of strontium^{89} in the period of maximal releases (1950–1951) and increases in the RBM dose from internal caesium^{137} exposure (Degteva *et al,* 2009). The increased range largely reflects the greater individualisation of the TRDS-2009 dose estimates.

Organisation of data for analysis. The data were organised as a highly stratified table of person-years and case counts. The stratification factors included time-varying 2-year-lagged cumulative RBM doses for both TRDS-2009 and TRDS-2000 doses with a zero dose category and 15 additional dose categories with lower bounds at 0, 0.005, 0.01, 0.025, 0.05, 0.075, 0.1, 0.15, 0.2, 0.25, 0.3, 0.5, 0.75, 1, and 1.5 Gy. Additional stratifying factors included sex, ethnicity, period of initial exposure (1950–1952, 1953–1960), calendar time (12 categories with cut points at 1 January of 1953, 1956, 1960, 1965, 1970, 1975, 1980, 1985, 1990, 1995, 2000, and 2005), attained age (16 5-year categories for ages 0–74 and a 75 + category), age at entry (eight categories with cut points at 10, 15, 20, 30, 40, 50, and 60), and time since first exposure (11 categories with cut points at 5, 10, 15, 20, 25, 30, 35, 40, 45, and 50 years).

Describing the radiation effect (excess relative risk models). Incidence rates were modelled using excess relative risk models of the form

$$B_0(a,s,c)\ [1+\mathrm{ERR}(d,z)]$$

in which $B_0(a,s,x)$ describes the rates in an unexposed population (baseline rates) as a function of age, sex, and other factors, whereas

the excess relative risk function, $\mathrm{ERR}(d,z)$ (Preston *et al,* 1994) describes the magnitude of the radiation-associated excess risk as a proportion of the baseline rate. The ERR is described as $r(d)f(z)$, where $r(d)$ is a dose response and $f(z)$ describes how the response at a given dose depends on factors other than dose (effect modification).

For the analyses reported here, the logarithm of the baseline rate was assumed to be proportional to sex-specific functions of log age with, as needed for specific outcomes, allowance for ethnicity and birth cohort effects.

For the basic dose–response model, the ERR was assumed to be linear in dose but we also considered models where the dose response was taken as a linear-quadratic, a pure quadratic function of dose, or threshold models in which the ERR was assumed to be 0 up to some threshold dose and taken as linear for higher doses. We also considered a model in which the ERR was allowed to vary freely over dose categories. These category-specific estimates were then smoothed using a weighted running average with weights proportional to the product of fixed weights and one over the asymptotic variance of the category-specific ERR estimates. Effect modifiers considered included sex, ethnicity, age at diagnosis, time since exposure, and age at exposure. As we are dealing with chronic exposures, analyses of time-since-exposure effects involve looking at whether the ERR per unit dose varies across doses received in different periods prior to diagnosis as opposed to time since the first exposure. To do this, we used data sets with time-dependent stratification on the TRDS-2009 dose accumulated in periods defined by the time since the dose was received. The periods considered here were 2–4, 5–9, 10–14, 15–19, and 20 or more years prior to diagnosis. Similarly, to assess the potential effects of age at exposure, the person-years and cases were stratified using time-dependent categories of the dose received in the 0–19, 20–29, 30–39, and 40 or greater age intervals.

Analyses were conducted using internal comparisons based on models fit with the Epicure Poisson-regression risk-modelling software (Preston *et al,* 1993). Tests and confidence intervals were based on direct evaluation of the profile likelihood (Cox and Hinckley, 1974).

RESULTS

Almost 60% of the cohort members were women, many were exposed before age 20, and most were living in Chelyabinsk Oblast at the time of exposure (Table 1). The higher proportion of women reflects deaths of adult males due to military service, accidents, or early deaths from disease. Cohort members identified with Tartar/Bashkir ethnicity make up about one-third of those exposed in Chelyabinsk Oblast while virtually all of those exposed in Kurgan Oblast were identified as Slavs. Most cohort members were initially exposed between 1950 and 1952, the period of maximal releases and exposure rates.

Individual annual dose rates declined rapidly with time since initial exposure and distance from the release point with almost no additional dose accumulation by the end of follow-up. In order to give some idea of representative dose rates during the periods of the greatest exposure, Table 1 presents average annual dose rates up to the time at which an individual received half of their total cumulative dose. The population average of these summary rates is 66 mGy per year. The variation by ethnicity reflects the fact that the Tartar/Bashkir villages were, on average, closer to the release point than the Slav villages. Over 90% of the cumulative RBM doses were attributed to the radioactive strontium exposures.

At the end of this follow-up period, 20% of the cohort were alive, 58% had died, and 22% were lost to follow-up (Table 2). There were 71 non-leukaemic haematological malignancies. The proportion of cases identified solely from death certificate has declined over time, ranging from about 25% for the years prior to 1990 to less than 10% over the last 17 years of follow-up. Of the 99 cases of leukaemia identified (Table 3), 52 were chronic leukaemias: 27 were CLL and 25 were chronic myeloid leukaemia

Table 1. Description of TRC by demographic characteristics and cumulative red bone marrow dose

	People		Cumulative marrow dose (Gy)				
Category	**Total**	**% Female**	**Median**	**Mean**	**90th %-tile**	**50%-tile rate (mGy/year)[a]**	**Dose from Strontium (%)**
Ethnicity							
Slav	22 451	58%	0.2	0.32	1.13	54	90
Tartar/Bashkir	5772	57%	0.63	0.75	2.01	105	92
Entry Oblast							
Chelyabinsk	17 864	57%	0.29	0.5	1.62	78	89
Kurgan	10 359	59%	0.21	0.26	0.76	39	97
Entry period							
1950–1952	23 216	58%	0.32	0.5	1.49	79	91
1953–1960	5007	57%	0.01	0.02	0.06	2	53
Age at first residence on river after 1949							
0–19	11 247	50%	0.37	0.56	1.75	85	92
20–39	9276	59%	0.21	0.34	1.17	48	90
40+	7770	67%	0.18	0.27	0.85	47	87
Total	28 223	58%	0.25	0.41	1.37	66	91

Abbreviation: TRC = Techa River Cohort.
[a]Mean of individual dose rates (mGy/year) at the time when 50% of a person's lifetime dose has been accumulated.

Table 2. Follow-up and vital status at the end of follow-up (31 December 2007) for eligible[a] cohort members by case status

	Haematopoietic malignancy		
Vital status at end of follow-up	**Yes**	**No**	**Total**
Alive	17	5667	5684
Noncancer deaths	24	12 624	12 648
Cancer deaths	123[b]	2219[c]	2343
Unknown cause of death	3	1461	1464
Lost to follow-up	3	6082	6085[d]
Total	170	28 053	28 223

[a]Excludes 1119 cohort members who had died or were lost to follow-up prior to 1 January 1953 and 388 who did not live in the catchment area at any time during the follow-up period.
[b]Includes 114 deaths from haematopoietic malignancies.
[c]Includes nine haematopoietic malignancy deaths among people with a prior solid cancer diagnosis.
[d]Includes 4183 cohort members who were known to have moved away from the Oblasts and 1902 people who were last known to be alive and living in the Oblasts prior to 2007.

Table 3. Distribution of leukaemia types and confirmation rates

Type of leukaemia	Cases	Histologic confirmation (%)	Mean age at diagnosis
Acute myeloid	8	100	48
Acute lymphoid	1	100	76
Other acute/subacute[a]	32	72	51
Chronic myeloid	25	88	57
Chronic lymphoid	27	89	64
Other/NOS[b]	6	50	62
Total	99	82	57

[a]Includes one acute monocytic leukaemia case, two acute erythremia cases, two subacute leukaemias, and 27 cases classified as acute leukaemia of unspecified type.
[b]Includes three cases classified as myeloid leukaemias of unspecified type and three classified as leukaemia of unspecified type.

(CML). In total leukaemia diagnoses were histologically confirmed for 82% of the cases.

Table 4 summarises the distribution of cases and crude incidence rates for selected haematopoietic malignancy categories by cohort characteristics and lagged cumulative dose. The dose-category-specific rates provide some suggestion of a trend with increasing dose that will be examined below.

Averaging over all ages (results not shown), modelled baseline rates were lower for women than men for all leukaemias as a group and for leukaemias other than CLL. Furthermore, the nature of the age-dependence differed by sex for both of these outcome groupings. Baseline rates did not vary significantly with birth cohort or ethnicity for either of these groupings.

Using a linear dose response for all leukaemias as a group, the ERR changed by 0.12 per 100 mGy increase in TRDS-2009 dose (95% CI 0.04–0.25; $P<0.001$). (This means that among people exposed to 100 mGy rates are estimated to be 12% greater than those for an unexposed population). With this dose–response model, we estimated that 32% of the 99 cases were associated with the radiation exposure. There was no evidence of a dose response for CLL (ERR per 100 mGy = 0.01, 95% CI < 0–0.12; $P>0.5$).

As there is no clear evidence of radiation effects on CLL rates in the literature or in these data, the remaining analyses focus on leukaemia other than CLL. For these leukaemias, the change in the ERR per 100 mGy in a linear dose–response model was 0.22 (95% CI 0.08–0.54; $P<0.001$). This fitted linear dose response is shown together with dose-category-specific ERR estimates in Figure 1. The addition of a quadratic term did not improve the model ($P>0.5$). A pure-quadratic dose–response model (ERR at 100 mGy 0.009; 95% CI 0.003–0.019; $P<0.001$), did not describe the data quite as well as the linear model. The right panel of Figure 1 shows a non-parametric smooth fit to the category-specific risk estimates. This smoothed curve, which does not rely on assumptions about the shape of the dose response, is similar to the linear fit over the low dose range. Although the data do not allow precise characterisation of the shape of the dose response, the data are consistent with linearity over the low dose range. Under the linear dose–response model, it was estimated that almost half of the 72 non-CLL cases in the cohort were associated with the radiation exposure (Table 5). There was no indication that the effect of doses from strontium exposure differed from doses received from other exposures (not shown); however, as 90% of the RBM dose received by TRC members arose for strontium exposure (Table 1), there is limited power to detect differences between the magnitude or nature of the dose response associated with dose arising from strontium exposure and that arising from exposures to other radionuclides.

The current incidence data for leukaemia other than CLL were also analysed using a linear model based on the TRDS-2000 doses. In this analysis, the ERR per 100 mGy was estimated to be 0.051 (95% CI 0.017–0.15, $P<0.001$), which is more than twice the TRDS-2009-based estimate, but similar to the TRDS-2000 estimate in our earlier analysis (Krestinina *et al,* 2010).

There was no statistically significant modification of the radiation-associated risk of non-CLL by sex (F:M ratio 1.0, 95% CI 0.14–6.7; $P>0.5$), or ethnicity (Tartar/Bashkir:Slav ratio 1.4, 95% CI 0.58–4.4; $P=0.4$). In a model in which the ERR was allowed to vary with age at diagnosis (i.e. attained age), the ERR was estimated to increase in proportion to age to the power 0.45 (95% CI −1.1 to 3.0), but this effect was not statistically significant ($P>0.5$).

To test for variation in the non-CLL risk with age at exposure, we carried out analyses in which the ERR/Gy was allowed to differ for doses received in four age-at-exposure groups (0–19, 20–29, 30–39, and 40 or more). There was no evidence of heterogeneity in the risk across these categories ($P=0.45$).

To examine time-since-exposure effects, we considered separate ERR estimates for doses received 2–4, 5–9, 10–14, 15–19, and 20 or more years prior to diagnosis. There was no evidence of significant heterogeneity across the five intervals ($P=0.45$), but there was a weak suggestion ($P=0.11$) that doses received 2–10 years prior to diagnosis were associated with a greater risk (ERR per 100 mGy 0.50, 95% CI 0.12–1.39) than that associated with doses received 10 or more years prior to diagnosis (ERR per 100 mGy 0.17, 95% CI 0.05–0.46). This pattern, although not quite as marked, is similar to that seen for the non-CLL risks associated with external doses in the Mayak worker cohort (Shilnikova *et al,* 2003) in which ERR per 100 mGy associated with doses received 2–4 years prior to death was 0.7, whereas that for doses received 5 or more years prior to death was 0.045. We also carried out some analyses to examine whether there were differences in the pattern of the time-since-exposure risks as a function of age at initial exposure. We considered people who were under and over 10 years of age at entry and also people who were under or over 20 at entry. There was no evidence of statistically significant difference for either comparison with *P*-values of >0.5 for the under/over 10

Table 4. Eligible haematopoietic malignancies and case counts and rates (per 100 000 PY) by selected factors

	Leukaemia										
	Total		Without CLL		Hodgkins disease		Non-Hodgkins lymphoma		Multiple myeloma		
Category	Cases	Rate	Cases	Rate	Cases	Rate	Cases	Rate	Cases	Rate	Person-years
Sex											
Male	45	13.2	31	9.1	7	2	13	3.8	4	1.2	341 721
Female	54	10.7	41	8.1	11	2.2	23	4.5	13	2.6	506 157
Ethnicity											
Slav	68	10.6	46	7.2	14	2.2	27	4.2	12	1.9	643 226
Tartar/Bashkir	31	15.1	26	12.7	4	2	9	4.4	5	2.4	204 652
Age at entry											
0–9	17	9.3	12	6.5	2	1.1	3	1.6	2	1.1	183 294
10–19	26	11.7	24	10.8	3	1.3	15	6.7	5	2.2	223 005
20–39	33	10.9	20	6.6	9	3	15	5	9	3	301 928
40+	23	17.7	16	12.3	4	3.1	3	2.3	1	0.8	129 650
Years since entry											
<5	5	0.7	5	0.7	1	0.1	0	0.0	0	0.0	68 813
5–9	6	0.5	5	0.4	3	0.3	4	0.3	0	0.0	119 385
10–19	23	1.1	18	0.9	3	0.1	1	0.0	2	0.1	207 261
20–29	19	1.1	15	0.9	3	0.2	7	0.4	0	0.0	172 133
30–39	12	0.9	5	0.4	5	0.4	8	0.6	5	0.4	134 104
40+	34	2.3	24	1.6	3	0.2	16	1.1	10	0.7	146 181
Attained age											
0–19	7	0.9	7	0.9	1	0.1	0	0.0	0	0.0	73 929
20–39	9	5.2	9	5.2	4	1.6	2	0.6	0	0	234 879
40–59	28	9	22	7	4	1.3	16	5.1	6	1.9	312 652
60–74	46	26.9	27	15.8	9	5.3	16	9.4	9	5.3	170 751
75+	9	16.2	7	12.6	0	0	2	3.6	2	3.6	55 667
Bone marrow dose (Gy)											
<0.01	12	12	6	6	3	3	4	4	0	0	100 034
0.01–0.5	6	5.9	2	2	3	2.9	2	2	0	0	102 300
0.5–0.1	5	9.1	4	7.3	1	1.8	5	9.1	2	3.6	55 078
0.1–0.15	4	6.8	3	5.1	0	0	4	6.8	2	3.4	58 992
0.15–0.3	16	10.7	10	6.7	4	2.7	5	3.3	3	2	149 934
0.3–0.5	13	10.6	10	8.2	2	1.6	3	2.5	3	2.5	122 393
0.5–1	22	14.4	20	13.1	2	1.3	8	5.2	5	3.3	152 752
1+	21	19.7	17	16	3	2.8	5	4.7	2	1.9	106 394
Total	99	11.7	72	8.5	18	2.1	36	4.2	17	2	847 877

comparison and $P = 0.25$ for the under/over 20 comparison. Furthermore, the estimate of the dose-window-specific ERRs did not exhibit clear patterns of decrease (or increase) with time since the dose was received (details not shown). However, these comparisons should be interpreted with caution as the power of the tests is limited.

Subgroups of non-CLL. The only widely recognised leukaemia subtype other than CLL with enough cases (25) for a type-specific risk assessment is CML. There was a significant linear dose response ($P = 0.003$) for CML with an ERR per 100 mGy estimate of 0.31 (95% CI 0.05–1.8). The risk for acute/subacute leukaemias as a group (41 cases including 8 AML, 1 ALL and 32 other cases – including acute NOS and subacute leukaemias) also exhibited a significant dose dependence ($P = 0.002$) with an estimate of the ERR at 100 mGY of 0.18 (95% CI 0.04–0.59).

Haematopoietic malignancies other than leukaemia. The baseline rates for NHL and MM increased substantially with birth year. The baseline rates for HL did not depend on either birth cohort or ethnicity.

For NHL (36 cases) and HL (18 cases), the ERR per 100 mGy estimates were <0 and not statistically significant ($P > 0.5$) with upper 95% confidence bounds of 0.07 and 0.17, respectively. The estimated ERR per 100 mGy for MM (17 cases) was 0.01 with an upper 95% confidence bound of 0.35 ($P > 0.5$).

DISCUSSION

These TRC observations provide evidence of an association between low-to-moderate doses at low dose rates environmental

exposures to ionising radiation and non-CLL incidence risk consistent with a linear dose–response effect. Using the best available individual doses, we estimate that 46.9% of leukaemias other than CLL could be attributed to radiation. We found no evidence that CLL was associated with radiation exposure in this population.

We estimate that incidence rates for leukaemias other than CLL among those who received a dose of 100 mGy were 20% higher than those in comparable unexposed individuals. This increase is less than half of the 50% increase reported in our previous analysis of the TRC leukaemia data (Krestinina *et al,* 2010). This change reflects the increase in individual dose estimates for TRDS-2009 that was largely a consequence of the improved understanding of the nature and timing of the releases. The most relevant changes were an increased contribution of strontium[89] during 1951, the period of maximum releases, and an increase in the RBM dose arising from cesium[137]. Other related factors (albeit to a lesser extent) were changes in the river transport model, revision of the strontium biokinetic models, and the increased individualisation of cohort member dose estimates.

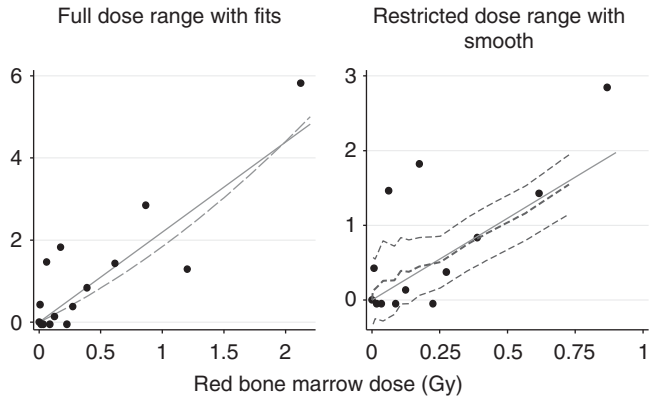

Figure 1. Dose response for leukaemias other than CLL. Both panels include non-parametric estimates of dose-category-specific excess relative risks (black points) and the fitted linear dose response (solid-grey curve). The left panel, which shows the full range of dose category means, also includes the fitted linear-quadratic (dashed grey curve) dose response. The data in the right panel are limited to the 0–1 Gy dose range. This panel includes a non-parametric fit to the category-specific ERR estimates (dark-grey dashed curve) and an indication of the uncertainty in this fit (light-grey dashed curves indicating plus and minus one standard error).

Although the general conclusion of a statistically significant increase in leukaemia incidence risk other than CLL is consistent with the atomic bomb survivor (ABS) data, the patterns with age as well as the shape of the dose response seem to differ. In the ABS data, the ERR for leukaemias other than CLL varies significantly with both attained age and age at exposure. Specifically, the ERR tends to decrease with increasing attained age but within any attained age group, the ERR/Gy increases with age at exposure (Hsu *et al,* 2013). We did not find statistically significant variation in the ERR by either age at first exposure or attained age in the TRC. There was also evidence of significant curvature of the dose–response curve in the ABS data, which we do not observe in the TRC. However, this is not surprising given the relatively low doses and limited dose range in the TRC. In the ABS data (Hsu *et al,* 2013) for an individual at an attained age of 70 who was exposed at age 30, the linear component of the dose–response curve is 0.08 (per 100 mGy) that is somewhat lower than our overall ERR/100 mGy of 0.22. Although it may appear that the effect in the TRC is larger than that of the ABS, there are large uncertainties and the estimates are not statistically significantly different. As such, there is no indication that leukaemia risks in this low-to-moderate dose, low-dose-rate population differ from those in the acutely exposed ABS population.

Comparison with other radiation-exposed populations. Studies of leukaemia risk among other environmentally exposed populations, specifically the Chernobyl cleanup workers from Belarus, Russia and the Baltic countries (Kesminiene *et al,* 2008; Ivanov *et al,* 2012), and Ukraine (Zablotska *et al,* 2013) report increased risks for all leukaemias as a group. In the Chernobyl workers in Russia an ERR of 0.50 at 100 mGy for non-CLL incidence in the 10-year period following the accident (1986–1997) (Ivanov *et al,* 2012) was reported and in the cleanup workers in Ukraine an ERR of 0.22 at 100 MGy for non-CLL incidence in the 20-year period following the accident (1986–2006) was reported (Zablotska *et al,* 2013). These estimates lie within the confidence bounds of our estimate. One substantive difference is the reported elevated risk for CLL (ERR of 0.26 with 95% CI of 0.002–0.8 at 100 mGy) in the Chernobyl studies not seen in the current cohort (Zablotska *et al,* 2013). Results from the Chernobyl studies reflect adults working within contaminated environments.

Studies in nuclear worker populations also provide risk information about low dose and dose rate exposures. The most recent estimates from the National Registry for Radiation Workers (Muirhead *et al*, 2009) report a statistically significant increase in non-CLL risk consistent with our results. A subsequent meta-analysis of 10 studies of protracted low-dose occupational and

Table 5. Observed and fitted cases of leukaemia other than CLL by TRDS-2009 cumulative dose categories

			Fitted cases		
Dose (Gy)[a]	PYR	Observed cases	Background	Excess	Attributable fraction (%)
<0.01	100 034	6	4.4	0	0
0.01–0.05	102 300	2	4.7	0.3	6
0.05–0.1	55 077	4	2.5	0.4	13.8
0.1–0.2	109 182	10	5.1	1.5	22.7
0.2–0.5	222 137	13	10.1	6.8	40.2
0.5–1.0	152 752	20	6.9	10.1	59.4
1.0>	106 395	17	4.6	14.7	76
Total	847 877	72	38.3	33.8	46.9

[a]2-Year lagged cumulative red bone marrow dose.

environmental exposures (including the previous estimate from our cohort) estimated a statistically significant dose–response association (ERR 0.19, CI (0.07–0.32) per 100 mGy) for leukaemia (excluding CLL) (Daniels and Schubauer-Berigan, 2011). This estimate would be lower if recalculated using the results of the analysis reported here.

Limitations and strengths of the study. There have been improvements in the quality and completeness of incidence data over time, and ongoing work to refine the dose estimates for members of TRC. Nonetheless, limitations of the data should be acknowledged. Loss to follow-up of 22% of TRC due to migration from the catchment area (14.8% of the cohort) and unknown vital status at the end of follow-up (6.7% of the cohort) reduce the statistical power of the study. Cause of death is unknown for 9% of deceased cohort members. For the first decades of follow-up (1950–1970), there was also a greater possibility of case under-ascertainment and a lower level of diagnostic confirmation. Although these factors reduce the statistical power of the study, particularly for subtype analysis, they would not be expected to bias the dose–response relationship effect as there was no clear relationship between any of these factors with dose. Although personal dose measurements are not available, the extensive individualised dose estimates do allow for modelling of the dose–response relationship.

The TRC is one of the few general population studies of protracted environmental radiation exposures. It provides information on low-to-moderate radiation exposures in males and females across a wide range of ages which is of particular interest in an era of increasing diagnostic medical radiation exposures (Linet *et al,* 2012). Risk estimates from this study are also informative for purposes of occupational radiation protection (International Commission on Radiological Protection, 2003). Additional strengths include the long follow-up period (55 years) enabling us to examine potential modification of the ERR at different time since exposure windows and detailed individualised residential histories allowing us to analyse only person-years and cases in the study area. Use of leukaemia incidence rather than mortality data increases the study power and data quality.

The present analysis utilises the best available dose estimates and shows an estimate of leukaemia risk that is approximately half that reported previously while remaining statistically significantly elevated. As such, the evidence for a chronic low-dose-rate radiation effect from this cohort for leukaemia risk remains solid.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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