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Leukemia incidence among people exposed to chronic radiation from the contaminated Techa River, 1953-2005

Ludmila Krestinina[1], **Dale L. Preston**[2], **Faith G. Davis**[3], **Svetlana Epifanova**[1], **Evgenia Ostroumova**[1], **Elaine Ron**[4], and **Alexander Akleyev**[1]

[1]Urals Research Center for Radiation Medicine, 68-a, Vorovsky St., Chelyabinsk, 454076, Russia

[2]Hirosoft International Corporation, 1335 H St. Eureka, CA 95501-2331, CA, USA

[3]School of Public Health, University of Illinois at Chicago, 1603 West Taylor Street, Chicago, IL 60612 USA

[4]Radiation Epidemiology Branch, National Cancer Institute, NIH, Bethesda, MD 20892-7238, USA

Abstract

Beginning in 1950, people living on the banks of the Techa River received chronic low-dose rate internal and external radiation exposures as a result of releases from the Mayak nuclear weapons plutonium production facility in the Southern Urals region of the Russian Federation. The Techa River cohort includes about 30,000 people who resided in riverside villages some time between 1950 and 1960. Cumulative red bone marrow doses range up to 2 Gy with a mean of 0.3 Gy. Between 1953 and 2005, 93 cases of leukemia, including 23 cases of chronic lymphatic leukemia (CLL), were ascertained among cohort members. A significant linear dose-response relationship was seen for leukemias other than CLL ($p< 0.001$), but not for CLL. The estimated excess relative risk per Gy was 4.9 (95% CI: 1.6; 14.3) for leukemias other than CLL and less than 0 (95% upper bound 1.4) for CLL.

Keywords

Techa River Cohort; leukemia; excess relative risk; radiation exposures

Introduction

This paper is one of a series of publications describing the Techa River cohort (TRC) which was established in 1967 by the Urals Center for Radiation Medicine (URCRM) to study the long-term health effects of chronic environmental radiation exposure to the riverside villages (Akleyev and Lyubchansky 1994; Kossenko et al. 1997, 2005; Degteva et al. 2000; Krestinina et al. 2007). The population living near the Techa River was exposed to low-dose rate radiation from radioactive releases from the Mayak nuclear weapons plutonium production facility into the Techa River between 1950 and 1956 (Akleyev and Lyubchansky

Corresponding author: Ludmila Krestinina, ludmila@urcrm.chel.su, tel. (351) 2327918, fax (351) 232 7913.

1994). The TRC is comprised of an unselected general population of men and women of all ages from two different ethnic groups who lived in similar conditions and have received comparable levels of health care. Cohort members were exposed to protracted external and internal radiation including the bone seeking radionuclide ^{90}Sr through contaminated food and drinking water. Because ^{90}Sr is incorporated into the bone marrow, quantifying the risk of leukemia is a prime interest for this study cohort.

Radiation is a well-established leukemia risk factor as indicated by acute or protracted external exposures among atomic bomb survivors (Preston et al. 1994; 2004) Chernobyl cleanup workers (Kesminiene et al.2008; Romanenko et al. 2008), endometrial cancer patients (Curtis et al. 1994), and Mayak workers (Shilnikova et al. 2003), among others. The TRC is one of the few populations that can provide quantitative estimates of the risk of leukemia following relatively low dose, low-dose rate environmental radiation exposures. Analyses of mortality in the TRC have revealed a dose-response relationship for leukemias other than CLL (non-CLL) (Krestinina et al. 2005). The analyses described in this paper differ from previous analyses in that they make use of data on incidence of non-CLL and CLL leukemias and involve extended follow-up. Because of the unique characteristics of the population, the nature of the exposures, and the length of follow-up, risk estimates from the TRC can play an important role in the development of radiation protection standards for the general public.

Material and methods

Cohort definition, catchment area, follow-up period

The Techa River, which is part of the Ob river system, originates near the Mayak complex and flows about 240 km until it merges with the Iset River. In the 1950's there were 41 villages along the river. The TRC includes 29,756 persons born before 1.1.1950 who lived in any of the Techa riverside villages during the period from 1950 to 1960. More than 80% of the cohort members lived near the river between 1950 and 1953, the period of highest radiation exposure. The cohort includes individuals of all ages, is about 58% female and is comprised of two major ethnic groups, with 80% being of Slav origin and 20% of Tartar or Bashkir origin. About 40% of the cohort members were less than 20 years old when first exposed.

Follow-up begins in 1953 (there are no reported leukemia cases in the cohort prior to 1953 but as discussed below ascertainment is unlikely to be complete from 1950 through 1952) and cohort members are considered to be at risk only for periods of time when they are known to have lived in Chelyabinsk or Kurgan Oblasts. Cohort members are at risk from the first date after 1952 that they lived in either Oblast. Cohort members are considered lost to follow-up when their vital status becomes unknown or when they have emigrated from the study catchment area. Table 1 summarizes vital status and follow-up data for TRC members through 31.12.2005. At this time, 21% of the cohort members were alive and living in the catchment area. Among the 56% of cohort members identified as deceased, the cause of death was established for 90%. Vital status at the end of follow-up was unknown for only 7.5% of cohort members remaining in the study catchment area, but follow-up was censored

for about 15% of the cohort when they emigrated from the catchment area (referred to as distal migrants).

Sources of information

Leukemia cases were ascertained from four main sources: URCRM medical records, regional oncology clinics, regional health centers and death certificates. Since 1950, leukemias have been ascertained from death certificates stored at the government (ZAGS) offices of Chelyabinsk and Kurgan oblasts (19% of all cases). In 1955 Dispensary No 1 of the Institute of Biophysics (subsequently Branch 4 of the Biophysics Institute and currently the URCRM) was given responsibility for the systematic observation and treatment of radiation-exposed individuals with hematological disorders. The medical records for leukemia patients diagnosed between 1953 and 1955 were obtained by URCRM from the Chelyabinsk region hospital. The URCRM was a key source of information on leukemia cases in the first two decades of follow-up, providing data on 39% of all leukemia cases. Since 1956, leukemia notification forms from the Chelyabinsk and Kurgan oblast oncology dispensaries have been linked to the TRC cohort roster and about 37% of all cases were identified from this source. Since the dispensaries are the major cancer treatment facilities in the study catchment area, they have become the primary source for newly diagnosed cases. The remaining cases (about 6% of the total) were ascertained from the records of health centers in Chelyabinsk and Kurgan oblasts. With these data sources, the ascertainment of leukemia cases is largely complete since 1953 for cohort members residing in Chelyabinsk Oblast or Kurgan Oblast. Description of information sources in greater detail provides (Kossenko et al. 2005).

Dosimetry

The population of the Techa riverside villages was exposed to external and internal radiation. External radiation exposure from gamma-emitting radionuclides (^{l37}Cs, ^{93}Zr, ^{95}Nb, ^{l03}Ru, ^{l06}Ru, and others) was a consequence of contamination of the river water and floodplains. Internal exposure resulted from consumption of water, milk and other food products containing radionuclides (primarily ^{89}Sr, ^{90}Sr, ^{137}Cs). Internal exposure was primarily a result of ^{90}Sr incorporation into the bone structure, for which the bone marrow was the main target-organ.

Red bone marrow doses were estimated using the TRDS-2000 dosimetry system (Degteva et al. 2000; Kossenko et al. 2005; Krestinina et al. 2005; 2007). The system provides individualized internal and external organ dose estimates and information on the uncertainty of these estimates. Estimates of annual total doses were derived from annual village mean dose estimates that allow for the nature of the releases (source term), distance from the release point, relationship of the typical residence to the river flood plain, source of drinking water, and other factors. These were then individualized to account for gender, age, residence history and other factors. The estimated maximum cumulative red bone marrow dose was 2 Gy, and the mean dose was 0.3 Gy. Total cumulative red bone marrow dose estimates were between 0.01 and 0.5 Gy for two-thirds of the cohort members while 19% had estimates in excess of 0.5 Gy. The current analyses were based on two-year lagged cumulative red bone marrow dose.

Data organization and statistical methods

Analyses of background rates and excess risks were carried out using Poisson regression methods (Clayton and Hills 1993; Preston 1993) in a highly stratified table of cases and person years for non-CLL and CLL to provide the most stable site specific estimates feasible with this cohort at this time. Cohort members were considered to be at risk from the earliest of January 1, 1953 or the date at which they first moved into one of the affected villages until their earliest of the date of cancer diagnosis or death. Person-years were accumulated only during periods in which a person was known to be living in Chelyabinsk or Kurgan Oblasts. The radiation effect was described using excess relative risk models (Preston 1993). Similar models have been used to describe radiation effects on cancer risks in the Life Span Study of atomic bomb survivors (Preston 1994; 2004; 1993), in the Mayak worker cohort (Shilnikova et al. 2003) and in the ETRC (Krestinina et al. 2005). Age, birth cohort, gender, ethnicity, and oblast of initial exposure were evaluated as potential risk factors. Linear, linear-quadratic and pure-quadratic dose-response models were considered. Gender, age at entry, attained age, and ethnicity were considered as potential dose-effect modifiers. The Epicure software (Preston et al. 1993) was used for constructing person-year tables and estimating risks.

Results

More than 830,000 person years have accumulated for cohort members residing in Chelyabinsk and Kurgan Oblast over the 53-year follow-up period. During this time 93 leukemia cases were identified, including 75 for which an incidence date could be determined and 18 which were identified solely from death certificates.

Table 2 provides summary information on the distribution of cohort members, person years, and leukemia cases by gender, ethnicity, age-at-exposure, and time since exposure. The crude rates in this table, which do not make allowance for possible dose effects, suggest that rates increase with time or age and are slightly higher for men than for women. Cohort members identified as Tartar or Bashkir ethnicity appear to have higher rates than those identified as Slavs. No leukemia cases were reported among cohort members prior to age 10 and only three cases (one acute and one chronic myeloid leukemia, and one acute leukemia of unspecified cell type) were identified among those aged 10-20 years (data not shown in table).

More than half of the cases (48 cases) were classified as chronic leukemias, 45% (42 cases) as acute or subacute leukemias, while the type of the leukemia could not be determined for 3% (3 cases) of the cases (Table 3). Five-year absolute survival rates were low, but this partly due to the cases diagnosed many years ago when treatment for leukemia was not very sophisticated.

Baseline risks

Log baseline rates for non-CLL leukemias were well-described using gender-dependent quadratic functions of log attained age. After allowing for a linear dose response there was no significant effect of ethnicity ($P > 0.5$) nor was there any evidence for a log-linear birth

cohort effect (P > 0.5). Non-CLL baseline rates for men rose fairly rapid with age increasing from about 0.1 cases per 10,000 person years at age 30 (95% CI 0.04; 0.3) to 0.9 (95% CI 0.4; 1.8) cases at age 70. At these ages, the corresponding baseline rate estimates for women were 0.3 (95% CI 0.1; 0.6) and 0.4 (95% CI 0.2; 0.7), respectively. This gender difference in the temporal pattern of the non-CLL baseline rates was statistically significant (P = 0.01).

The log baseline CLL rates could be described by a quadratic function of log attained age with male rates being 2.1 times the female rates (95% CI 0.9; 4.9), P = 0.08). The fitted rates were essentially 0 up to age 35 and peaked around age 70 when the fitted rates were 1.1 for men (95% CI 0.5; 2.0) and 0.5 for women (95% CI 0.2; 0.9) and decreased slightly at older ages. There was no evidence of ethnic differences (P > 0.5) or a log-linear birth cohort effect (P=0.3) on the CLL baseline rates. CLL cases make up more than half of the cases diagnosed among cohort members in their 50's and 60's.

Radiation risk estimates

There was a statistically significant linear dependence on dose for non-CLL leukemias (P < 0.001). The ERR per Gy estimate was 4.9 with a 95% confidence interval of 1.6 to 14. There was no indication of non-linearity in the non-CLL leukemia dose response (P > 0.5) and the estimated curvature was close to 0 (-0.12 with a 95% CI < -0.5; 17) (Figure 1). Tests for gender or ethnic differences in the dose response provided no indication of effects, P > 0.5. Allowing the dose response to depend on attained age, age at exposure, or time since first exposure did not improve the fit of the model (P > 0.5) and the estimates of the changes were small. In contrast, we found no indication of a dose response for CLL (P > 0.5) and the ERR per Gy estimate was negative (< -0.2 per Gy) with an upper 95% confidence bound of 1.4.

Table 4 presents the number of person-years and cases in categories of cumulative 2-year – lagged red bone marrow dose. The table also includes estimates of the number of radiation-associated non-CLL cases. It was estimated that 59% (95% CI 32%; 80%) of the non-CLL leukemia cases were associated with the radiation-exposure. The proportion of radiation-associated cases was higher for those exposed to more than 0.5 Gy.

Discussion

For over 50 years, the TRC of about 30,000 people with environmental low-dose low-dose-rate radiation exposure has been followed to evaluate radiation-related health effects. Our current results demonstrate a statistically significant linear dependence (p<0.001) of the excess relative risk of non-CLL leukemia incidence on cumulative dose to red bone marrow with almost 60% of the non-CLL cases in the cohort attributable to radiation exposure. The ERR per Gy of 4.9 for non-CLL in this analysis was lower, albeit still statistically compatible with the estimate (6.5; 95% CI 1.8; 24) from an early mortality analyses (Krestinina et al. 2005). Since we are using the same dose estimates and there is little evidence that the ERR is changing with time or age in this cohort, the difference in the ERR estimates is due primarily to the extended follow-up period and the addition of many incident cases. The present analysis includes about 50% more cases than were used in the mortality analyses. The suggestion that the reduction in risk is related to the additional cases

is supported by the similar risk estimate (ERR per Gy 4.6; 95% CI: 1.7; 12.3) found in a case-control study of 83 incident leukemia cases conducted in the TRC before TRDS2000 was available (Ostroumova et al. 2007).

Recently two studies of leukemia risk in Chernobyl clean-up workers, who also received low-dose protracted radiation exposure, were published (Kesminiene 2008; Romanenko 2008). The non-CLL ERRs per Gy were 2.73 (95% CI < 0; 13.5) for Ukrainian workers (Romanenko 2008) and 5.0 (90% CI -0.04; 57) for workers from Belarus, Russia and the Baltic countries. The risks in the three studies appear to be statistically compatible. It is of note, that the current TRC non-CLL risk estimate is also consistent with an ERR per Gy of 4 for non-CLL mortality in the atomic bomb survivors who received an acute dose of radiation (Preston et al. 1994).

For more than a decade, we have been focusing on improving the completeness of follow-up and quality of cause of death information. Thus, the proportion of individuals with unknown vital status at the end of the follow-up was reduced to 7.5% and the proportion of deceased cohort members with unknown cause of death was reduced to 10%. These changes led to an increase in statistical power and narrower confidence intervals around the point estimates of risk. The current risk estimates will be updated when a revised dosimetry system becomes available.

Acknowledgments

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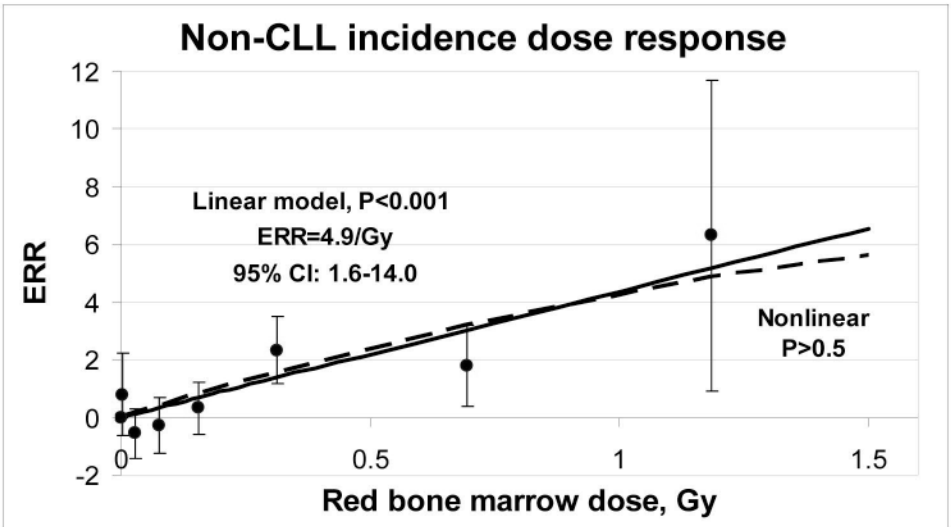

Fig.1. Non-CLL Leukemia dose response function : linear model -solid line, linear-quadratic model- dot-dash line, nonparametric model- points with 95% confidence interval

Table 1

Vital status for TRC members as of 31.12.2005

Vital Status	N	%
Alive	6,363	21.4
Deceased	16,619	55.9
Cause of death known	*15,025*	*90.4*
Cause of death unknown	*1,594*	*9.6*
Vital status unknown	2,219	7.5
Distal migrants	4,555	15.3
Total	29, 756	100.0

Table 2

Selected characteristics of leukemia cases and TRC cohort members[a]:1953-2005

Category	People	Person Years	Leukemia Cases			Rate (per 10,000 PY)	
			Any	%DCO[b]	Non-CLL[c]	Any	Non-CLL
Gender							
Male	12,565	336,660	42	26%	30	1.25	0.89
Female	17,191	495,821	51	14%	40	1.03	0.81
Ethnicity							
Tartar & Bashkir	5,950	200,594	31	6%	26	1.55	1.30
Slav	23,806	631,887	62	26%	44	0.98	0.70
Age at exposure							
<20	11,769	397,045	40	20%	34	1.01	0.86
20-40	9,640	296,550	31	16%	20	1.05	0.67
>=40	8,347	138,886	22	23%	10	1.58	1.15
Years since first exposure (average age)							
0 – 5 (32)[d]	*e*	68,684	5	0%	5	0.73	0.73
- 10 (35)		119,439	6	0%	5	0.50	0.42
- 20 (41)		206,818	23	39%	18	1.11	0.87
- 30 (48)		171,488	18	22%	15	1.05	0.87
- 40 (55)		133,216	12	17%	5	0.90	0.38
40+ (63)		132,836	29	10%	22	2.18	1.66
Total	29,756	832,482	93	19%	70	1.12	0.84

[a] Catchment area residents only

[b] % Death certificate only

[c] Leukemias other than chronic lymphocytic leukemia (CLL)

[d] Average attained age for this time-since exposure category

[e] Number of people not shown since this is a time-dependent factor

Table 3

Distribution of leukemias by histologic type: Techa River Cohort 1953-2005

Type	Incident cases	DCO	Total	Mean age at diagnosis	Five-year absolute Survival[a]
Acute leukemias					
Myeloid	8	0	8	48	12%
Other specified types[b]	3	0	3	63	--[c]
Unspecified cell types	19	12	31	52	6%
Chronic leukeimias					
Lymphocytic	22	1	23	62	56%
Myeloid	22	3	25	57	37%
Other or unspecified leukemias					
Myeloid	1	2	3	56	--[c]
Total	75	18	93	55	30%

[a] Based on non-DCO cases

[b] Includes: one acute monocytic leukemia and two acute erythremic myelosis

[c] Not computed due to small number of cases

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Table 4

Distribution of observed and expected leukemia cases by red bone marrow dose category

Dose category, Gy	PYK	Non-CLL[a]		CLL oases[c]
		Cases	Excess[b]	
<0.01	103,499	6	0	5
- 0.1	137,364	3	1	3
-0.2	171,109	8	4	5
-0.5	254,262	31	14	5
-1	140,848	15	17	5
>=1	25,399	7	5	0
Total	832,482	70	41	23

[a] Leukemias other than chronic lymphocytic leukemia (CLL)

[b] Excess case estimate from a linear dose response model with no effect modification

[c] Excess case estimates not shown since there was no evidence of a dose response (P > 0.5)