УДК 616.1:314.14-614.876 (574)

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MORTALITY FROM CARDIOVASCULAR DISEASES IN THE POPULATION OF KAZAKHSTAN EXPOSED TO RADIATION

Abstract

This paper reports an analysis of theSemipalatinsk historical cohort exposed to radioactive fallout from nuclear testing inthe vicinity of the Semipalatinsk nuclear test site, Kazakhstan. The cohort study, which includes 19,545 persons of exposed and comparison villages in theSemipalatinsk region, had been set up in the 1960s and comprises 582,656 personyearsof follow-up between 1960 and 1999. Radiation dose estimates in thiscohort range from 0 to 630 mGy (whole body external). Overall, the exposedpopulation showed a high mortality from cardiovascular disease. A dose-response relationship that was foundwhen analyzing the entire cohort could completely be explained by differencesbetween the baseline rates in exposed and unexposed groups. When taking thisdifference into account no statistically significant dose-response relationship for allcardiovascular disease was found.

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-cancereffects. An increased risk for both heart disease and stroke was first demonstrated instudies of patients who underwent high-dose therapeutic radiation schemes for thetreatment of Hodgkin's disease *(1)*, breast cancer *(2, 3)* and peptic ulcer *(4)*. The firstevidence of an increased risk of circulatory disease risks at lower doses was reportedfrom the Life Span Study (LSS) of Japanese atomic bomb survivors *(5)*. The resultsare suggestive of a linear no threshold risk for circulatory disease in the dose range 0to 4 Sv (weighted dose to the colon, defined as external gamma ray dose + 10 xexternal 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) and0.12 (90 % CI: 0.02-0.22), respectively. A study among Chernobyl liquidatorsreported an increased risk of cerebrovascular disease when the dose exceeded 150mGy (external gamma dose) within a time period of not more than six months *(6)*.

A recent review concluded that there is neither a convincing mechanisticexplanation for the induction of cardiovascular disease at low and moderate dosesnor is the epidemiological evidence persuasive *(7)*. At least, it is suggestive, andfurther epidemiological research was encouraged by previous reviews *(8, 9)*.The authors of a review of health effects from nuclear testing worldwidepointed to the potential of on-going epidemiological research of populations exposedto fallout from Soviet nuclear testing for helping to establish current radiation riskestimates (*10)*. In this present analysis, the risk of cardiovascular disease isdescribed for the Semipalatinsk historical cohort, for which analyses have alreadybeen reported with respect to solid cancer mortality *(11, 12)*. Between 1949 and1989, more than 450 nuclear tests were conducted at the Semipalatinsk Nuclear TestSite (SNTS), Kazakhstan *(13)*. Areas inhabited by a total of more than ten thousandpeople north-east and south-east of SNTS were considerably affected by falloutmainly due to 118 atmospheric and surface nuclear tests carried out from 1949 to1962.

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 comparingrates 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, to a large extent, based on the archives of the ScientificResearch Institute for Radiation Medicine and Ecology (SRIRME), Semipalatinsk,and have been described in detail elsewhere *(11, 14)*. SRIRME is the successorinstitute of the "Dispanser No. 4", a local research institution founded in 1957 for thepurpose of investigating the health impact of fallout exposures. Routine datacollection had started in the early 1960s and continued through the years of Sovietrule; in the 1990s those data were computerized and the follow-up was extended. Forthis 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 theSemipalatinsk region. Ten highly exposed and six comparison settlements werechosen for a cohort study. Cohort sampling included the exposed villages ofCheremushka, Dolon, Kainar, Kanonerka, Kaskabulak, Karaul, Kundyzdy, Mostik,Sarzhal and Znamenka. Inclusion criteria for the exposed group were date of birthprior to January 1, 1961 and confirmed permanent residence in the exposedsettlement from date of their birth until the end of 1962, when atmospheric nucleartesting was terminated. Thus, the cohort's exposed group includes 9,850 permanentresidents of the above settlements. The medical follow-up included yearlyexaminations and medical care of the population in the villages and, if required, indistrict and regional health centers.

Further, six comparison villages located several hundreds of kilometerseast/south-east of the Semipalatinsk test site were included for comparison. Inclusioncriteria for this comparison group were date of birth prior to January 1, 1961 andpermanent residence in the villages of Bol'shaiaBukon, Ivanovka, Karandykol, Kokpekty, Preobrazhenka, or Ulguli-Malshi. The comparison group was frequency-matchedto the exposed group by gender and age and includes 9,604 permanentinhabitants of these villages.A further inclusion criterion applied at the time of the establishment of bothexposed 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 examplecancer or infectious disease such as tuberculosis or brucellosis) when the cohort wasset up. Regular updates ensured to maintain a complete vital status follow-upincluding emigration information during the entire follow-up period. For deceasedcohort 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-upprocedures and ascertainment of causes of death were independent of exposurestatus. Quality control of coding procedures *(15)*, searches for duplicates andplausibility checks have been performed within the cohort database.To what extent ethnicity can be used as a surrogate variable for socioeconomicconditions and/or lifestyle still requires evaluation, but since dietary habitsin Kazakhstan have been reported to vary between the Kazakh and Russianpopulation *(16)*, we also stratified the cohort by ethnicity. Following the availableclassification in the data, "ethnicity" was coded as a binary variable, labeled "Kazakh"and "Russian" for cohort members of central Asian descent and Russian/otherEuropean descent, respectively.For this analysis, a dosimetric approach was used based on estimatingindividual doses for times and locations where historical data were available. For asmall subset of the exposed population, this approach did not allow to calculate anindividual dose. Those individuals were not included in the risk analysis.Subsequently, the number of individuals, the number of person-years and the doseestimates differ from those used in a previous analysis *(11)*.

Exposure data

For the purpose of a study on thyroid diseases amongst the population living in thevicinity of the Semipalatinsk nuclear test site, the NCI developed a dosimetry systembased on a joint U.S./Russian dose reconstruction methodology that combines theexperience of dose-reconstruction scientists in Russia and the U.S. *(17, 18)*. Themethod is similar, with some unique aspects, to methods used in other studies toestimate doses from nuclear weapons testing fallout. Basically, the dosereconstruction was based on fallout deposition from a total of 11 different testsconducted at the SNTS between August 29, 1949 and September 25, 1962 identifiedby Russian experts as the only ones that might have resulted in effective doses ofmore than 5 mSv to the local population *(19)*. The approach is described with moredetail elsewhere *(20)*. Table 1 gives an overview on the mean external dose and thedose 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, coveringa 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 ethnicity-standardized ratesare given for the cohort under study. This is done for the entire population and for thetwo ethnic groups of Kazakhs and Russians separately. All confidence limits givenare those of 95%. For those comparing rates between the two ethnic groups,Greenland/Robins confidence limits for Mantel-Haenszel weighted relative risks areused. For each cohort member, person-years were accumulated from 1 January1960 or from birth, whichever came later, until death, end of follow-up on 31December 1999, or the date of emigration, whichever came first.For risk analysis only those subjects were taken into account for whom a dosecould be estimated, i.e., 17,303 out of 19,454 (89%); 2,151 (11%) subjects had to beexcluded from the analyses. Amongst the excluded 2,151 subjects, 372 of all 3,340death cases from cardiovascular disease occurred (11%). Out of 17,303 subjects, afurther 1,465 had to be excluded because their date of birth was later than thenuclear test relevant for their specific settlement. Thus, the final cohort for riskanalysis comprised 15,838 subjects delivering 470,732 person-years with overall2,985 cases of cardiovascular disease. Since there were no nuclear tests relevant forthe unexposed group, none of the individuals from this group was excluded.For each cohort member, person-years were accumulated from 1 January1960 until death, end of follow-up on 31 December 1999, or the date of emigration,whichever came first. A time-lag of 10 years was used, i.e. 129 cases occurringwithin the first 10 years after the relevant test were omitted from therisk analysis. This time-lag is irrelevant for the test in 1949. A first comparison wasmade between the exposed cohort and the control group. For dose-responseanalyses, Poisson regression methods were used to fit relative risk models using thesoftware program EPICURE with the DATAB and AMFIT packages *(22)*.Data are cross-classified by various time-dependent variables. Age atexposure was classified in 10-years-categories 0-9, 10-19, …, 60-69, 70+. The samecategories were chosen for attained age and for time since exposure. Calendarperiod of observation is categorized as 1960-1969, 1970-1979, 1980-1989, 1990-1999, ethnicity as Kazakh and Russian. Two types of analyses were performed:categorical analyses without assumptions on the form of the dose-responserelationship, and a linear Poisson regression model. In the categorical analysesdoses were categorized into six groups referring to exposure of 0, 0-.05, 0.05-0.1,0.1-0.3, 0.3-0.6, and 0.6+ Gy. In the linear Poisson regression model the excessrelative risk (ERR) per unit dose and the corresponding 95% confidence limits werecalculated.

Results

Descriptive results

Table 1 shows the main characteristics of the study population. The entirecohort consisted of 19,454 persons of which 14,228 (73.1%) were Kazakhs and5,226 (26.9%) were Russians. There was a high percentage of migrated personsamong the two groups (12.1% for Kazakhs and 31.4% for Russians), while 36.9% ofthe Kazakh and 43.3% of the Russian cohort members were deceased at the end offollow-up. Emigration also differed between the comparison and the exposed group:12.4 % of the comparison group and 22.1 % of the exposed group of the historicalcohort had emigrated.

Table 1.

Historical Cohort by Ethnicity and Vital Status.

Nationality	Vital status			Total
	Deceased	Alive	Emigrated	
Kazakh	5249	7252	1727	14228
%	36.9%	51.0 %	12.1 %	73.1 %
Russian	2261	1325	1640	5226
%	43.3 %	25.4 %	31.4 %	26.9 %
Total	7510	8577	3367	19454
%	38.6 %	44.1 %	17.3 %	100.0 %

Table 2 gives the number of all cardiovascular deaths and of person-yearsbroken down by ethnicity, gender and age group. The rates given are directly ageand 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 bothethnic groups

combined were person-years weighted for ethnicity. For all deaths dueto 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 twoethnic groups, the rates given for the entire cohort population are additionallyadjusted for ethnicity. While there is no difference between the two ethnic groups forheart disease (RR=1.01), the relative risk for stroke is 1.27 [1.11;1.45] for Russianscompared to Kazakhs.

Table 2.

Mortality rates from CVD in relation on nationality and sex.

Group	Nationality	Sex	N (abs.)	a Adjusted rate	b Adjusted rate
Exposed	Kazakh	Male	708	840.3	828.3
		Fem.	709		
	Russian	Male	326	807.4	
		Fem.	239		
Control	Kazakh	Male	367	348.4	386.8
		Fem.	547		
	Russian	Male	202	499.3	
		Fem.	242		

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.

There was a clear secular trend of increasingrisks 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. Thesecular trend is similar for males and females.

Risk analysis

Dose estimates were limited to cohort subjects residing in locations for whichhistorical information on fallout deposition was available or could be reasonablyinterpolated from nearby locations. All analyses were restricted to those subjects forwhom a dose estimate was available.

The relative risks in the exposed group compared to the comparison group aregiven in Table 3 for three groups of diagnoses: cardiovascular disease (ICD9 390-459), heart disease (410-429), and stroke (430-438). The comparison was adjustedfor attained age, gender, ethnicity, and calendar period. For the exposed group, theoutcomes are presented for those with and without dose estimates. There was anincreased risk amongst the exposed for all three disease categories (see Table 4).For cardiovascular disease, the relative risk in the exposed cohort with doseestimates was 2.27 [2.10;2.45] in relation to the comparison group. The respectivefigures for heart disease and for stroke are 2.23 [2.02;2.46] and 2.20 [2.00;2.65],respectively.

Table 3.

Relative Risk Estimates for the Exposed Group Compared to the Comparison Group for CVD, for Heart Disease and for Stroke.

Cause of death	Exposed group		Comparison group		RR	95% CI
	N of cases	Person-years	N of cases	Person-years		
CVD	1498	172250	1358	298482	2,27	(2.10; 2.45)
Heart diseases	878		843		2,23	(2.02; 2.46)
Stroke	453		386		2,20	(2.0; 2.65)

Because of the large difference in mortality from cardiovascular diseasebetween the exposed and the comparison group and because of a comparablefinding for cancer mortality *(11)*, Table4 gives the relative risk estimates in six-dose categories for all the groups of diagnoses as well as the respective values forERR/Gy, assuming a linear dose-response relationship. When including thepopulations from the exposed and the unexposed villages into the analysis, there is asignificant dose-response relationship. Also it can be seen that the riskamong the exposed is roughly twice as high as among the unexposed, independentof the dose category.

Thus, it is necessary to test for a dose-response relationshiponly among the cohort members from the exposed villages. Here, for none of theselected causes of death a dose-response relationship was detectable.The estimates for ERR/Gy were non-significant in all instances, i.e., forcardiovascular disease it was 0.02 [-0.32;0.37], for heart disease it was 0.06 [-0.39;0.52], and for stroke it was -0.06 [-0.65;0.54]. Similar results were obtainedwhen the population from the comparison group was included, but stratification byexposure status (yes/no) was included in the analysis (see Table 6c).Further, it was tested whether the estimates for risk per unit dose differbetween Kazakhs and Russians. For all cardiovascular disease, when stratifying byattained age, gender, calendar period and exposure status (yes/no), risk estimateswere 0.12 [-0.30;0.54] and -0.19 [-0.78;0.39], respectively.

Table 4

Relative Risk Estimates among the Exposed for Different Dose Categories for CVD, for Heart Disease and for Stroke, All Settlements with Dose Estimates.

Cause of death	Dose category (Gy)						ERR/Gy
	0	>0-0.05	>0.05-0.1	>0.1-0.3	>0.3-0.6	0.6+	
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)
Heart diseases	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)
Stroke	1,00	2.39 (2.00; 2.85)	2,40 (1.96; 2.92)	1.74 (1.29; 2.92)	2.33 (1.56; 3.47)	2.13 (1.35; 3.34)	2.96 (1.77; 4.14)

Discussion

We conducted a radiation risk analysis amongst the Semipalatinsk historical cohort inrelation to deaths from cardiovascular disease. A dose-response relationship for thecohort could completely be explained by differences between the baseline rates inexposed and unexposed groups. When taking this difference into account nostatistically significant dose-response relationship was detected for all cardiovasculardisease, heart disease, or stroke.There was a significantly higher risk among those residing adjacent to the testsite than among those living in villages of the comparison area. This pattern wasseen for all diagnoses under study. An important difference between the exposedand the comparison area is the fact that the population in the control area was amore or less stable one, while that in the exposed villages to a large extent were resettledfrom other locations (i.e., those of German descent during World War II) orwho came in during Khrushchev's New Land policy that began in 1954. Because ofthis large difference in risk, dose-response analyses were meaningful only whenrestricted to the exposed cohort or stratified by exposure status. In the cohort, wefound clear secular trends showing increasing risks in later years compared to thefirst years of follow-up. We found no statistically significant relation between previousradiation exposure from nuclear testing and subsequent mortality risks from any ofthe death causes under study. Nonetheless, the point estimate for the ERR/Gy of0.02 for mortality from all cardiovascular disease (ICD9 390-459) is compatible withthe 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 ourstudy point in the opposite direction. We also tested whether there might be a doseresponserelationship when only looking at ischemic heart disease (ICD9 410-414).This was not the case, ERR/Gy was 0.03 [-0.44;0.50].Our results were based on a time lag of 10 years. It has been suggested thatthe radiation related risk for cardiovascular disease mortality shows up more than 15years after exposure *(3)*. Thus, we repeated the analyses using a time lag of 20years with stratification by attained age, gender, ethnicity, calendar period andexposure status. This resulted in higher point estimates with wide confidenceintervals: cardiovascular disease 0.15 [-0.26;0.55], for heart disease 0.20 [-0.34;0.74], and for stroke 0.10 [-0.62;0.82].

A strength of our cohort study is the prospective character of the study's datacollection which had begun in the 1960s and was carried out with regular updates ofcause-of-death and migration information from the rural administration. Thiscontributed to an excellent completeness of follow-up records; losses to follow-upwere exclusively due to emigration. Whereas emigration rates were low and did notdiffer by exposure status between 1960 and 1990, a substantial increase inemigration 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 and22.1 % of the exposed group of the historical cohort had emigrated. However, it hasbeen shown elsewhere that this did not influence results on solid cancer risk basedon this cohort *(11)*. But it cannot be excluded, that the higher risks observed in thelast decade of the 40-years 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 whostayed.

We are well aware of the discussion of dose estimates for the populationresiding close to the Semipalatinsk nuclear test site *(22)*. We were able to base ouranalysis on a dosimetry system which was developed by NCI for the purpose of astudy on thyroid diseases *(20)* and which is based on the experience from otherstudies requiring dose estimation from nuclear testing *(e.g. 23)*. In the context of thisanalysis, the dose assessment is for external whole body dose from gamma raysemitted from fallout deposited on the ground. As discussed earlier, we could notderive dose estimates for individuals from all villages included in the cohort studybecause there is no archival data on fallout deposition available for those locations. Itis assumed to be highly unlikely that information from those villages which were notcovered by dosimetry system would change the results substantially, becauseexposures in those villages were in the same dose range as the others when originalKazakh dose estimates were taken into account (see *(11*): Cheremushka is locatedclose to Dolon and exposure there might be comparable to that of Dolon; Kaskabulak, Kundyzdy and Mostik are supposed to have doses comparable toKanonerka or Znamenka). On the other hand, if the subjects in those settlementswere less exposed than those from the exposed area with available dose estimatesand if there was a radiation related risk, the lower risk amongst those from theexposed area without available dose estimates might be explained by exposuredifferences. But this cannot be tested because of missing information.The current dosimetry avoided the overestimation that is derived from theoriginal Kazakh dosimetry as used in *(11)* and is in good agreement with othermeasures of external exposure, e.g., thermoluminescence signals in bricks and EPRmeasurements of human tooth enamel *(22)*. Here it may be worth noting thatbecause of the energetic nature of gamma rays from fallout (several hundred keV ormore), the doses to all organs are similar and the dose to the heart wasapproximated as the dose to the whole body. It is not clear, to what extent internalexposure was relevant for the dose to the heart of the exposed population, butneither the heart nor the circulatory system concentrate any of the nuclides that mightbe ingested. The exposure primarily results from maintaining residence in thecontaminated areas for the first month after fallout deposition with the first few daysthe 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 underway so it is difficult to knowto what degree the true slope of the dose-response function might be masked due touncertainties in dose. We believe, however, that the uncertainties for external dosein 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 onthe order of a geometric standard deviation of 1.5 to 2.0 depending on whether theexposure took place near to a location where actual exposure-rate measurementswere available, or whether the exposure took place at a location that requiredinterpolation of data. We based our conclusions about that level of uncertainty fromdetailed analyses made on other cohorts who received external exposure from fallout(see for example, *(23)*).Though an increase in atherosclerosis and heart diseases has been reportedin animal experiments and in humans after high-dose radiotherapy *(25)*, only a fewstudies have systematically assessed cardiovascular data in the low-dose range. Themost compelling evidence of such radiation effects comes from the Life Span Studyof the atomic bomb survivors *(5)*. Doses ranged from 0 to 4 Sv whole-body dosesfrom external gamma and some neutron radiation. For mortality from heart diseasesand from stroke linear dose-response relationships were observed. For heartdiseases, 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 significantquadratic dose

response relationship for the incidence of myocardial infarction wasreported among those exposed at age lower than 40 years *(26)*. Analyses of clinicaldata of the AHS-study showed significantly higher total serum cholesterol levels *(27)* and higher blood pressure *(28)* among the irradiated compared to unirradiatedsubjects.

A recent review of epidemiological studies on the risk of cardiovasculardisease following radiation exposure concluded that high radiation doses to the heartand coronary arteries received in the course of certain radiotherapy procedures leadto an increased risk of circular diseases, but that the epidemiological evidence forsuch an effect in the range of low and moderate doses is rather suggestive thanpersuasive *(8).* However, a meta-analysis concluded that a radiation induced riskcannot be excluded *(7)*. With respect to individual studies, a pooled cohort studyamong radiation workers revealed no indication for a radiation related risk forcardiovascular disease *(29)*. Inconclusive results were derived from cohort studiesamong radiologists or radiological technologists. Here, only a cohort study among90, 852 U.S. radiological technologists was positive *(30)*. Excess circulatory diseasemortality was found among those who started working in the early years whenexposures had been high. A similar trend was observed for deaths fromcerebrovascular diseases and ischemic heart diseases. Among miners exposed toradon and its progeny, no relationship between coronary heart disease and radonwas found *(31, 32)*. For a German uranium miners cohort, there was also noindication for an effect from long-lived radionuclides or from external gammaradiationin the range of 0 to 909 mSv *(31)*.

Though not statistically significant, there is a remarkable difference in thedose-response relationship between the Kazakhs and the Russians, showing ahigher risk amongst the first. This finding is unexplained with the current analysis.While these differences do not affect the overall conclusions of this study, futureassessment of lifestyle and cultural attributes of these two ethnic groups couldprovide valuable information of the cardiovascular disease risks.An observation of the study findings from the Semipalatinsk historical cohortidentified the relative young age of cardiovascular death in the study cohort. This isparticularly significant given the perceived 'healthy' condition of the cohort. Thehigher rates of cardiovascular disease at younger ages are consistent with othergeographic areas including the southeastern portion of the United States where therates of cardiovascular disease and stroke have been long recognized as greaterthan other parts of the country with similar population demographic *(33, 34)*. As anexample, considering the southeastern states of the US, the annual mortality rate(standardized to the Kazakh study population) for all cardiovascular diseases is126.1 per 100,000 individuals and year *(35)*. And the cardiovascular diseasemortality rates are higher for the Kazakhstan cohort than amongst this high risk USpopulation. The disease risks occurring at higher rates at earlier ages may beassociated with different etiologies including: exposure to factors increasing diseaserisks and exposure in fetal and early life that affect the disease process *(36-38)*.These observations support further investigation. Specifically, studies should includean 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 thecurrent knowledge insofar that doses leading to an increased risk for deaths fromcardio-vascular diseases seem to have either to be very high or to have a high doserate. The latter is also supported by results from the Chernobyl liquidators *(6)*. Thatwould go together with radiobiological considerations *(8, 39)*. According to these, epidemiologic findings are compatible with radiobiological data from experimentalanimals. The critical target structure appears to be the endothelial lining of bloodvessels, in particular arteries, leading to early functional alterations such as proinflammatoryresponses and other changes, which are slowly progressive *(40)*. Hoelspeculated that if direct damage to the arterial endothelial cells is the cause for CVDeffects 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-doseionizing radiation might be different from that for high-dose radiation with respect tocardiovascular diseases *(42)*. Regarding our study, the vast majority of receiveddoses are well below 0.5 Gy (mean 0.09 Gy), but it cannot be ruled out that a smalleffect of radiation exposure is masked by the strong secular trend, which reflects theconstant decrease in life expectancy from the 1960s to the 1990s *(43)* or could notbe detected because of limited power. Nonetheless, our findings are supported bythe fact that a dose-response relationship for circulatory diseases among the atomicbomb survivors could not be observed at doses below 0.5 Gy *(44)*.

Still, it remains unclear why the cardiovascular disease risk among thoseresiding in close proximity to the test site is so much higher than among the controlgroup. These results also support the consideration of environmental exposures inthe further investigations regarding the mechanisms associated with excesscardiovascular disease risks.

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