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Mortality from Cardiovascular Diseases in the Semipalatinsk Historical Cohort, 1960–1999, and its Relationship to Radiation Exposure

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Abstract

The data on risk of mortality from cardiovascular disease due to radiation exposure at low or medium doses are inconsistent. This paper reports an analysis of the Semipalatinsk historical cohort exposed to radioactive fallout from nuclear testing in the vicinity of the Semipalatinsk Nuclear Test Site, Kazakhstan. The cohort study, which includes 19,545 persons of exposed and comparison villages in the Semipalatinsk region, had been set up in the 1960s and comprises 582,656 person-years of follow-up between 1960 and 1999. A dosimetric approach developed by the U.S. National Cancer Institute (NCI) has been used. Radiation dose estimates in this cohort range from 0 to 630 mGy (wholebody external). Overall, the exposed population showed a high mortality from cardiovascular disease. Rates of mortality from cardiovascular disease in the exposed group substantially exceeded those of the comparison group. Dose–response analyses were conducted for both the entire cohort and the exposed group only. A dose–response relationship that was found when analyzing the entire cohort could be explained completely by differences between the baseline rates in exposed and unexposed groups. When taking this difference into account, no statistically significant dose–response relationship for all cardiovascular disease, for heart disease, or for stroke was found. Our results suggest that within this population and at the level of doses estimated, there is no detectable risk of radiation related mortality from cardiovascular disease.

INTRODUCTION

It is well established that exposure to ionizing radiation increases the risk for cancer. There is increasing interest in the extent to which radiation might induce non-cancer effects. An increased risk for both heart disease and stroke was first demonstrated in studies of patients who underwent high-dose therapeutic radiation schemes for the treatment of Hodgkin's disease (1), breast cancer (2, 3) and peptic ulcer (4).

The first evidence of an increased risk of circulatory disease risks at lower doses was reported from the Life Span Study (LSS) of Japanese atomic bomb survivors (5). The results are suggestive of a linear no-threshold risk for circulatory disease in the dose range 0 to 4 Sv (weighted dose to the colon, defined as external c-ray dose z 103 external neutron dose). The corresponding estimates for the excess relative risk (ERR) per Sv for heart disease and for stroke were 0.17 (90% CI: 0.08– 0.26) and 0.12 (90% CI: 0.02–0.22), respectively. A study

among Chernobyl liquidators reported an increased risk of cerebrovascular disease when the dose exceeded 150 mGy (external c-ray dose) within a period of not more than 6 months (6). A recent review concluded that there is not a convincing mechanistic explanation for the induction of cardiovascular disease at low and moderate doses, nor is the epidemiological evidence persuasive (7). At least, it is suggestive, and further epidemiological research was encouraged in previous reviews (8, 9).

The authors of a review of health effects from nuclear testing worldwide pointed to the potential of ongoing epidemiological research on populations exposed to fallout from Soviet nuclear testing for helping to establish current radiation risk estimates (10). In this present analysis, the risk of cardiovascular disease is described for the Semipalatinsk historical cohort, for which analyses have already been reported with respect to solid cancer mortality (11, 12). Between 1949 and 1989, more than 450 nuclear tests were conducted at the Semipalatinsk Nuclear Test Site (SNTS), Kazakhstan (13). Areas inhabited by a total of more than 10,000 people northeast and southeast of SNTS were considerably affected by fallout mainly due to 118 atmospheric and surface nuclear tests carried out from 1949 to 1962.

The aim of this paper is to describe the mortality from cardiovascular disease (CVD) and to characterize the association of radiation dose in terms of comparing rates between two groups of the cohort and of internal comparisons within the cohort.

MATERIAL AND METHODS

Study Population and Follow-up

The cohort data were based to a large extent on the archives of the Scientific Research Institute for Radiation Medicine and Ecology (SRIRME), Semipalatinsk, and have been described in detail elsewhere (11, 14). SRIRME is the successor institute of the “Dispanser No. 4,” a local research institution founded in 1957 for the purpose of investigating the health impact of fallout exposures. Routine data collection started in the early 1960s and continued through the years of Soviet rule; in the 1990s those data were computerized and the follow-up was extended. For this analysis, follow-up information was available over a period of 40 years (1960–1999). Cohort definition dates back to the early 1960s when “Dispanser No. 4” implemented a long-term study on health effects in the exposed population of the Semipalatinsk region. Ten highly exposed and six comparison settlements were chosen for a cohort study. Cohort sampling included the exposed villages of Cheremushka, Dolon, Kainar, Kanonerka, Kaskabulak, Karaul, Kundyzdy, Mostik, Sarzhal and Znamenka. Inclusion criteria for the exposed group were date of birth prior to January 1, 1961 and confirmed permanent residence in the exposed settlement fromdate of their birth until the end of 1962, when atmospheric nuclear testing was terminated. Thus the cohort’s exposed group includes 9,850 permanent residents of the above settlements. The medical follow-up included yearly examinations and medical care of the population in the villages and, if required, in district and regional health centers.

Further, six comparison villages located several hundreds of kilometers east/southeast of the Semipalatinsk test site were included for comparison. Inclusion criteria for this comparison group were date of birth prior to January 1, 1961 and permanent residence in the villages of Bol’shaia Bukon, Ivanovka, Karandykol, Kokpekty, Preobrazhenka or Ulguli-Malshi. The comparison group was frequency-matched to the exposed group by gender and age and includes 9,604 permanent inhabitants of these villages.

A further inclusion criterion applied at the time of the establishment of both exposed and unexposed sub-cohorts was “good general health” at start of follow-up. This led to the

exclusion of persons diagnosed with severe disease (for example, cancer or infectious disease such as tuberculosis or brucellosis) when the cohort was set up. Regular updates ensured that a complete vital status follow-up including emigration information was maintained during the entire follow-up period. For deceased cohort members, copies of death registration acts were stored in the archives of the "Dispanser No. 4."

Later, causes of death were coded according to ICD-9. Follow-up procedures and ascertainment of causes of death were independent of exposure status. Quality control of coding procedures (15), searches for duplicates, and plausibility checks have been performed within the cohort database.

To what extent ethnicity can be used as a surrogate variable for socioeconomic conditions and/or lifestyle still requires evaluation, but since dietary habits in Kazakhstan have been reported to vary between the Kazakh and Russian populations (16), we also stratified the cohort by ethnicity. Following the available classification in the data, "ethnicity" was coded as a binary variable, labeled "Kazakh" and "Russian" for cohort members of central Asian descent and Russian/other European descent, respectively.

For this analysis, a dosimetric approach was used based on estimating individual doses for times and locations where historical data were available. For a small subset of the exposed population, this approach did not allow us to calculate an individual dose. Those individuals were not included in the risk analysis. Subsequently, the number of individuals, the number of person-years and the dose estimates differ from those used in a previous analysis (11). Details are given below.

Exposure Data

For the purpose of a study on thyroid diseases among the population living in the vicinity of the Semipalatinsk nuclear test site, the NCI developed a dosimetry system based on a joint U.S./ Russian dose reconstruction methodology that combines the experience of dose-reconstruction scientists in Russia and the U.S. (17, 18). The method is similar, with some unique aspects, to methods used in other studies to estimate doses from nuclear weapons testing fallout. Basically, the dose reconstruction was based on fallout deposition from a total of 11 different tests conducted at the SNTS between August 29, 1949 and September 25, 1962 identified by Russian experts as the only ones that might have resulted in effective doses of more than 5 mSv to the local population (19). The approach is described with more detail elsewhere (20). Table 1 gives an overview on the mean external dose and the dose range for those villages for which the NCI dosimetry provides information, i.e., the control area and the settlements of Dolon, Kainar, Kanonerka, Karaul, Sarzhal and Znamenka. Dose estimates are available for 7,705 exposed individuals, covering a range from 0–0.63 Gy with a mean dose of 0.09 Gy.

Statistical Methods

In a first step, age specific and age-, gender- and ethnicitystandardized rates are given for the cohort under study. This is done for the entire population and for the two ethnic groups of Kazakhs and Russians separately. All confidence limits given are 95%. For those comparing rates between the two ethnic groups, Greenland/ Robins confidence limits for Mantel-Haenszel weighted relative risks are used. For each cohort member, person-years were accumulated from 1 January 1960 or from birth, whichever came later, until death, end of follow-up on 31 December 1999, or the date of emigration, whichever came first.

For risk analysis, only those subjects were taken into account for whom a dose could be estimated, i.e., 17,303 out of 19,454 (89%); 2,151 (11%) subjects had to be excluded from the analyses. Among the excluded 2,151 subjects, 372 of all 3,340 death cases from

cardiovascular disease occurred (11%). Out of 17,303 subjects, a further 1,465 had to be excluded because their date of birth was later than the nuclear test relevant for their specific settlement. Thus the final cohort for risk analysis comprised 15,838 subjects delivering 470,732 person-years with overall 2,985 cases of cardiovascular disease. Since there were no nuclear tests relevant for the unexposed group, none of the individuals from this group were excluded.

For each cohort member, person-years were accumulated from 1 January 1960 until death, end of follow-up on 31 December 1999, or the date of emigration, whichever came first. A lag time of 10 years was used; i.e., 129 cases occurring within the first 10 years after the relevant test (see Table 1) were omitted from the risk analysis. This lag time is irrelevant for the test in 1949. A first comparison was made between the exposed cohort and the control group. For dose– response analyses, Poisson regression methods were used to fit relative risk models using the software program EPICURE with the DATAB and AMFIT packages (22).

Data are cross-classified by various time-dependent variables. Age at exposure was classified in 10-year categories 0–9, 10–19, …, 60–69, 70z. The same categories were chosen for attained age and for time since exposure. Calendar period of observation is categorized as 1960–1969, 1970–1979, 1980–1989 and 1990–1999 and ethnicity as Kazakh and Russian. Two types of analyses were performed: categorical analyses without assumptions on the form of the dose– response relationship, and a linear Poisson regression model. In the categorical analyses doses were categorized into six groups referring to exposure of 0, 0–0.05, 0.05–0.1, 0.1–0.3, 0.3–0.6 and 0.6z Gy. In the linear Poisson regression model the excess relative risk (ERR) per unit dose and the corresponding 95% confidence limits were calculated.

RESULTS

Descriptive Results

Table 2 shows the main characteristics of the study population. The entire cohort consisted of 19,454 persons, of which 14,228 (73.1%) were Kazakhs and 5,226 (26.9%) were Russians. There was a high percentage of emigrated persons among the two groups (12.1% for Kazakhs and 31.4% for Russians), while 36.9% of the Kazakh and 43.3% of the Russian cohort members were deceased at the end of follow-up. Emigration also differed between the comparison and the exposed groups: 12.4% of the comparison group and 22.1% of the exposed group of the historical cohort had emigrated.

Table 3 gives the numbers for all cardiovascular deaths and for person-years broken down by ethnicity, gender and age group. The rates given are directly age and gender standardized for each of the two ethnic groups, with the entire population (control and exposed area) for each of the ethnic groups as standard. Rates for both ethnic groups combined were person-years weighted for ethnicity. For all deaths due to cardiovascular disease, the relative risk for Russians compared to Kazakhs is 1.15 (1.07; 1.24). Since there are considerable differences in the rates between the two ethnic groups, the rates given for two ethnic groups for heart disease (RR 5 1.01), the relative risk for stroke is 1.27 (1.11; 1.45) for Russians compared to Kazakhs (data not shown).

As can be seen from Table 4, there was a clear secular trend of increasing risks for death from any of the three groups of diagnoses with later calendar period. That is why stratification for risk analysis was also done by calendar period. The secular trend is similar for males and females (data not shown).

Risk Analysis

Dose estimates were limited to cohort subjects residing in locations for which historical information on fallout deposition was available or could be reasonably interpolated from nearby locations. All analyses were restricted to those subjects for whom a dose estimate was available.

The relative risks in the exposed group compared to the comparison group are given in Table 5 for three groups of diagnoses: cardiovascular disease (ICD-9 390– 459), heart disease (410–429), and stroke (430–438). The comparison was adjusted for attained age, gender, ethnicity and calendar period. For the exposed group, the outcomes are presented for those with and without dose estimates. There was an increased risk among the exposed for all three disease categories (see Table 5). For cardiovascular disease, the relative risk in the exposed cohort with dose estimates was 2.27 (2.10; 2.45) in relation to the comparison group. The respective figures for heart disease and for stroke are 2.23 (2.02; 2.46) and 2.30 (2.00; 2.65), respectively. The risk estimates for individuals without dose estimates were slightly lower than for the individuals with dose estimate information: cardiovascular disease, 1.85 (1.65; 2.08), heart disease, 1.88 (1.62; 2.19), and stroke, 2.01 (1.62; 2.49).

Because of the large difference in mortality from cardiovascular disease between the exposed and the comparison group and because of a comparable finding for cancer mortality (11), Tables 6a–c give the relative risk estimates in six dose categories for all the groups of diagnoses as well as the respective values for ERR/Gy, assuming a linear dose–response relationship. When the populations from the exposed and the unexposed villages are included in the analysis, there is a significant dose–response relationship (Table 6a). It can also be seen that the risk among the exposed is roughly twice as high as among the unexposed, independent of the dose category.

Thus it is necessary to test for a dose–response relationship only among the cohort members from the exposed villages. Here, a dose–response relationship was not detectable for any of the selected causes of death (Table 6b). The estimates for ERR/Gy were nonsignificant in all instances; i.e., for cardiovascular disease it was 0.02 (20.32; 0.37), for heart disease it was 0.06 (20.39; 0.52), and for stroke it was 20.06 (20.65; 0.54).

Similar results were obtained when the population from the comparison group was included, but stratification by exposure status (yes/no) was included in the analysis (see Table 6c). Further, we tested whether the estimates for risk per unit dose differ between Kazakhs and Russians. For all cardiovascular disease, when stratifying by attained age, gender, calendar period and exposure status (yes/no), risk estimates were 0.12 (20.30; 0.54) for Kazakhs and 20.19 (20.78; 0.39) for Russians.

DISCUSSION

We conducted a radiation risk analysis among the Semipalatinsk historical cohort in relation to deaths from cardiovascular disease. A dose–response relationship for the cohort could be explained completely by differences between the baseline rates in exposed and unexposed groups. When taking this difference into account, no statistically significant dose–response relationship was detected for all cardiovascular disease, heart disease or stroke.

There was a significantly higher risk among those residing adjacent to the test site than among those living in villages of the comparison area. This pattern was seen for all diagnoses under study. An important difference between the exposed and the comparison area is that the population in the control area was a more or less stable one, while that in the exposed villages to a large extent were resettled from other locations (i.e., those of German

descent during World War II) or who came in during Khrushchev's New Land policy that began in 1954. Because of this large difference in risk, dose– response analyses were meaningful only when restricted to the exposed cohort or stratified by exposure status. In the cohort, we found clear secular trends showing increasing risks in later years compared to the first years of follow-up. We found no statistically significant relationship between previous radiation exposure from nuclear testing and subsequent mortality risks from any of the death causes under study. Nonetheless, the point estimate for the ERR/Gy of 0.02 for mortality from all cardiovascular disease (ICD-9 390–459) is compatible with the one of 0.03 reported from a meta-analysis by Little et al. (7). While Little et al. reported a higher risk per unit dose for stroke than for heart, the results from our study point in the opposite direction. We also tested whether there might be a significant dose–response relationship when looking only at ischemic heart disease (ICD-9 410–414). This was not the case; the ERR/Gy was 0.03 (20.44; 0.50). Our results were based on a lag time of 10 years. It has been suggested that the radiation-related risk for cardiovascular disease mortality shows up more than 15 years after exposure (3). Thus we repeated the analyses using a lag time of 20 years with stratification by attained age, gender, ethnicity, calendar period and exposure status. This resulted in higher point estimates with wide confidence intervals: cardiovascular disease, 0.15 (20.26; 0.55), heart disease, 0.20 (20.34; 0.74), and stroke, 0.10 (20.62; 0.82).

A strength of our cohort study is the prospective character of the study's data collection, which had begun in the 1960s and was carried out with regular updates of cause of death and migration information from the rural administration. This contributed to an excellent completeness of follow-up records; losses to follow-up were exclusively due to emigration. Whereas emigration rates were low and did not differ by exposure status between 1960 and 1990, a substantial increase in emigration rates, in particular in the exposed group and here among the Russians, occurred during the 1990s: by the end of 1999, 12.4% of the comparison group and 22.1% of the exposed group of the historical cohort had emigrated. However, it has been shown elsewhere that this did not influence results on solid cancer risk based on this cohort (11). However, it cannot be excluded that the higher risks observed in the last decade of the 40-year follow-up might be due to a "healthy migrant" effect; i.e., those who left the study area were in a better health condition than those who stayed.

We are well aware of the discussion of dose estimates for the population residing close to the Semipalatinsk nuclear test site (22). We were able to base our analysis on a dosimetry system that was developed by NCI for the purpose of a study on thyroid diseases (20) and that is based on the experience from other studies requiring dose estimation from nuclear testing [e.g. 23]. In the context of this analysis, the dose assessment is for external whole-body dose from c rays emitted from fallout deposited on the ground. As discussed earlier, we could not derive dose estimates for individuals from all villages included in the cohort study because no archival data on fallout deposition are available for those locations. It is highly unlikely that information from those villages that were not covered by the dosimetry system would change the results substantially, because exposures in those villages were in the same dose range as the others when original Kazakh dose estimates were taken into account [see ref. (11): Cheremushka is located close to Dolon, and exposure there might be comparable to that of Dolon; Kaskabulak, Kundyzdy and Mostik are assumed to have doses comparable to Kanonerka or Znamenka]. On the other hand, if the subjects in those settlements were less exposed than those from the exposed area with available dose estimates and if there was a radiation-related risk, the lower risk among those from the exposed area without available dose estimates might be explained by exposure differences. However, this cannot be tested because of missing information.

The current dosimetry avoided the overestimation that is derived from the original Kazakh dosimetry as used in ref. (11) and is in good agreement with other measures of external

exposure, e.g., thermoluminescence signals in bricks and EPR measurements of human tooth enamel (22). Here it may be worth noting that because of the energetic nature of c rays from fallout (several hundred keV or more), the doses to all organs are similar and the dose to the heart was approximated as the dose to the whole body. It is not clear to what extent internal exposure was relevant for the dose to the heart of the exposed population, but neither the heart nor the circulatory system concentrates any of the nuclides that might be ingested. The exposure results primarily from maintaining residence in the contaminated areas for the first month after fallout deposition, with the first few days being the most important in terms of exposure.

Another point is the magnitude of uncertainty in individual doses. At this stage, a quantitative and rigorous uncertainty analysis is under way, so it is difficult to know to what degree the true slope of the dose–response function might be masked due to uncertainties in dose. We believe, however, that the uncertainties for external dose in this study are primarily of the Berkson type rather than of the classical error type, and in that case, the slope of the dose response generally remains unbiased (24). Individual external dose uncertainties are known, based on other studies, to be of the order of a geometric standard deviation of 1.5 to 2.0 depending on whether the exposure took place near to a location where actual exposure-rate measurements were available or whether it took place at a location that required interpolation of data. We based our conclusions about that level of uncertainty from detailed analyses made on other cohorts who received external exposure from fallout [see for example ref. (23)].

Though an increase in atherosclerosis and heart diseases has been reported in animal experiments and in humans after high-dose radiotherapy (25), only a few studies have systematically assessed cardiovascular data in the low-dose range. The most compelling evidence of such radiation effects comes from the Life Span Study of the atomic bomb survivors (5). Doses ranged from 0 to 4 Sv whole-body doses from external c radiation and some neutron radiation. For mortality from heart diseases and from stroke linear dose–response relationships were observed. For heart diseases, the ERR/Sv was 0.17 (90% CI: 0.08–0.26); for stroke, it was 0.12 (0.02–0.22). From the Adult Health Study (AHS) of the atomic bomb survivors, a significant quadratic dose– response relationship for the incidence of myocardial infarction was reported among those exposed at age lower than 40 years (26). Analyses of clinical data of the AHS showed significantly higher total serum cholesterol levels (27) and higher blood pressure (28) among the irradiated compared to unirradiated subjects.

A recent review of epidemiological studies on the risk of cardiovascular disease after radiation exposure concluded that high radiation doses to the heart and coronary arteries received in the course of certain radiotherapy procedures lead to an increased risk of circular diseases, but that the epidemiological evidence for such an effect in the range of low and moderate doses is suggestive rather than persuasive (8). However, a metaanalysis concluded that a radiation- induced risk cannot be excluded (7). With respect to individual studies, a pooled cohort study among radiation workers revealed no indication for a radiation-related risk for cardiovascular disease (29).

Inconclusive results were derived from cohort studies among radiologists or radiological technologists. Here only a cohort study among 90,852 U.S. radiological technologists was positive (30). Excess circulatory disease mortality was found among those who started working in the early years when exposures had been high. A similar trend was observed for deaths from cerebrovascular diseases and ischemic heart diseases. Among miners exposed to radon and its progeny, no relationship between coronary heart disease and radon was found

(31, 32). For a German uranium miners cohort, there was also no indication for an effect from long-lived radionuclides or from external c radiation in the range of 0 to 909 mSv (31).

Though not statistically significant, there is a remarkable difference in the dose–response relationship between the Kazakhs and the Russians, showing a higher risk among the first. This finding is unexplained with the current analysis. While these differences do not affect the overall conclusions of this study, future assessment of lifestyle and cultural attributes of these two ethnic groups could provide valuable information on the cardiovascular disease risks.

An observation of the study findings from the Semipalatinsk historical cohort identified the relative young age of cardiovascular death in the study cohort. This is particularly significant given the perceived “healthy” condition of the cohort. The higher rates of cardiovascular disease at younger ages are consistent with other geographic areas, including the southeastern portion of the U.S., where the rates of cardiovascular disease and stroke have long been recognized as being greater than in other parts of the country with similar population demographic (33, 34). As an example, considering the southeastern states of the U.S., the annual mortality rate (standardized to the Kazakh study population) for all cardiovascular diseases is 126.1 per 100,000 individuals and year (35). The cardiovascular disease mortality rates are higher for the Kazakhstan cohort than among this high-risk U.S. population. The disease risks occurring at higher rates at earlier ages may be associated with different etiologies, including exposure to factors increasing disease risks and exposure in fetal and early life that affect the disease process (36–38). These observations support further investigation. Specifically, studies should include an assessment of traditional cardiovascular risk factors, including hypertension, hyperlipidemia and diabetes, with environmental exposures.

Our results of no observable dose–effect relationship are consistent with the current knowledge insofar that doses leading to an increased risk for deaths from cardiovascular diseases seem either to be very high or to have a high dose rate. The latter is also supported by results from the Chernobyl liquidators (6). That would go together with radiobiological considerations (8, 39). According to these, epidemiological findings are compatible with radiobiological data from experimental animals. The critical target structure appears to be the endothelial lining of blood vessels, in particular arteries, leading to early functional alterations such as proinflammatory responses and other changes, which are slowly progressive (40). Hoel speculated that if direct damage to the arterial endothelial cells is the cause for CVD effects, this might explain why such effects cannot be observed at doses below 0.5 Sv (41). Little et al. suggested that the biological mechanism for fractionated low-dose ionizing radiation might be different from that for high- dose radiation with respect to cardiovascular diseases (42). Regarding our study, the vast majority of received doses are well below 0.5 Gy (mean 0.09 Gy), but it cannot be ruled out that a small effect of radiation exposure is masked by the strong secular trend, which reflects the constant decrease in life expectancy from the 1960s to the 1990s (43) or could not be detected because of limited power. Nonetheless, our findings are supported by the fact that a dose–response relationship for circulatory diseases among the atomic bomb survivors could not be observed at doses below 0.5 Gy (44).

It remains unclear why the cardiovascular disease risk among those residing close to the test site is so much higher than among the control group. However, our results do support the consideration of environmental exposures in the further investigations regarding the mechanisms associated with excess cardiovascular disease risks.

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TABLE 1

Exposure Characteristics of the Cohort by Settlement

				Dose (Gy)			
		Persons	**Date of test**	**Mean**	**Minimum**	**Maximum**	**SD**
Settlement	Control area	9,604	n.a.[a]	0	0	0	0
	Cheremushka	538	29 Aug 1949	n.a.	n.a.	n.a.	n.a.
	Dolon	941	29 Aug 1949	0.39	0.0001	0.63	0.250
	Kainar	757	24 Sep 1951	0.06	0	0.11	0.042
	Kanonerka	1,239	29 Aug 1949	0.09	0.0002	0.15	0.059
	Karaul	2,836	12 Aug 1953	0.05	0	0.08	0.026
	Kaskabulak	515	12 Aug 1953	n.a.	n.a.	n.a.	n.a.
	Kundyzdy	613	12 Aug 1953	n.a.	n.a.	n.a.	n.a.
	Mostik	485	29 Aug 1949	n.a.	n.a.	n.a.	n.a.
	Sarzhal	1,013	12 Aug 1953	0.06	0	0.09|	0.033
	Znamenka	913	24 Aug 1956	0.02	0.0006	0.03	0.008
Exposed and available estimate		7,699		0.09	0	0.63	0.145

[a] Not available, not applicable.

TABLE 2

Historical Cohort by Ethnicity and Vital Status

			Vital status			Total
			Deceased	**Alive**	**Emigrated**	**Ethnicity (%)**
Ethnicity	Kazakh	Count	5249	7252	1727	14228
		Percentage of vital status	36.9%	51.0%	12.1%	73.1%
	Russian	Count	2261	1325	1640	5226
		Percentage of vital status	43.3%	25.4%	31.4%	26.9%
Total		Count	7510	8577	3367	19454
		Percentage of vital status	38.6%	44.1%	17.3%	100.0%

TABLE 3

Ethnicity, Gender and Age Specific Person-Years, Number of Deathe from Cardiovasular Disease (ICD-9 390–459) in all Villages of the Historical Cohort (no lag time), Broken Down by Exposed and control Area

Area	Ethnicity	Gender	Age group	Person-years	Cases	Age-specific rate	Adjusted rate[a]	Adjusted rate[b]
Control area	Kazakh	male	0–9	7827.2	0	0.0	348.4	386.8
			10–19	16069.4	0	0.0		
			20–29	21154.7	0	0.0		
			30–39	24721.2	4	16.2		
			40–49	19964.2	4	20.0		
			50–59	13426.1	31	230.9		
			60–69	7059.1	110	1558.3		
			70+	1837.2	218	11865.9		
		Female	0–9	8340.7	0	0.0		
			10–19	16785.9	0	0.0		
			20–29	22436.8	1	3.8		
			30–39	26659.0	2	9.1		
			40–49	21883.5	7	46.2		
			50–59	15146.5	31	348.8		
			60–69	8886.7	170	1913.0		
			70+	2219.7	336	15136.9		
	Russian	male	0–9	1390.0	0	0.0	499.3	
			10–19	3434.0	0	0.0		
			20–29	5407.9	0	0.0		
			30–39	6794.8	0	0.0		
			40–49	5953.1	9	169.1		
			50–59	4291.6	24	560.2		
			60–69	2396.2	78	3264.1		
			70+	592.0	91	15371.9		
		female	0–9	1524.3	0	0.0		
			10–19	3672.5	0	0.0		
			20–29	5654.8	0	0.0		
			30–39	7304.0	1	18.4		
			40–49	6616.4	6	100.1		
			50–59	4964.4	23	463.3		
			60–69	3250.8	99	3045.4		
			70+	781.0	113	14392.0		
Exposted area	Kazakh	male	0–9	4767.8	0	0.0	840.3	828.3
			10–19	12598.3	0	0.0		
			20–29	19967.9	1	5.0		
			30 –39	22593.4	6	26.6		
			40–49	19424.8	25	128.7		
			50–59	13133.5	157	1195.4		

Area	Ethnicity	Gender	Age group	Person-years	Cases	Age-specific rate	Adjusted rate[a]	Adjusted rate[b]
			60–69	4952.2	395	7976.2		
			70 +	761.0	124	16294.2		
		female	0–9	4818.1	0	0.0		
			10–19	13740.3	0	0.0		
			20–29	21750.1	0	0.0		
			30–39	243982	8	32.8		
			40–49	21041.5	22	104.6		
			50–59	13899.1	109	784.2		
			60–69	6846.2	372	5433.7		
			70+	978.1	198	20242.5		
	Russian	male	0–9	1794.7	1	55.7	807.4	
			10–19	4476.2	0	0.0		
			20–29	6805.0	0	0.0		
			30–39	8643.8	1	11.6		
			40–49	7665.4	12	156.5		
			50–59	5649.8	33	584.1		
			60–69	2571.3	205	7972.6		
			70 +	267.4	74	27673.6		
		female	0–9	1938.0	0	0.0		
			10–19	4663.7	0	0.0		
			20–29	7324.9	0	0.0		
			30–39	9243.1	2	21.6		
			40–49	8111.3	12	1.17		
			50–59	6187.4	22	355.6		
			60–69	2869.2	133	4635.5		
			70+	380.7	70	18385.2		

Notes. Mortality rates are directly age and gender standardized; rates for both ethnic groups combined are person-years weighted for ethnicity; rates are given per 100,000 person-years.

[a] Age- and gender-standardized mortality rates for the two ethnic groups.

[b] Person-year weighted age- and gender-standardized mortality rates for both ethnic groups combined.

TABLE 4

Relative risk Estimates for the Control and the Exposed Area (with and without dose estimates) for Different Periods for Cardiovascular Disease, for Heart diseas and for Stroke, Adjusted for Gender, Attained Age, and Ethnicity with No Lag time

	1960–1969		**1970–1979**		**1980–1989**		**1990–1999**	
				Control area				
Person-years	**91,161**		**81,232**		**69,608**		**56,480**	
	RR		**RR**	**CI**	**RR**	**CI**	**RR**	**CI**
CVD	1.00		1.65	(1.34; 1.95)	1.65	(1.40; 1.93)	1.44	1.23; 1.68)
Cases	*261*		*311*		*386*		*400*	
Heart	1.00		1.71	(1.38; 2.12)	1.71	(140; 2.10)	1.54	(1.26 1.88)
Cases	*162*		*188*		*236*		*257*	
Stroke	1.00		1.36	(1.01; 1.84)	1.19	(0.89; 1.59)	1.03	(0.77; l.38)
Cases	*88*		*94*		*101*		*103*	
				Exposed area, with dose estimates				
Person-years	72,545		62,408		51,695		37,110	
	RR		RR	CI	RR	CI	RR	CI
CVD	1.00		l.56	(1.34; 1.82)	1.57	(1.35; 1.82)	2.14	(1.85 2.47)
Cases	*326*		*373*		*375*		*136*	
Heart	1.00		1.46	(1.19; l.78)	1.56	(128; 1.90)	2.28	(1.89; 2.74)
Cases	*194*		*206*		*217*		*328*	
Stroke	1.00		1.58	(1.21; 2.07)	1.51	(1.15; 1.98)	2.05	(1.59; 2.65)
Cases	*103*		*117*		*113*		*161*	
				Exposed area, without dose estimates				
Person-years	20,051		16,861		13,884		9,690	
	RR		RR	CI	RR	CI	RR	CI
CVD	1.00		1.17	(0.84; 1.63)	0.94	(0.79; 1.28)	1.40	(1.06; 1.85)
Cases	*88*		*64*		*85*		*135*	
Heart	1.00		1.22	(0.80; 1.85)	0.92	(0.62; 1.36)	1.17	(0.96; 1.95)
Cases	*54*		*41*		*52*		*84*	
Stroke	1.00		1.14	(0.64; 2.04	0.84	(0.49; 1.45)	1.24	(0.75; 2.03)
Cases	*30*		*21*		*25*		*39*	

TABLE 5

Relative Risk Estimates for the Exposed Group Compared to the Comparison Group for Cardiovascular Disease, for Heart Disease and for Stroke, Adjusted for Gender, Attained Age, Ethnicity and Time

	Exposed group		Comparison group			
	With dose estimates		Not exposed			
CoD	**Cases**	**Person-years**	**Cases**	**Person-years**	**RR**	**95% CI**
CVD	1498	172,250	1358	298,482	2.27	(2.10; 245)
heart	878		843		2.23	(2.02; 2.6)
stroke	453		386		2.30	(2.00; 2.65)
	Without dose estimates					
CVD	355	43,757	1358	298,482	1.85	(1.65; 2.08)
heart	220		843		1.88	(1.62; 2.19)
stroke	111		386		2.01	(1.62; 2.49)

Note. 10-year lag time, settlements with dose estimates and without dose estimates

TABLE 6a

Relative Risk Estimates among the Exposed for Different Dose Categories for Cardiovascular Disease, for Heart Disease and for Stroke, Adjusted for Gender, Attained Age, Ethnicity and Calendar Period as Well as Estimates for ERR/Gy, 10-Year Lag Time, All Settlements with Dose Estimates

	Dose category (Gy)						
	0	**>0–0.05**	**>0.05–0.1**	**>0.1–0.3**	**>0.3–0.6**	**0.6 +**	**ERR/Gy**
Person-years	314,117	70,775	49,965	20,465	7,651	7,759	
CVD	1.00	2.22 (2.02; 2.45)	2.29 (2.05; 2.55)	1.89 (1.61; 2.21)	2.15 (1.72; 2.70)	2.26 (1.77; 2.88)	3.15 (2.48; 3.81)
Cases	*1,491*	*604*	*436*	*175*	*80*	*70*	
Heart disease	1.00	2.17 (1.91; 2.46)	2.23 (1.93; 2.57)	1.91 (1.56; 2.34)	1.95 (1.44; 2.66)	2.42 (1.78; 3.29)	3.22 (2.33; 4.10)
Cases	*926*	*348*	*253*	*107*	*43*	*44*	
Stroke	1.00	2.39 (2.00; 2.85)	2.40 (1.96; 2.92)	1.74 (1.29; 2.37)	2.33 (1.56; 3.47)	2.13 (1.35; 3.34)	2.96 (1.77; 4.14)
Cases	*420*	*192*	*134*	*47*	*26*	*20*	

TABLE 6b

Relative Risk Estimated among the Exposed for Different Dose Categories for Cardiovascular Disease, for Heart Disease and for Stroke, Adjusted for Gender, Attained Age, Ethnicity and Calendar Period as Well as Estimates for ERR/Gy, 10-Year Lag Time, Exposed Settlements with Dose Estimates

	Dose category (Gy)						
	0	**>0–0.05**	**>0.05–0.1**	**>0.1–0.3**	**>0.3–0.6**	**0.6 +**	**ERR/Gy**
Person-years	15,635	70,775	49,965	20,465	7,651	7,759	
CVD	1.00	1.06 (0.88; 1.28)	1.08 (0.89; 1.31)	0.97 (0.77; 1.21)	1.07 (0.81; 1.42)	1.05 (0.78; 1.40)	0.02 (−0.32; 0.37)
Cases	*133*	*604*	*436*	*175*	*80*	*70*	
Heart disease	1.00	1.01 (0.79; 1.28)	1.02 (0.80; 1.31)	0.97 (0.72; 1.29)	0.96 (0.66; 1.38)	1.07 (0.74; 1.55)	0.06 (−0.39; 0.52)
Cases	*83*	*348*	*253*	*107*	*43*	*44*	
Stroke	1.00	1.29 (0.90; 1.87)	1.28 (0.87; 1.86)	1.02 (0.65; 1.58)	1.31 (0.78; 2.19)	1.12 (0.64; 1.96)	−0.06 (−0.65; 0.54)
Cases	*34*	*192*	*134*	*47*	*26*	*20*	

TABLE 6c

Relative Risk Estimates among the Exposed for Different Dose Categories for Cardiovascular Disease, for Heart Disease and for Stroke, Adjusted for Gender, Attained Age, Ethnicity, Calendar Period and Exposure Status (yes/no) and Estimates for ERR/Gy, 10-Year Lag Time, All Settlements with Dose Estimates

	Dose category (Gy)						
	0	**>0– 0.05**	**>5–0.1**	**>0,1–0.3**	**>0.3–0.6**	**0.6 +**	**ERR/Gy**
Person-years	314,117	70,775	49,965	20,465	7,651	7,759	
CVD	1.00	1.06 (0.88; 1.28)	1.08 (0.89; 1.31)	0.97 (0.77; 1.21)	1.07 (0.81; 1.42)	1.04 (0.78; 1.40)	0.02 (−0.32; 0.36)
Cases	*1,491*	*604*	*436*	*175*	*80*	*70*	
Heart disease	1.00	1.00 (0.79; 1.28)	1.02 (0.79; 1.30)	0.96 (0.72; 1.29)	0.95 (0.66; 1.38)	1.07 (0.74; 1.55)	0.06 (−0.39; 0,52)
Cases	*926*	*348*	*253*	*107*	*43*	*44*	
Stroke	1.00	1.28 (0.89; 1.85)	1.27 (0.87; 1.85)	1.01 (0.65; 1.57)	1.30 (0.78; 2.17)	1.12 (0.64; 1.94)	−0.06 (−0.65; 0.54)
Cases	*420*	*192*	*134*	*47*	*26*	*20*	