CARDIOVASCULAR AND CEREBROVASCULAR DISEASES IN THE EXTENDED COHORT OF MAYAK NUCLEAR WORKERS

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Abstract – A second analysis of incidence and mortality from ischemic heart disease (IHD) and cerebrovascular diseases (CVD) in relation to external gamma-ray and/or internal alpha-particle exposures accounting for non-radiation factors in the expanded cohort of 18,763 workers (25.3 % of whom were females) first employed at one of the main facilities of Mayak Production Association (Mayak PA) in 1948-1972 and followed-up to the end of 2005 was performed. After adjusting for non-radiation factors and internal dose to liver, risk of IHD and CVD incidence statistically significantly increased with total gamma-ray dose. Risk of CVD incidence – but not mortality – statistically significantly increased with total absorbed dose to liver from internal alpha-particle radiation. There was a statistically significantly increasing trend in IHD mortality with increasing total absorbed dose to liver from internal alpha-particle radiation, which tended to be lower and statistically insignificant if follow-up was restricted to Ozyorsk residence or adjustment for external gamma-ray dose was used. The ERR/Gy estimates obtained in this study agreed with ones obtained in the previous (first) analysis of Mayak workers and other large occupational studies, although the risk estimates for the CVD incidence were higher as compared with estimate from the Japanese A-bomb survivors study.
Key words: circulatory diseases; occupational exposure; gamma-rays; alpha-particle radiation; Mayak workers

INTRODUCTION

The first study (Azizova et al 2010a,b) in a cohort of 12,210 Mayak workers first employed at one of the main facilities during the first ten years of operations (1948–1958) showed a statistically significant effect of external and internal exposures on circulatory diseases. It should be noted that the work environment during the first years of the Mayak PA operations was the most unfavorable, when workers were exposed to high doses of both external gamma-rays and internal alpha-particle radiation due to plutonium intake. The aim of this study was to assess incidence and mortality risks from ischemic heart disease (IHD) and cerebrovascular diseases (CVD) in an expanded cohort with an additional 6,553 workers first employed in 1959-1972 in relation to dose of external and internal exposures taking non-radiation factors into account.

MATERIAL AND METHODS

The study cohort included 18,763 workers (25.3% females) first employed at one of the main facilities of Mayak , i.e. reactors, radiochemical and plutonium plants, in 1948-1972 regardless of gender, age, nationality, occupation, and other characteristics. Approximately 82% of workers started their employment at ages less than 30 y. The overwhelming majority (88.3%) of workers had the permanent workplace at one of the main facilities. The mean duration of work at the main facilities was 13–15 y.

In this study dose estimates and occupational histories from *Doses-2005* dosimetry system were used (Fountos and Rabovsky 2007; Vasilenko et al 2007a,b). To be noted, workers employed at the reactors could be only exposed to external gamma-rays, however, workers employed at radiochemical and plutonium production facilities could be exposed to both external gamma-rays and internal alpha-particle radiation from incorporated plutonium.

Individual annual external gamma-ray doses were known for all workers from the study cohort. The mean total gamma-ray dose for the whole period of employment at the Mayak PA (± standard deviation, SD) was 0.66±0.84 Gy (95% percentile 2.53 Gy) for males and 0.52±0.69 Gy (95% percentile 1.98 Gy) for females; the mean annual gamma-ray dose was 0.08±0.14 Gy (95% percentile 0.33 Gy) for males and 0.07±0.12 Gy (95% percentile 0.31 Gy) for females. More than a half (62.2%) of all workers were exposed to total gamma-ray dose less than 0.5 Gy, while 22.1% of workers were exposed in doses more than 1 Gy.

Internal plutonium body burden was measured in 33% of workers (30.0% of workers first employed before 1958 and 38.5% of workers first employed between 1959 and 1972). Amongst those who were monitored, the mean plutonium body burden (±SD) was 1.53 ± 6.00 kBq (95% percentile 5.49 kBq) in males and 2.94 ± 19.41 kBq (95% percentile 5.36 kBq) in females. The absorbed dose to liver was used a surrogate of the dose to muscles, which is likely to be similar to the dose to blood vessels. Despite the fact that dose to liver may differ from dose to muscles they are strongly correlated. Therefore, dose to liver was used to study risk of IHD and CVD in relation to alpha-particle radiation from incorporated plutonium. Amongst those who were monitored, total absorbed dose to liver from internal alpha-particle radiation was 0.26 ± 0.90 Gy (95% percentile 1.01 Gy) for males and 0.56 ± 3.75 Gy (95% percentile 1.33 Gy) for females. More than a half (65.8%) of monitored workers were exposed to total absorbed dose to liver from internal α-radiation less than 0.1 Gy.

Vital status as of 31 December 2005 was known for 94.4% of cohort members, at that it was known that 56.6% deceased and 43.4% were alive. For those workers, who did not migrated from Ozyorsk (residents), vital status was known virtually for all (99.96%) but four individuals. It was known that about 46% of cohort members migrated from Ozyorsk by 31 December 2005 (migrants). Mean age (± SD) of workers, who were known to be alive by the end of 2005, was 67.1±7.8 y among males and 73.8±6.9 among females. Mean age (± SD) at death for those workers known to have died by the end of follow-up was 60.3±13.3 y among males and 68.0±12.3 among females.

Data on morbidity for the whole period of living in Ozyorsk till the end of follow-up was collected for 95% of workers from the studied cohort. It could not be possible to collect primary data for only 5% of workers due to loss of all the medical documentation. Cause of death was known for 95.7% of cohort members (99.2% of Ozyorsk residents and 91.3% of migrants), who were known to have died. All diseases and causes of death were coded in accordance with the International Classification of Diseases of the 9th revision (ICD-9) (Guide 1980). Sources of morbidity information were archival and current medical cards, case histories and were described in detail earlier elsewhere (Azizova et al 2008). Basic sources of information on date and cause of death for Ozyorsk residents and migrants were different. Basic sources of information on date and cause of death for residents were medical cards, case histories, log files of “Emergency medical care”, autopsy records, forensic medical examination records, medical death certificate and dearth certificate of the Civil Registration Office (Azizova et al 2008). Data on vital status, date and cause of death for migrants were provided by the Epidemiological laboratory of the Southern Urals Biophysics Institute (SUBI) from the constantly updated Medical-Dosimetry Register for Mayak workers.

Procedure for search and collection of this information was described in detail earlier elsewhere (Koshurnikova et al 1999).

Data on non-radiation factors such as smoking (91.5%), alcohol consumption (86.5%), blood pressure (95.2%), body mass index (79.6%) etc, which play important role in the development of circulatory diseases, was also collected. All collected primary dosimetry and medical data were entered into the “Clinic” medical-dosimetry database (Azizova et al 2008).

Effects studied include incidence of and mortality from IHD (ICD-9 codes: 410-414) and CVD (ICD0-9 codes: 430-438). Period of follow-up started from the date of employment at one of the main facilities and continued until the earliest of: date of IHD or CVD diagnosis (in case of incidence analysis); date of death or 31 December 2005 for those workers, who were known to be alive; date of migration from Ozyorsk or date of “last medical information” in case of unknown vital status.

In general, the second analysis of the expanded cohort of Mayak workers first employed during 1948-1972 used the same approach as the first analysis of workers employed during the first ten years of Mayak operation (Azizova et al 2010a,b). Comparisons were made within the studied cohort.

Analysis included calculations of relative risks (RR) for the categories of one or more factors with adjustment for other variables, 95% confidence intervals (CI) for RRs and p-values for tests on statistical significance by likelihood methods using AMFIT module of EPICURE software (Preston et al 1993). I addition to categorical analysis, models for trends were fitted in relation to exposure dose by Poisson regression using AMFIT module of EPICURE software. In particular, excess relative risk per Gray (ERR/Gy), i.e. risk minus 1, was described by linear trend in relation to external or internal exposures with adjustment (via stratification) for non-radiation factors.

In the main analyses adjustment via stratification was made for gender, attained age (<20, 20 – 25, …, 80 – 85, >85), calendar period (1948 – 1950, 1951 – 1955, 1956 – 1960, …, 1996 – 2000), period of the first employment at one of the main facility (1948 – 1953, 1954 – 1958), facility (reactors, radiochemical or plutonium), smoking (ever-smoker, never-smoker, unknown) and alcohol consumption (ever-consumed, never-consumed, unknown). Sensitivity analyses were also performed to study effect of:

- additional adjustments for non-radiation factors in the analyses of radiation factors (hypertension [without/with hypertension, unknown], body mass index [< normal, normal, > normal, unknown], duration of employment [<1, 1 – 5, 5 – 10, 10 – 20, 20 – 30, >30]);
- adjustment for internal dose in the analysis of external exposure and vice versa;
- using different lag periods (0, 5, 10, 15 and 20 y) for dose of external and internal exposures.

Above this, variation of radiation risks in relation to gender, facility or attained age was also analyzed.

Two approaches were used for lagging external and internal doses. The main approach implied that the first *x* years following the start of radiation work were omitted when lagging external/internal doses by *x* years (delayed entry). The sensitivity analyses were performed with person-years calculated from the start of radiation work, while the first *x* years following the start of work were assigned to the zero dose category when lagging external/internal doses by *x* years.

To allow for the possibility that radiation might affect CVD risk by modifying levels of blood pressure (Preston et al 2003; Ivanov et al 2001) and body mass index (Telnov 1985), the level of these factors at the time of preliminarily medical examination (before employment at Mayak PA) was considered, in order to avoid systematic errors that might arise through adjusting for values of these factors at later times. In contrast, smoking and alcohol consumption were classified at the time of last information (for the mortality analysis) or at the time of last information prior to the first diagnosis of CVD (for the incidence analysis).

The risk analysis with regard to internal exposure was restricted to workers monitored for potential intake of plutonium. The incidence analysis was restricted to the period of workers' residence in Ozyorsk, because the information on incidence and non-radiation risk factors was missing for migrants after their departure from Ozyorsk.

RESULTS

Numbers of cases and deaths identified in the study cohort by 31 December 2005 and corresponding numbers of person-years for the analyses are shown in Table 1.

Table 1. Numbers of cases and deaths identified in the study cohort by 31 December 2005 and corresponding numbers of person-years for the analyses.

Disease	Incidence/Mortality	Number of cases/deaths	Person-years
IHD	Incidence	6134	351635
	Mortality	2629	717459
CVD	Incidence	7326	336738
	Mortality	1495	717459

External exposure

RRs for IHD and CVD incidence and mortality according to the categories of the total absorbed gamma-ray doses (<0.2 Gy; 0.2 – 0.5 Gy; 0.5 – 1.0 Gy; and > 1.0 Gy), as well as estimates of ERR/Gy are shown in Table 2.

Table 2. RRs and ERR/Gy (95% CI) for IHD and CVD incidence and mortality according to the dose categories of external gamma-ray exposure (main analysis based on 0-year lag period).

	RRs (vs. <0.2 Gy)			ERR/Gy
	0.2 – 0.5 Gy	0.5 – 1.0 Gy	> 1.0 Gy	
IHD incidence	0.90 (0.82; 0.98)	0.95 (0.86; 1.04)	1.10 (0.99; 1.21)	0.10 (0.05; 0.15)
IHD mortality	0.95 (0.83; 1.08)	0.94 (0.82; 1.09)	1.09 (0.95; 1.26)	0.06 (-0.01; 0.13)
CVD incidence	1.12 (1.04; 1.22)	1.21 (1.10; 1.32)	1.61 (1.47; 1.76)	0.41 (0.32; 0.50)
CVD mortality	0.91 (0.77; 1.08)	1.09 (0.91; 1.32)	0.97 (0.80; 1.18)	0.03 (-0.06; 0.12)

Table 2 shows that IHD incidence risk is decreased among workers exposed to external gamma-ray dose 0.2-0.5 Gy as compared with workers exposed to lower doses. Evidence of the revealed decreased risk of IHD incidence was mainly related to females (results not shown). It could be seen that evidence of increased risk of IHD incidence among workers exposed to doses above 1 Gy was marginal. Adjustments for blood pressure, body mass index, duration of employment and internal alpha-particle radiation had little effect on the findings. There was a statistically significant increasing trend in IHD incidence with total dose of external gamma-ray exposure (Fig.1). Evidence of the trend I IHD incidence with external exposure was related mainly to males, workers at the reactors and radiochemical facility.

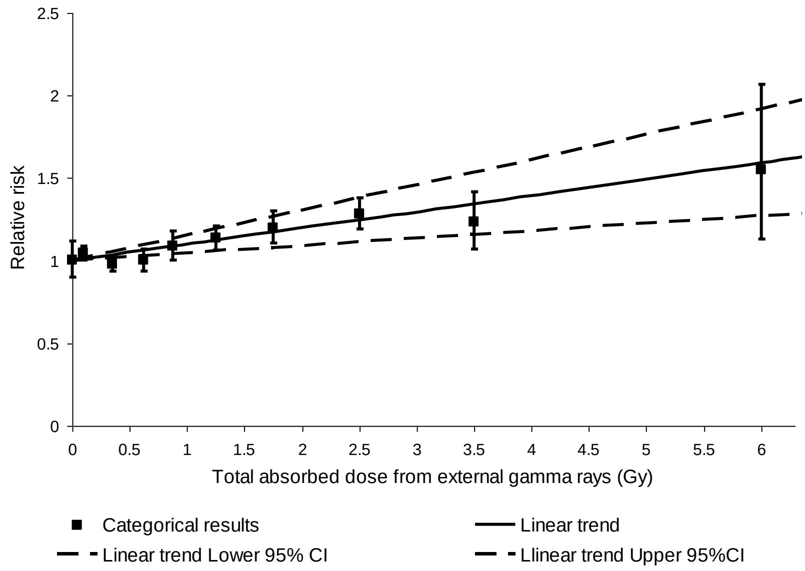

Fig.1. IHD incidence in relation to total external gamma-ray dose: ERR/Gy = 0.10 (95% CI 0.05; 0.15) based on 0-lag period.

Table 2 shows that CVD incidence was statistically significantly higher among workers exposed to external gamma-rays in total dose above 0.2 Gy as compared with workers exposed to lower doses. This finding did not change much for different lag periods, using additional adjustments for non-radiation factors (blood pressure, body mass index, duration of employment). The evidence of these differences was present even if additional adjustment for external gamma-ray dose was used and also in the analyses by gender and facility.

There was statistically significantly increasing trend in CVD incidence with increasing total gamma-ray doses (Fig. 2). Adjustments for blood pressure, body mass index, duriation of employment and internal exposure had little effect on ERR/Gy estimate. ERR/Gy among females was statistically significantly higher as compared with males (p-value for interaction = 0.015), although it was statistically significantly above zero among both males and females.

There were no statistically significant differences in IHD or CVD mortality either between the categories of the total external gamma-ray dose (Table 2). The estimates of ERR/Gy were all consistent with no excess risk.

Internal exposure

RRs for IHD and CVD incidence and mortality according to the categories of the total absorbed alpha-particle liver doses (<0.025 Gy; 0.025 – 0.1 Gy; 0.10 – 0.50 Gy; and > 0.50 Gy), as well as estimates of ERR/Gy are shown in Table 3.

Table 3 shows that risk of IHD incidence was statistically significantly higher among workers exposed to internal alpha-particle radiation in total dose to liver >0.10 Gy as compared with workers exposed to total dose to liver <0.025 Gy based on 0-year lag period; however this finding was sensitive to using other lag periods and introducing additional adjustments. There was no statistically significant trend (ERR/Gy) for IHD incidence with total absorbed dose to liver from internal alpha-particle radiation either with or without adjustment for external gamma-ray dose. At this estimates of ERR/Gy for IHD incidence in relation to total dose of internal alpha-particle radiation was statistically significantly higher among males than among females (p-value for interaction = 0.04).

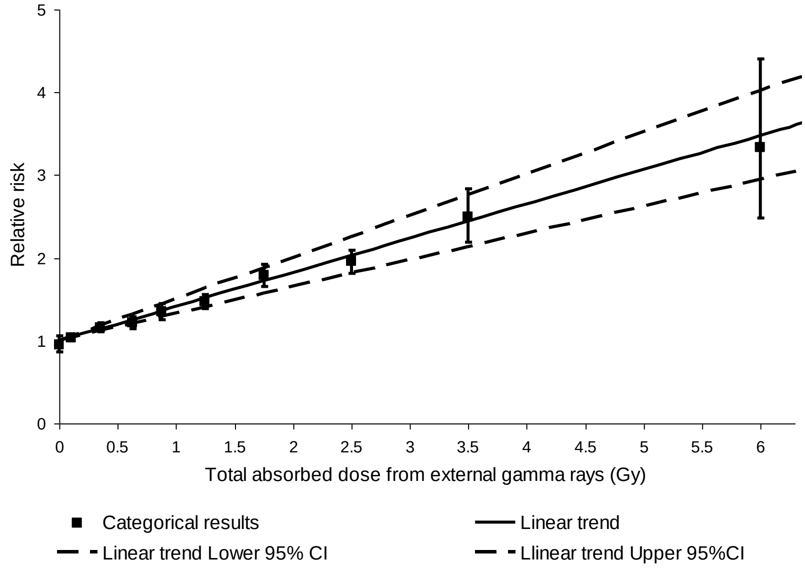

Fig.2. CVD incidence in relation to total absorbed dose of external gamma-rays: ERR/Gy = 0.41 (95% CI 0.32; 0.50) based on 0-lag period.

Table 3. RRs and ERR/Gy (95% CI) for IHD and CVD incidence and mortality according to the liver dose categories of internal alpha-particle exposure (main analysis based on 0-year lag period).

	RRs (vs. <0.025 Gy)			ERR/Gy
	0.025 – 0.10 Gy	0.10 – 0.50 Gy	> 0.50 Gy	
IHD incidence	0.99 (0.91; 1.08)	1.12 (1.01; 1.24)	1.21 (1.02; 1.42)	0.01 (-0.01; 0.03)
IHD mortality	1.31 (1.08; 1.59)	1.46 (1.17; 1.81)	1.87 (1.38; 2.53)	0.26 (0.07; 0.46)
CVD incidence	1.09 (1.00; 1.17)	1.23 (1.12; 1.35)	1.57 (1.34; 1.84)	0.10 (0.03; 0.15)
CVD mortality	0.85 (0.64; 1.11)	1.12 (0.83; 1.50)	1.02 (0.65; 1.61)	0.14 (-0.08; 0.37)

Risk of IHD mortality was statistically significantly higher among workers exposed to internal alpha-particle radiation in total dose to liver >0.025 Gy using 0-, 5- and 10-year lag period and in dose >0.10 Gy using 15- and 20-year lag period as compared with workers exposed to total internal alpha-particle dose to liver <0.025 Gy. This finding did not change if additional adjustments were used. There was a statistically significantly increasing trend in IHD mortality with liver dose from internal alpha-particle exposure, but estimate of ERR/Gy became lower and statistically non-significant if follow-up was restricted to Ozyorsk or adjustment for external exposure was used. The evidence for this trend related primarily to males as well workers from radiochemical facility, although results were consistent between males and females as well as between radiochemical and plutonium facilities workers (p-value for interaction > 0.05).

CVD incidence was statistically significantly higher among workers exposed to internal alpha-particle radiation in total dose to liver >0.025 Gy as compared with workers exposed to lower doses irrespectively of using additional adjustments for other non-radiation factors. There was borderline evidence of such difference when different lag periods or adjustment for external exposure were used.

There was statistically significant increasing trend in CVD incidence with increasing total absorbed internal alpha-particle dose to liver (Fig. 3). Estimate of ERR/Gy for CVD incidence increased with increasing lag period. Adjustment for body mass index, employment duration and external exposure did not change the ERR/Gy estimate much. The evidence for this trend related mainly to males rather than females (p-value for interaction < 0.001) as well as radiochemical rather than plutonium facility workers (p-value for interaction = 0.001).

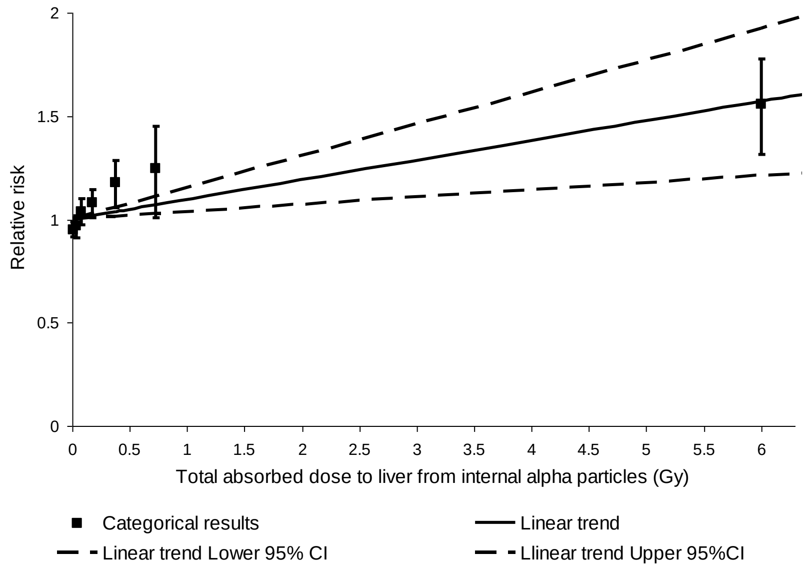

Fig.3. CVD incidence in relation to total absorbed dose to liver from internal alpha-particle radiation: ERR/Gy = 0.10 (95% CI 0.03; 0.15) based on 0-year lag period.

CVD mortality statistically significantly did not differ between categories of the total absorbed liver dose from internal alpha-particle exposure (Table 3) and there was no statistically significant trend in CVD mortality in relation to internal alpha-particle liver dose.

Exclusion of the first years of follow-up did not have great effect on the obtained results from the analyses of both external and internal exposures. findings for the different categories of attained age were too imprecise to judge whether RRs for IHD and CVD incidence and mortality varied between categories of attained age.

Comparison with other cohorts

Estimates of ERR/Gy for IHD and CVD incidence and mortality in this study agree with the estimates obtained in the previous study of Mayak worker cohort (Azizova et al 2010a,b) and studies of other cohorts exposed to external radiation with low LET (Table 4). It should be mentioned that ERR/Gy estimate for CVD incidence was higher than corresponding estimate for A-bomb survivors (Yamada et al 2004).

At present there is no information on risk estimates for IHD and CVD in cohort of workers exposed to internal alpha-particle radiation from incorporated plutonium so it is not feasible to compare risk estimates obtained in the current study. It should be only mentioned that total absorbed liver dose from internal alpha-particle radiation due to incorporated plutonium would be higher that dose to vessels/chambers of the heart, and ERR/Gy estimate obtained in the current study using liver dose would be lower the corresponding ERR/Gy estimate obtained using dose to blood vessels.

Table 4. Comparison of ERR/Gy estimates for IHD and CVD after external exposure to low LET radiation.

Cohort	Mean dose (Gy)	Mortality or incidence	Lag period (years)	Number of deaths or cases	ERR/Gy
Ischemic heart disease					
Japanese A-bomb survivors: Life Span Study (Shimizu et al 2010)[1]	0.20[2]	Mortality	5	3252	0.02[3] (95% CI 0.10, 0.15)
Japanese A-bomb survivors: Adult Health Study (Yamada et al 2004)	0.57[4]	Incidence	13	1546	0.05[5] (95% CI -0.05, 0.16)
Mayak workers, 1948-1958, followed to 2000 (Azizova et al 2010a)	0.84	Mortality	10	1461	0.07 (95% CI -0.02, 0.15)
Mayak workers, 1948-1972, followed to 2005 (this study)	0.63	Mortality	10	2583	0.06 (95% CI -0.01, 0.13)
Mayak workers, 1948-1958, followed to 2000 (Azizova et al 2010a)	0.84	Incidence	10	3133	0.12 (95%CI 0.05, 0.19)
Mayak workers, 1948-1972, followed to 2005 (*this study*)	0.63	Incidence	10	5274	0.11 (95% CI 0.05, 0.18)
Nuclear workers (international) (Vrijheid et al 2007)	0.018[6]	Mortality	10	5821	-0.01 (95% CI -0.59, 0.69)
BNFL workers (UK) (McGeoghegan et al 2008)	0.053	Mortality	15	3567	0.70[7] (90% CI 0.33, 1.11)
UK National Registry for Radiation Workers (Muirhead et al 2009)	0.025	Mortality	10	7168	0.26 (95% CI -0.05, 0.61)
Chernobyl recovery operations workers (Ivanov et al 2006)	0.109	Incidence	-[8]	10942	0.41 (95% CI 0.05, 0.78)
Cerebrovascular diseases					
Japanese A-bomb survivors: Life Span Study (Shimizu et al 2010)[9]	0.20[2]	Mortality	5	9622	0.09[3] (95% CI 0.01, 0.17)
Japanese A-bomb survivors: Adult Health Study (Yamada et al 2004)	0.57[4]	Incidence	13	729	0.07 (95% CI -0.08, 0.24)
Mayak workers, 1948-1958, followed to 2000 (Azizova et al 2010b)	0.84	Mortality	10	744	-0.02 (95% CI -0.12, 0.08)
Mayak workers, 1948-1972, followed to 2005 (this study)	0.63	Mortality	10	1480	0.04 (95% CI -0.06, 0.13)
Mayak workers, 1948-1958, followed to 2000 (Azizova et al 2010a)	0.84	Incidence	10	3840	0.45 (95% CI 0.34, 0.56)
Mayak workers, 1948-1972, followed to 2005 (this study)	0.63	Incidence	10	7264	0.40 (95% CI 0.30, 0.49)
Nuclear workers (international) (Vrijheid et al 2007)	0.018[6]	Mortality	10	1224	0.88 (95% CI -0.67, 3.16)

[1] Values given are for deaths from ICD 9 codes 410-414 during 1950-2003.
[2] Weighted sum of gamma and neutron doses to the colon among survivors with doses of 0.005 Sv or more (1).
[3] Not adjusted for smoking or alcohol.
[4] Weighted sum of gamma and neutron shielded kerma doses. Doses to the Japanese A-bomb survivors arose predominantly from gamma radiation.
[5] Adjusted for smoking and alcohol.
[6] Dose to lung.
[7] Based on underlying cause of death. Results based on underlying and contributory causes combined are similar to these for IHD and higher ERR/Gy for CVD.
[8] Not cited in paper.
[9] Values given are for deaths from ICD 9 codes 430-438 during 1950-2003.

BNFL workers (UK) (McGeorghegan et al 2008)	0.053	Mortality	15	1018	0.43[7] (90% CI -0.10, 1.12)
UK National Registry for Radiation Workers (Muirhead et al 2009)	0.025	Mortality	10	1817	0.16 (95% CI -0.42, 0.99)
German uranium miners (Kreuzer et al 2006)	0.041	Mortality	5	1297	0.09 (95% CI -0.6, 0.8)
Chernobyl recovery operations workers (Ivanov et al 2006)	0.109	Incidence	-[8]	12832	0.45[3] (95% CI 0.11, 0.80)

CONCLUSION

Having adjusted to non-radiation factors there was statistically significant increasing risk of IHD and CVD with external gamma-ray dose and CVD incidence with total absorbed liver dose from internal alpha-particle radiation. ERR/Gy estimates agreed with estimates from the previous study and were generally compatible with estimates from the large-scale studies, although estimate for CVD incidence in relation to external exposure was higher as compared with estimate from the Japanese A-bomb survivors study.

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