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ORIGINAL PAPER

# Cerebrovascular diseases in nuclear workers first employed at the Mayak PA in 1948–1972

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**Abstract** Incidence and mortality from cerebrovascular diseases (CVD) (430–438 ICD-9 codes) have been studied in a cohort of 18,763 workers first employed at the Mayak Production Association (Mayak PA) in 1948–1972 and followed up to the end of 2005. Some of the workers were exposed to external gamma-rays only while others were exposed to a mixture of external gamma-rays and internal alpha-particle radiation due to incorporated $^{239}$Pu. After adjusting for non-radiation factors, there were significantly increasing trends in CVD incidence with total absorbed dose from external gamma-rays and total absorbed dose to liver from internal alpha radiation. The CVD incidence was statistically significantly higher among workers with total absorbed external gamma-ray doses greater than 0.20 Gy compared to those exposed to lower doses; the data were consistent with a linear trend in risk with external dose. The CVD incidence was statistically significantly higher among workers with total absorbed internal alpha-radiation doses to liver from incorporated $^{239}$Pu greater than 0.025 Gy compared to those exposed to lower doses. There was no statistically significant trend in CVD mortality risk with either external gamma-ray dose or internal alpha-radiation dose to liver. The risk estimates obtained are generally compatible with those from other large occupational studies, although the incidence data point to higher risk estimates compared to those from the Japanese A-bomb survivors. Further studies of the unique cohort of Mayak workers chronically exposed to external and internal radiation will allow improving the reliability and validating the radiation safety standards for occupational and public exposure.

## Introduction

The emergence of evidence for a statistically significant trend in mortality from cerebrovascular disease (CVD) in the Life Span Study (LSS) of Japanese Atomic Bomb survivors (Preston et al. 2003) has prompted a search for supporting evidence in other exposed populations. In particular, evidence has been sought to clarify the extent to which the risk per unit dose seen in the LSS following acute high-dose exposure to external radiation of low linear energy transfer (LET) also applies to chronic or fractionated exposure and whether the risk (per unit dose) is similar for low-dose exposures. It is also very important to gather information on CVD risks after internal exposure (for example, to alpha-particle emitters such as $^{239}$Pu) because the LSS did not provide any information on such risks and because many workers have received and continue to receive such exposures.

In response to this need for more information, CVD incidence and mortality were investigated in a cohort of Mayak Production Association (PA) workers. The first analysis (Azizova et al. 2010) of the cohort of 12,210 workers first employed at one of the main Mayak plants during 1948–1958 and followed up through the end of 2000 found a statistically significant increasing trend in CVD

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incidence, but not mortality, with both total external gamma-ray dose and internal liver dose from alpha-particle radiation due to incorporated $^{239}$Pu. It was found that while the CVD incidence trend with external doses appeared to be broadly consistent with a linear dose response, the CVD incidence trend with internal doses appeared to show some degree of non-linearity. However, interpretation of these results was difficult due to large uncertainties in the risks at low doses and because the trend estimates in CVD incidence with internal liver dose varied between men and women and also between workers at the radiochemical plant and the plutonium production plant.

This paper presents the second analysis of CVD incidence and mortality risks in the expanded cohort of Mayak workers with additional 6,553 workers first employed during 1959–1972 and exposed to lower external and/or internal doses and with follow-up extended by 5 years through the end of 2005.

## Materials and methods

The study cohort includes all workers first employed at one of the main Mayak plants (reactors, radiochemical or plutonium production plants) during 1948–1972, regardless of gender, age, nationality, occupation, and other characteristics. Workers, who used to work at more than one plant, were included in the cohort only once. Workers who were involved in radiation incidents/accidents with single gamma-neutron exposure at high dose rates and who developed acute radiation syndrome, as well as workers exposed to other radionuclides, were excluded from the study cohort. The methods of identifying the cohort of Mayak workers have been described previously (Koshurnikova et al. 1999; Azizova et al. 2008).

The cohort includes 18,763 individuals, of whom 4,744 (25.3%) are women. More than half (65%) of these workers were first employed during the first 10 years of operations at the Mayak PA (1948–1958). For the overwhelming majority (88%) of workers, only one of the main plants was the permanent workplace. The mean duration of work at the main plants was 13–15 years. About 82% of workers started their employment at ages less than 30 years. The male and female workers started their work at the Mayak PA at a mean (±1 standard deviation, SD) age of 24.4 ± 7.2 years and 26.5 ± 7.6 years, respectively.

Work histories and dose estimates from the dosimetry system "*Doses-2005*" established in the framework of Russian–American project on radiation health effects research (Fountos and Rabovsky 2007; Vasilenko et al. 2007a, b) were used in the present study.

The analysis of CVD incidence and mortality accounted for different types of exposures, i.e., workers at the reactors were exposed to external gamma-rays, whereas workers at the radiochemical and plutonium production plants, in addition to external gamma-rays, could be exposed to internal alpha radiation from incorporated $^{239}$Pu.

It should be noted that individual dosimetric monitoring of external exposure was performed at Mayak PA from the beginning of operations there. Regular monitoring of internal exposure among those who might have been exposed to $^{239}$Pu began later during the 1960s (Vasilenko et al. 2007a, b). Results of individual monitoring of external and internal exposure were recorded in individual dosimetric cards and journals. The data contained in these documents formed the basis for the establishment of the dosimetric database for Mayak PA workers.

Individual annual doses from external gamma-rays are available for all workers in the study cohort. The mean (±SD) total dose from external gamma-rays for the whole period of employment was 0.66 ± 0.84 Gy (95% percentile of 2.53 Gy) for men and 0.52 ± 0.69 Gy (95% percentile of 1.98 Gy) for women; the mean annual doses from external gamma-rays were 0.08 ± 0.14 Gy (95% percentile of 0.33 Gy) and 0.07 ± 0.12 Gy (95% percentile of 0.31 Gy), respectively. Over half (62.2%) of workers were exposed to external gamma-rays with total dose less than 0.5 Gy, while 22.1% of workers were exposed with total dose greater than 1 Gy. Annual external gamma-ray doses varied over time and tended to be highest during 1949–1953 (see Fig. 1 from Vasilenko et al. 2007a).

$^{239}$Pu body burden was measured only in 33% workers (30.0% workers first employed before 1958 and 38.5% workers first employed in 1959–1972). Among those who were monitored, the mean (±SD) $^{239}$Pu body burden was 1.53 ± 6.00 kBq (95% percentile of 5.49 kBq) for men and 2.94 ± 19.41 kBq (95% percentile of 5.36 kBq) for women. As in the first analysis, the absorbed dose to liver was used as a surrogate of the dose to muscles, which is likely to be similar to the dose to blood vessels and the chambers of the heart. Although doses to liver and muscles would differ, they should be highly correlated with each other. Thus, the liver dose was used to look for dose–response relationship between alpha-radiation exposure to incorporated $^{239}$Pu and CVD risk. Among those who were monitored, the total absorbed dose (±SD) to liver from internal alpha radiation was 0.26 ± 0.90 Gy (95% percentile of 1.01 Gy) for men and 0.56 ± 3.75 Gy (95% percentile of 1.33 Gy) for women. Over half (65.8%) of workers monitored were exposed to internal alpha radiation that resulted in a total absorbed dose to liver of less than 0.1 Gy.

Vital status as of December 31, 2005, was known for 94.4% of cohort members; of them, 56.6% were known to have died and 43.4% were known to be alive. For individuals who continued to be residents of Ozyorsk, vital status was known for all but four persons (99.96%). About

46% of cohort members migrated from Ozyorsk as of December 31, 2005. The mean (±SD) age of workers known to be alive at the end of 2005 was 67.1 ± 7.8 years for men and 73.8 ± 6.9 years for women. The mean (±SD) age of workers at death was 60.3 ± 13.3 years for men and 68.0 ± 12.3 years for women.

The information on disease incidence for the whole period of residence in Ozyorsk up to the end of follow-up was collected for 95.0% of workers in the study cohort. The primary data could not be found for 5.0% of workers only due to the loss of medical records. The cause of death was known for 95.7% of cohort members (99.2% of Ozyorsk residents and 91.3% of migrants).

All diseases and causes of death were coded according to International Classification of Diseases, Revision 9 (ICD-9) (Guide to International statistical classification of diseases, traumas and causes of death 1980). Among the information sources on incidence, there were archived and current medical cards, and case histories, as described earlier (Azizova et al. 2008). The main sources of information on the date and cause of death for Ozyorsk residents and migrants were different. The main sources of information on the date and cause of death for the city residents were medical cards, case histories, emergency ambulance registration journals, post-mortem examination protocols, forensic medical examination journals, medical certificate of death, and death records at the Civil Registration Office (Azizova et al. 2008). The information on vital status, date, and cause of death for migrants was provided by the SUBI Laboratory of Epidemiology from the constantly maintained Medical Dosimetry Registry of Mayak workers; the information retrieval and collection procedures were described elsewhere (Koshurnikova et al. 1999).

The information on various non-radiation factors such as smoking (91.5%), alcohol consumption (86.5%), blood pressure (95.2%), body mass index (79.6%), which can play an important role in CVD, was collected for the study cohort. The primary dosimetry and medical data collected were entered into the "Clinic" Medical Dosimetry Database (Azizova et al. 2008).

The effects studied were both incidence and mortality from CVD (ICD-9 codes: 430–438). The follow-up period started from the date of first employment at one of the main Mayak PA plants and continued until the earliest of:

- date of the first diagnosis of CVD (for the incidence analysis); date of death; or December 31, 2005, for those known to be alive at that time;
- date of departure from Ozyorsk or the date of "last medical information" for those with unknown vital status.

The current analyses of the expanded cohort of workers first employed at one of the main facilities during 1948–1972 was performed similar to our previous study of workers employed during the first 10 years of operations at the Mayak PA (Azizova et al. 2010) using the AMFIT module of EPICURE (Preston et al. 1993). All comparisons were performed within the study cohort of Mayak workers.

The analyses involved calculating relative risks (RRs) for categories of factors with adjustments for other variables, the 95% confidence intervals (CI) for the RRs, and *p*-values from tests of statistical significance were obtained via likelihood-based methods. Attention was initially directed to the analyses of risks from non-radiation factors, following which radiation factors were analyzed with adjustment through stratification for non-radiation factors.

In addition to the categorical analyses, the excess relative risk (ERR) (i.e., the relative risk minus 1) was modeled by a linear trend with external or internal dose with adjustment through stratification for non-radiation factors using Poisson regression methods.

In the main analyses, adjustment was made for gender, attained age (<20, 20–25, …, 80–85, >85 years), calendar period (1948–1950, 1951–1955, 1956–1960, …, 2001–2005), period of first employment at the main plant (1948–1953, 1954–1958, 1959–1963, 1964–1968, 1969–1972), plant (reactors, radiochemical or plutonium production),[1] smoking (ever-smoker, never-smoker, unknown),[2] and alcohol consumption (ever-drinker, never-drinker, unknown).[3]

Sensitivity analyses were conducted to examine the impact of:

- introducing additional non-radiation factors for which adjustment was made in the analyses of radiation factors (hypertension[4] [without, with, unknown], body mass index[5] [<norm, norm, >norm, unknown], duration of work [<1, 1–5, 5–10, 10–20, 20–30, >30 years]);
- adjusting for internal dose in the analyses of external dose and vice versa;
- using various lag-periods (0, 5, 10, 15, and 20 years) for external and internal doses.

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[1] The category of 'plutonium production plant' includes workers, who have ever worked at the plutonium production plant; the category of 'radiochemical plant' includes those, who have worked at the radiochemical plant, but never at the plutonium production plant; the category of 'reactors' includes workers, who have worked at the reactors, but never at the other two plants.

[2] The 'never smokers' are workers, who have claimed to be never smokers at several medical examinations.

[3] The 'never drinkers' are workers, who have claimed to be never drinkers at several medical examinations.

[4] The 'hypertension' is a condition in which the arterial blood pressure is over 140/90 mm hg.

[5] The 'normal body mass index' is equal to 18.5–24.99 kg/m$^2$.

Furthermore, examination was made of how radiation risks might vary by gender, between Mayak PA main plants, and by attained age. *p*-values for interaction analyses were calculated using likelihood-based methods.

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) as in studies of other cohorts of radiation workers such as the UK National Registry for Radiation Workers (Muirhead et al. 2009). This reduces the impact of possible differences in mortality and incidence between the periods shortly after starting radiation work and subsequently associated the selection of persons into work. The second approach implied that person-years were 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 circulatory disease risk by modifying levels of blood pressure (Ivanov et al. 2001; Preston et al. 2003) and body mass index (Telnov 1985), the level of these factors at the time of pre-employment medical examination 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 circulatory disease (for the incidence analysis).

The risk analysis with regard to internal exposure was restricted to workers monitored for potential intake of $^{239}$Pu. The incidence analysis was restricted to the period of workers' residence in Ozyorsk, because the information on incidence and non-radiation factors was missing for migrants after their departure from Ozyorsk.

This record-based epidemiological study did not require any contact with the cohort members. The project was reviewed and approved by the Institutional Review Board of the Southern Urals Biophysics Institute (SUBI).

## Results

As of December 31, 2005, there were 7,326 cases of CVD registered in the study cohort during 336,738 person-years of follow-up, and 1,495 deaths from CVD during 717,459 person-years. The major contribution (98.0%) to CVD incidence was made by chronic forms (ICD-9 codes: 433, 437, 438). The main contribution (62.2% in the whole cohort and 81.9% in Ozyorsk residents) to mortality from CVD was made by acute forms (ICD-9 codes: 430, 431, 432, 434, 435, 436).

### Non-radiation factors

It is known that various non-radiation factors, such as gender, age, smoking, hypertension, excess body mass, can play a significant role in the development of CVD. These risk factors were re-examined for the expanded cohort, and the results were generally consistent with those of the first analysis (see supplementary Table S1 on the web-site); only the notable differences are reported here.

As expected, rates of incidence and mortality from CVD were significantly lower among women versus men and increased with age among both men and women. CVD incidence was significantly lower among workers first employed at the one of the main Mayak PA plant after 1953 compared to those employed in 1948–1953, both for men and for women. However, CVD incidence did not vary greater between post-1953 cohorts. The CVD mortality analysis showed that it was only significantly higher among workers first employed in 1959–1963 compared to those employed before 1953 for both sexes.

The CVD incidence was statistically significantly higher among both men and women at the radiochemical and plutonium production plants as compared to those at the reactors. However, there were no statistically significant differences in mortality from CVD in the study cohort with regard to plant. There were no statistically significant differences in CVD incidence according to the age at starting employment whereas CVD mortality increased with increasing age at starting employment.

As expected, in view of the possible loss to follow-up among migrants, mortality from CVD was significantly lower among those who left Ozyorsk compared to the city residents.

Smoking among men was statistically significantly associated with increased CVD incidence and mortality, whereas there was no such evidence for women. However, the numbers of CVD cases and deaths among female smokers was relatively small compared to the numbers among female never-smokers, reflecting the low prevalence of smoking among women (4.1%), whereas most (71.6%) of the men were smokers. There were no statistically significant differences in CVD incidence and mortality between never-drinkers and current or ex-drinkers for both women and men (the portion of never-drinkers was 5.8% among men and 54.9% among women).

CVD incidence and mortality among men was statistically significantly higher for those who had hypertension at the pre-employment medical examination compared to those who did not have this condition at that time. For women, a similar pattern was observed, but the differences were not statistically significant. CVD mortality was statistically significantly higher for female workers who had increased body mass at the pre-employment medical examination compared to those who had normal body mass. In contrast, there were no statistically significant differences in relation to body mass in incidence and mortality from CVD for men and CVD incidence for women.

### Radiation factors

#### *External exposure*

RRs of incidence and mortality from CVD by categories of total absorbed dose from external gamma-rays (<0.2 Gy, 0.2–0.5 Gy, 0.5–1.0 Gy, >1.0 Gy) along with estimates of ERR/Gy based on a linear model are given in Tables 1 and 2.

Categorical analysis revealed that CVD incidence was statistically significantly increased for workers with total dose from external gamma-rays greater than 0.2 Gy compared to those exposed to lower doses (Table 1). The findings depended neither on the lag-period (0, 5, 10, 15, 20 years) nor on additional adjustments for other non-radiation factors (hypertension, body mass index, duration of employment). The marginal evidence of existing differences with external dose remained even after adjustment for internal dose, as well as in analyses of CVD incidence with regard to plant and gender.

There was a significantly increasing trend in CVD incidence with external gamma-rays dose (Fig. 1). Table 1 shows that adjustment for hypertension, body mass index, duration of employment, and internal dose as well as restriction to workers at different plants did not affect much estimates of ERR/Gy. ERR/Gy was statistically significantly higher for women as compared to men ($p$-value = 0.015 for interaction effect), although it was statistically significantly raised among both men and women. There was no evidence of variation in the ERR/Gy by attained age. No significant effect modification was observed by smoking and alcohol consumptions. Exclusion of the first years of follow-up did not affect the incidence findings.

In the CVD mortality analyses (Table 2), for none of the total dose categories were the risks statistically significantly different from the baseline category (less than 0.2 Gy) and neither the addition of extra adjusting factors nor the use of restricted datasets altered this result. The estimates of ERR/Gy were all consistent with no excess risk. The findings were generally too imprecise to judge whether the relative risks varied by attained age, although there was some borderline evidence that the ERR/Gy for CVD mortality in relation to external dose decreased log-linearly with increasing attained age (Table 2).

#### *Internal exposure*

RRs of incidence and mortality from CVD by categories of total absorbed dose to liver from internal alpha radiation (<0.025 Gy, 0.025–0.10 Gy, 0.10–0.50 Gy, >0.5 Gy) along with estimates of ERR/Gy based on a linear model are given in Tables 3 and 4.

Categorical analyses revealed that CVD incidence was statistically significantly higher among workers with total internal alpha-radiation liver dose greater than 0.025 Gy compared to those with lower dose regardless of adjustment for other non-radiation factors (Table 3). Analyses incorporating different lag-periods, adjustment for external exposure, exclusion of the first years of follow-up, exclusion adjustment for smoking and alcohol consumption, or analysis by gender or plant had only a marginal effect on the results.

There was a statistically significant increasing trend in CVD incidence with total liver dose from internal alpha radiation (Fig. 2). Similar to our previous study (Azizova et al. 2010), ERR/Gy for CVD incidence increased with lag-period, excluding the early years of follow-up did not have a notable influence on the findings of the lagged analyses. Adjustment for body mass index, duration of employment, and external dose as well as exclusion of adjustment for smoking and alcohol consumption did not affect much estimates of ERR/Gy though ERR/Gy was slightly higher after adjustment for hypertension.

The revealed trend in CVD incidence with internal dose related largely to attained age of 50–59 years though variations of ERR/Gy by categories of attained age were statistically insignificant. The evidence for this trend related primarily to men than women ($p$-value <0.001 for interaction effect) and workers of the radiochemical plant rather than plutonium workers ($p$-value = 0.001 for interaction effect).

There were no statistically significant differences in RRs from CVD mortality by categories of total liver dose from internal alpha-particle radiation nor was the trend (ERR/Gy) significantly different from zero (Table 4). The analyses incorporating different lag-periods or additional adjustments for other non-radiation factors did not affect the results. No significant effect modification was observed by smoking and alcohol consumptions. There was no significant impact on the categorical or trend analyses of restriction of follow-up to Ozyorsk or adjustment for external dose nor was there significant variation by plant or gender. There was insufficient data for a reliable analysis by attained age.

## Discussion

Medical and biological effects of occupational exposure at Mayak PA have been little known to the world scientific community and not accounted for in the development of radiation safety standards and radiation protection

**Table 1** CVD incidence: analyses by external dose

| | <0.2 Gy | | 0.2–0.5 Gy | | 0.5–1.0 Gy | | >1.0 Gy | | ERR/Gy (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| | RR | No. of cases | RR (95% CI) | No. of cases | RR (95% CI) | No. of cases | RR (95% CI) | No. of cases | |
| Main analysis, 0 years lag | 1 | 2,507 | 1.123 (1.036, 1.218) | 1,533 | 1.208 (1.103, 1.323) | 1,250 | 1.608 (1.466, 1.764) | 1,976 | 0.413 (0.324, 0.502) |
| *Main analyses, in which the first x years following the start of radiation work were omitted when lagging doses by x years* | | | | | | | | | |
| Main analysis, 5 years lag | 1 | 2,453 | 1.121 (1.034, 1.216) | 1,525 | 1.183 (1.078, 1.297) | 1,187 | 1.589 (1.446, 1.745) | 1,850 | 0.383 (0.295, 0.470) |
| Main analysis, 10 years lag | 1 | 2,358 | 1.144 (1.052, 1.243) | 1,471 | 1.180 (1.073, 1.299) | 1,103 | 1.596 (1.447, 1.760) | 1,658 | 0.397 (0.303, 0.491) |
| Main analysis, 15 years lag | 1 | 2,298 | 1.131 (1.039, 1.232) | 1,395 | 1.198 (1.086, 1.321) | 1,036 | 1.607 (1.455, 1.777) | 1,471 | 0.429 (0.328, 0.530) |
| Main analysis, 20 years lag | 1 | 2,211 | 1.086 (0.995, 1.186) | 1,295 | 1.139 (1.028, 1.261) | 910 | 1.543 (1.389, 1.713) | 1,212 | 0.379 (0.278, 0.480) |
| *Main analyses, in which the first x years following the start of radiation work were assigned to a "zero dose" category when lagging doses by x years* | | | | | | | | | |
| Main analysis, 5 years lag | 1 | 2,704 | 1.133 (1.046, 1.228) | 1,525 | 1.197 (1.093, 1.311) | 1,187 | 1.611 (1.470, 1.767) | 1,850 | 0.392 (0.305, 0.479) |
| Main analysis, 10 years lag | 1 | 3,034 | 1.126 (1.038, 1.222) | 1,471 | 1.160 (1.057, 1.274) | 1,103 | 1.562 (1.421, 1.717) | 1,658 | 0.374 (0.285, 0.462) |
| Main analysis, 15 years lag | 1 | 3,364 | 1.122 (1.033, 1.219) | 1,395 | 1.182 (1.075, 1.300) | 1,036 | 1.593 (1.446, 1.755) | 1,471 | 0.419 (0.322, 0.515) |
| Main analysis, 20 years lag | 1 | 3,849 | 1.103 (1.013, 1.201) | 1,295 | 1.157 (1.048, 1.276) | 910 | 1.570 (1.420, 1.736) | 1,212 | 0.387 (0.290, 0.485) |
| Main analysis but unadjusted for smoking and alcohol consumption, 0 years lag | 1 | 2,507 | 1.105 (1.024, 1.193) | 1,533 | 1.194 (1.095, 1.301) | 1,250 | 1.553 (1.422, 1.697) | 1,976 | 0.391 (0.308, 0.474) |
| *Adding to stratification (0 years lag)* | | | | | | | | | |
| Hypertension | 1 | 2,507 | 1.120 (1.029, 1.219) | 1,533 | 1.172 (1.064, 1.290) | 1,250 | 1.597 (1.448, 1.761) | 1,976 | 0.415 (0.321, 0.508) |
| BMI | 1 | 2,507 | 1.090 (0.999, 1.189) | 1,533 | 1.191 (1.080, 1.313) | 1,250 | 1.566 (1.416, 1.731) | 1,976 | 0.407 (0.312, 0.503) |
| Employment duration | 1 | 2,507 | 1.121 (1.023, 1.229) | 1,533 | 1.194 (1.077, 1.323) | 1,250 | 1.591 (1.430, 1.771) | 1,976 | 0.421 (0.318, 0.523) |
| Internal dose | 1 | 2,507 | 1.068 (0.976, 1.167) | 1,533 | 1.124 (1.016, 1.244) | 1,250 | 1.477 (1.329, 1.640) | 1,976 | 0.348 (0.254, 0.441) |
| *Analyses (0 years lag) restricted to workers at* | | | | | | | | | |
| Reactors | 1 | 369 | 1.181 (0.992, 1.406) | 391 | 1.290 (1.071, 1.553) | 431 | 1.598 (1.311, 1.949) | 440 | 0.426 (0.222, 0.631) |
| Radiochemical plant | 1 | 440 | 1.073 (0.925, 1.245) | 754 | 1.156 (0.983, 1.360) | 604 | 1.626 (1.390, 1.902) | 1,386 | 0.437 (0.310, 0.564) |
| Plutonium plant | 1 | 1,698 | 1.153 (1.020, 1.303) | 388 | 1.216 (1.039, 1.422) | 215 | 1.461 (1.214, 1.758) | 150 | 0.354 (0.192, 0.516) |
| Males (0 years lag) | 1 | 1,443 | 1.126 (1.020, 1.242) | 1,069 | 1.179 (1.059, 1.313) | 927 | 1.556 (1.394, 1.736) | 1,529 | 0.353 (0.260, 0.447) |
| Females (0 years lag) | 1 | 1,064 | 1.113 (0.965, 1.283) | 464 | 1.297 (1.092, 1.541) | 323 | 1.766 (1.483, 2.102) | 447 | 0.635 (0.403, 0.868) |
| *Attained age (0 years lag)* | | | | | | | | | |
| <40 | 1 | 19 | 1.496 (0.648, 3.454) | 12 | 1.466 (0.578, 3.720) | 11 | 3.145 (1.330, 7.438) | 40 | 1.365 (−0.418, 3.147) |
| 40–49 | 1 | 429 | 1.149 (0.959, 1.377) | 246 | 1.230 (1.012, 1.495) | 230 | 1.673 (1.387, 2.018) | 575 | 0.438 (0.265, 0.612) |
| 50–59 | 1 | 1,293 | 1.040 (0.933, 1.160) | 797 | 1.119 (0.988, 1.269) | 606 | 1.529 (1.343, 1.741) | 889 | 0.383 (0.259, 0.508) |
| 60–69 | 1 | 667 | 1.164 (0.995, 1.361) | 441 | 1.238 (1.038, 1.477) | 373 | 1.469 (1.222, 1.765) | 441 | 0.313 (0.155, 0.471) |
| 70+ | 1 | 99 | 0.814 (0.420, 1.579) | 37 | 1.422 (0.660, 3.064) | 30 | 1.637 (0.718, 3.731) | 31 | 0.279 (−0.473, 1.031)<br>$p = 0.122$[a] |

*CI* confidence interval

[a] Test for a log-linear trend in the ERR/Gy with attained age

**Table 2** CVD mortality: analyses by external dose

| | <0.2 Gy | | 0.2–0.5 Gy | | 0.5–1.0 Gy | | >1.0 Gy | | ERR/Gy (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| | RR | No. of deaths | RR (95% CI) | No. of deaths | RR (95% CI) | No. of deaths | RR (95% CI) | No. of deaths | |
| Main analysis, 0 years lag | 1 | 609 | 0.909 (0.765, 1.079) | 281 | 1.093 (0.906, 1.319) | 250 | 0.972 (0.800, 1.180) | 354 | 0.032 (−0.060, 0.124) |
| *Main analyses, in which the first x years following the start of radiation work were omitted when lagging doses by x years* | | | | | | | | | |
| Main analysis, 5 years lag | 1 | 607 | 0.902 (0.759, 1.071) | 280 | 1.099 (0.910, 1.326) | 249 | 0.970 (0.798, 1.179) | 352 | 0.031 (−0.061, 0.123) |
| Main analysis, 10 years lag | 1 | 605 | 0.903 (0.760, 1.073) | 278 | 1.116 (0.924, 1.347) | 247 | 0.989 (0.814, 1.203) | 350 | 0.036 (−0.057, 0.130) |
| Main analysis, 15 years lag | 1 | 603 | 0.879 (0.738, 1.046) | 269 | 1.128 (0.935, 1.362) | 245 | 1.002 (0.823, 1.219) | 345 | 0.048 (−0.049, 0.144) |
| Main analysis, 20 years lag | 1 | 598 | 0.867 (0.727, 1.035) | 259 | 1.153 (0.953, 1.394) | 239 | 0.997 (0.818, 1.216) | 333 | 0.045 (−0.052, 0.142) |
| *Main analyses, in which the first x years following the start of radiation work were assigned to a "zero dose" category when lagging doses by x years* | | | | | | | | | |
| Main analysis, 5 years lag | 1 | 613 | 0.902 (0.760, 1.072) | 280 | 1.099 (0.911, 1.327) | 249 | 0.971 (0.799, 1.180) | 352 | 0.031 (−0.061, 0.123) |
| Main analysis, 10 years lag | 1 | 619 | 0.903 (0.760, 1.073) | 278 | 1.116 (0.925, 1.346) | 247 | 0.990 (0.814, 1.203) | 350 | 0.037 (−0.057, 0.130) |
| Main analysis, 15 years lag | 1 | 635 | 0.876 (0.736, 1.042) | 269 | 1.125 (0.933, 1.358) | 245 | 0.997 (0.820, 1.212) | 345 | 0.046 (−0.050, 0.143) |
| Main analysis, 20 years lag | 1 | 663 | 0.876 (0.735, 1.045) | 259 | 1.163 (0.962, 1.405) | 239 | 1.011 (0.830, 1.231) | 333 | 0.051 (−0.047, 0.150) |
| Main analysis but unadjusted for smoking and alcohol consumption, 0 years lag | 1 | 609 | 0.922 (0.786, 1.083) | 281 | 1.130 (0.946, 1.349) | 250 | 0.973 (0.809, 1.171) | 354 | 0.021 (−0.064, 0.107) |
| *Adding to stratification (0 years lag)* | | | | | | | | | |
| Hypertension | 1 | 609 | 0.968 (0.806, 1.161) | 281 | 1.119 (0.915, 1.367) | 250 | 1.012 (0.822, 1.246) | 354 | 0.040 (−0.058, 0.139) |
| Body mass index | 1 | 609 | 0.911 (0.755, 1.099) | 281 | 1.121 (0.915, 1.374) | 250 | 1.037 (0.840, 1.281) | 354 | 0.037 (−0.062, 0.136) |
| Employment duration | 1 | 609 | 0.953 (0.796, 1.141) | 281 | 1.154 (0.946, 1.409) | 250 | 0.991 (0.805, 1.220) | 354 | 0.021 (−0.071, 0.113) |
| Restricting follow-up to Ozyorsk (0 years lag) | 1 | 375 | 0.830 (0.662, 1.041) | 168 | 1.007 (0.781, 1.299) | 153 | 0.799 (0.615, 1.036) | 222 | −0.041 (−0.136, 0.054) |
| Also adjusting for internal dose (0 years lag) | 1 | 375 | 0.809 (0.626, 1.045) | 168 | 1.035 (0.780, 1.372) | 153 | 0.894 (0.666, 1.200) | 222 | 0.004 (−0.121, 0.128) |
| *Analyses (0 years lag) restricted to workers at* | | | | | | | | | |
| Reactors | 1 | 110 | 0.818 (0.577, 1.158) | 70 | 1.165 (0.816, 1.663) | 88 | 0.993 (0.674, 1.462) | 79 | 0.067 (−0.141, 0.275) |
| Radiochemical plant | 1 | 119 | 0.978 (0.731, 1.309) | 144 | 1.002 (0.726, 1.383) | 110 | 0.930 (0.685, 1.263) | 246 | 0.004 (−0.104, 0.112) |
| Plutonium plant | 1 | 380 | 0.867 (0.650, 1.155) | 67 | 1.154 (0.832, 1.601) | 52 | 1.058 (0.704, 1.588) | 29 | 0.084 (−0.161, 0.328) |
| Males (0 years lag) | 1 | 349 | 0.938 (0.757, 1.162) | 186 | 1.162 (0.930, 1.451) | 189 | 1.100 (0.876, 1.383) | 288 | 0.058 (−0.052, 0.168) |
| Females (0 years lag) | 1 | 260 | 0.865 (0.649, 1.151) | 95 | 0.939 (0.654, 1.347) | 61 | 0.674 (0.459, 0.990) | 66 | −0.039 (−0.206, 0.129) |
| *Attained age (0 years lag)* | | | | | | | | | |
| <40 | 1 | 8 | 1.623 (0.395, 6.663) | 4 | 0.742 (0.071, 7.731) | 1 | 3.062 (0.485, 19.350) | 4 | 0.557 (−1.776, 2.891) |
| 40–49 | 1 | 19 | 1.274 (0.545, 2.979) | 11 | 0.714 (0.217, 2.350) | 4 | 2.091 (0.717, 6.093) | 9 | 0.450 (−0.738, 1.638) |
| 50–59 | 1 | 80 | 1.208 (0.778, 1.876) | 42 | 1.641 (1.000, 2.693) | 34 | 1.605 (0.924, 2.789) | 43 | 0.278 (−0.169, 0.726) |
| 60–69 | 1 | 155 | 1.037 (0.770, 1.396) | 98 | 1.110 (0.802, 1.537) | 87 | 0.809 (0.571, 1.148) | 104 | −0.057 (−0.180, 0.065) |
| 70+ | 1 | 347 | 0.753 (0.595, 0.952) | 126 | 1.004 (0.779, 1.293) | 124 | 0.898 (0.694, 1.161) | 194 | 0.027 (−0.093, 0.146) |
| | | | | | | | | | $p = 0.046$[a] |

*CI* confidence interval

[a] Test for a log-linear trend in the ERR/Gy with attained age

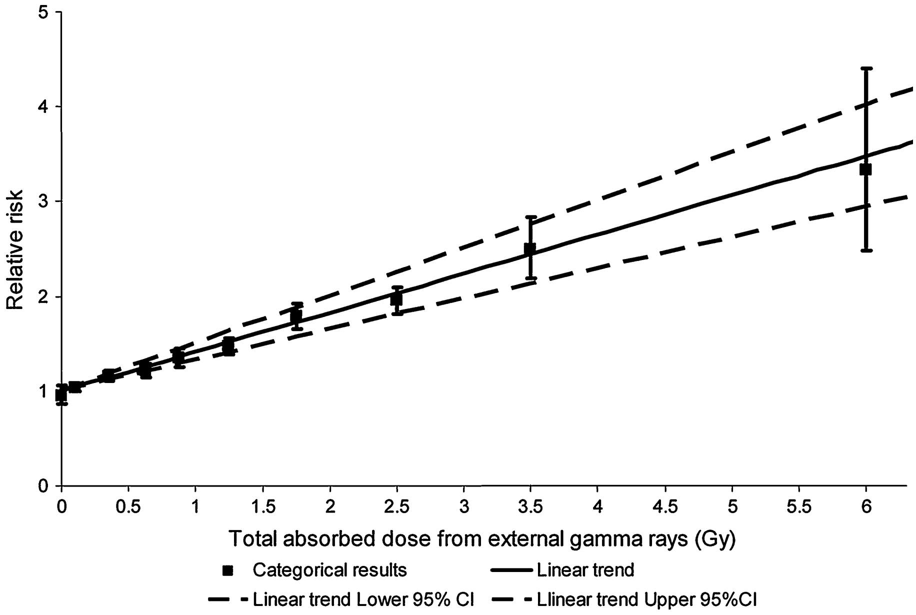

**Fig. 1** CVD incidence in relation to total absorbed dose from external gamma-rays. ERR/Gy = 0.413 (95% CI 0.324, 0.502) based on 0 year lag. *CI* confidence interval

guidelines. Follow-up of the Mayak worker cohort offers a unique opportunity to assess effects of chronic radiation exposure with both high and low dose rate in humans. The regular medical follow-up, epidemiological, and dosimetry studies of the Mayak workers cohort have been performed for almost 60 years. Major advantages of the cohort include the following: (a) the long-term follow-up (more than 60 years until now); (b) large size of the study cohort, which is being extended now to include additional workers both employed at the auxiliary plant and at later times; (c) a wide range of individually measured external and internal doses (maximum total dose up to 9 Gy); (d) heterogeneity by gender, age, ethnicity, and initial health status; (e) almost complete information on health effects and vital status (~90%); (f) existing data on non-radiation factors such as smoking, alcohol consumption, hypertension, excess body mass.

The second (current) analysis of CVD incidence and mortality was performed similar to the first analysis of the cohort of workers first employed at the Mayak PA in 1948–1958 (Azizova et al. 2010) though it included workers employed after 1958 and thus exposed to lower doses. This study had high statistical power to detect trends in CVD incidence and mortality risks with external and internal doses. The follow-up was almost complete for the period of residence in Ozyorsk. The extension of the follow-up by 5 years from 2000 to 2005 has increased the number of cases and deaths from CVD by more than 1.6 times, as well as the corresponding number of person-years of follow-up compared with our previous analysis. The quality control checks confirmed that the primary data used in the present analysis were highly complete and accurate. External doses were available for all the cohort members, while internal doses were only provided for a part of workers; therefore, the internal exposure analysis was restricted to workers monitored for plutonium body burden.

The present study demonstrated a statistically significant effect of non-radiation factors such as gender, age, smoking, hypertension, body mass index on CVD incidence and mortality, which is consistent with the findings of our first analysis and other studies on nuclear workers. The present study—unlike many others (Donahue et al. 1986; Hillbom and Kaste 1983; Kanareikin et al. 1987), including analyses of incidence and mortality from ischemic heart disease in the same cohort (Azizova et al. 2011)—revealed no effect of alcohol consumption on either incidence or mortality from CVD.

Of notice was that the later a worker has been employed at the Mayak PA, the lower risk of both CVD incidence and mortality was. The most unfavorable radiation environment was observed during the first 10 years of the Mayak PA operation, when workers were exposed to higher doses (Koshurnikova et al. 1999).

The extension of the study cohort and follow-up period increased statistical power of the study, especially in the range of lower doses, compared with our first analysis. In particular, the present analysis demonstrated statistically significantly increased risk of CVD incidence for workers with total external gamma-rays dose greater than 0.2 Gy compared to those with lower doses. However, the evidence of increased risk for workers with doses of 0.2–0.5 Gy was marginal when using different lag-periods and adjustments for body mass index or internal dose. Trend estimates for CVD incidence with external exposure were consistent with a linear model and were statistically significantly above zero for both

**Table 3** CVD incidence: analyses by internal liver dose

| | <0.025 Gy | | 0.025–0.1 Gy | | 0.1–0.5 Gy | | >0.5 Gy | | ERR/Gy (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| | RR | No. of cases | RR (95% CI) | No. of cases | RR (95% CI) | No. of cases | RR (95% CI) | No. of cases | |
| Main analysis, 0 years lag | 1 | 1,748 | 1.085 (1.003, 1.172) | 1,658 | 1.231 (1.122, 1.351) | 980 | 1.570 (1.341, 1.838) | 219 | 0.095 (0.035, 0.154) |
| *Main analyses, in which the first x years following the start of radiation work were omitted when lagging doses by x years* | | | | | | | | | |
| Main analysis, 5 years lag | 1 | 2,069 | 1.063 (0.984, 1.149) | 1,479 | 1.265 (1.149, 1.392) | 810 | 1.561 (1.317, 1.851) | 178 | 0.139 (0.057, 0.221) |
| Main analysis, 10 years lag | 1 | 2,298 | 1.066 (0.985, 1.154) | 1,290 | 1.296 (1.170, 1.436) | 630 | 1.717 (1.423, 2.073) | 140 | 0.228 (0.104, 0.351) |
| Main analysis, 15 years lag | 1 | 2,513 | 1.106 (1.018, 1.201) | 1,078 | 1.346 (1.199, 1.513) | 442 | 1.834 (1.471, 2.288) | 96 | 0.388 (0.191, 0.586) |
| Main analysis, 20 years lag | 1 | 2,612 | 1.103 (1.006, 1.209) | 805 | 1.404 (1.220, 1.617) | 271 | 1.800 (1.332, 2.433) | 50 | 0.731 (0.371, 1.090) |
| *Main analyses, in which the first x years following the start of radiation work were assigned to a "zero dose" category when lagging doses by x years* | | | | | | | | | |
| Main analysis, 5 years lag | 1 | 2,138 | 1.066 (0.986, 1.152) | 1,479 | 1.267 (1.152, 1.394) | 810 | 1.557 (1.314, 1.845) | 178 | 0.135 (0.054, 0.215) |
| Main analysis, 10 years lag | 1 | 2,545 | 1.072 (0.991, 1.160) | 1,290 | 1.303 (1.177, 1.443) | 630 | 1.722 (1.427, 2.077) | 140 | 0.229 (0.106, 0.353) |
| Main analysis, 15 years lag | 1 | 2,989 | 1.118 (1.030, 1.214) | 1,078 | 1.364 (1.214, 1.531) | 442 | 1.861 (1.494, 2.320) | 96 | 0.411 (0.209, 0.614) |
| Main analysis, 20 years lag | 1 | 3,479 | 1.110 (1.013, 1.215) | 805 | 1.408 (1.224, 1.620) | 271 | 1.800 (1.334, 2.430) | 50 | 0.729 (0.374, 1.084) |
| Main analysis but unadjusted for smoking and alcohol consumption, 0 years lag | 1 | 1,748 | 1.069 (0.992, 1.151) | 1,658 | 1.212 (1.109, 1.326) | 980 | 1.598 (1.371, 1.863) | 219 | 0.117 (0.053, 0.181) |
| *Adding to stratification (0 years lag)* | | | | | | | | | |
| Hypertension | 1 | 1,748 | 1.103 (1.017, 1.197) | 1,658 | 1.255 (1.138, 1.383) | 980 | 1.621 (1.371, 1.917) | 219 | 0.215 (0.113, 0.318) |
| Body mass index | 1 | 1,748 | 1.095 (1.008, 1.189) | 1,658 | 1.249 (1.132, 1.378) | 980 | 1.564 (1.323, 1.850) | 219 | 0.155 (0.066, 0.244) |
| Employment duration | 1 | 1,748 | 1.116 (1.025, 1.214) | 1,658 | 1.293 (1.169, 1.429) | 980 | 1.607 (1.355, 1.906) | 219 | 0.120 (0.042, 0.197) |
| External dose | 1 | 1,748 | 1.053 (0.965, 1.149) | 1,658 | 1.145 (1.030, 1.274) | 980 | 1.454 (1.206, 1.754) | 219 | 0.110 (0.018, 0.203) |
| *Analyses (0 years lag) restricted to workers at* | | | | | | | | | |
| Reactors | – | | – | | – | | – | | – |
| Radiochemical plant | 1 | 792 | 1.112 (1.002, 1.234) | 1,031 | 1.223 (1.083, 1.382) | 621 | 1.567 (1.215, 2.022) | 73 | 0.517 (0.239, 0.796) |
| Plutonium plant | 1 | 781 | 1.064 (0.940, 1.203) | 580 | 1.268 (1.094, 1.470) | 352 | 1.582 (1.290, 1.939) | 146 | 0.042 (0.000, 0.084) |
| Males (0 years lag) | 1 | 1,184 | 1.077 (0.983, 1.181) | 1,078 | 1.212 (1.085, 1.354) | 651 | 1.624 (1.349, 1.956) | 153 | 0.314 (0.166, 0.462) |
| Females (0 years lag) | 1 | 564 | 1.104 (0.954, 1.277) | 580 | 1.276 (1.073, 1.516) | 329 | 1.455 (1.081, 1.957) | 66 | 0.013 (−0.014, 0.040) |
| *Attained age (0 years lag)* | | | | | | | | | |
| <40 | 1 | 23 | 1.644 (0.784, 3.447) | 14 | 1.880 (0.696, 5.078) | 6 | 2.297 (0.491, 10.740) | 2 | −0.001 (−0.588, 0.585) |
| 40–49 | 1 | 399 | 1.261 (1.068, 1.490) | 303 | 1.372 (1.125, 1.673) | 181 | 1.791 (1.358, 2.361) | 72 | 0.054 (−0.023, 0.131) |
| 50–59 | 1 | 899 | 1.102 (0.991, 1.224) | 805 | 1.341 (1.179, 1.524) | 481 | 1.604 (1.277, 2.015) | 102 | 0.192 (0.071, 0.313) |
| 60–69 | 1 | 401 | 0.933 (0.802, 1.085) | 493 | 1.003 (0.841, 1.196) | 289 | 1.373 (0.966, 1.951) | 43 | 0.179 (−0.085, 0.444) |
| 70+ | 1 | 26 | 1.589 (0.645, 3.913) | 43 | 0.711 (0.239, 2.121) | 23 | – | 0 | −0.388 (−3.890, 3.115) |
| | | | | | | | | | $p = 0.226^{a}$ |

*CI* confidence interval

[a] Test for a log-linear trend in the ERR/Gy with attained age

**Table 4** CVD mortality: analyses by internal liver dose

| | <0.025 Gy | | 0.025–0.1 Gy | | 0.1–0.5 Gy | | >0.5 Gy | | ERR/Gy (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| | RR | No. of deaths | RR (95% CI) | No. of deaths | RR (95% CI) | No. of deaths | RR (95% CI) | No. of deaths | |
| Main analysis, 0 years lag | 1 | 121 | 0.845 (0.642, 1.113) | 179 | 1.115 (0.830, 1.498) | 178 | 1.022 (0.650, 1.607) | 35 | 0.143 (−0.080, 0.367) |
| *Main analyses, in which the first x years following the start of radiation work were omitted when lagging doses by x years* | | | | | | | | | |
| Main analysis, 5 years lag | 1 | 144 | 0.902 (0.688, 1.182) | 172 | 1.168 (0.873, 1.563) | 166 | 1.187 (0.744, 1.894) | 31 | 0.186 (−0.078, 0.450) |
| Main analysis, 10 years lag | 1 | 162 | 0.988 (0.761, 1.282) | 177 | 1.174 (0.878, 1.570) | 142 | 1.296 (0.806, 2.084) | 29 | 0.231 (−0.084, 0.546) |
| Main analysis, 15 years lag | 1 | 190 | 1.041 (0.810, 1.339) | 172 | 1.168 (0.872, 1.565) | 118 | 1.397 (0.860, 2.270) | 26 | 0.303 (−0.092, 0.697) |
| Main analysis, 20 years lag | 1 | 229 | 1.025 (0.799, 1.315) | 160 | 1.010 (0.744, 1.370) | 88 | 1.458 (0.887, 2.397) | 23 | 0.364 (−0.119, 0.846) |
| *Main analyses, in which the first x years following the start of radiation work were assigned to a "zero dose" category when lagging doses by x years* | | | | | | | | | |
| Main analysis, 5 years lag | 1 | 144 | 0.907 (0.692, 1.188) | 172 | 1.175 (0.878, 1.572) | 166 | 1.197 (0.750, 1.910) | 31 | 0.189 (−0.077, 0.454) |
| Main analysis, 10 years lag | 1 | 165 | 1.002 (0.772, 1.300) | 177 | 1.192 (0.891, 1.594) | 142 | 1.321 (0.821, 2.126) | 29 | 0.238 (−0.081, 0.557) |
| Main analysis, 15 years lag | 1 | 197 | 1.061 (0.825, 1.365) | 172 | 1.191 (0.889, 1.597) | 118 | 1.425 (0.877, 2.316) | 26 | 0.311 (−0.087, 0.710) |
| Main analysis, 20 years lag | 1 | 242 | 1.053 (0.820, 1.351) | 160 | 1.035 (0.762, 1.405) | 88 | 1.500 (0.912, 2.467) | 23 | 0.381 (−0.111, 0.873) |
| Main analysis but unadjusted for smoking and alcohol consumption, 0 years lag | 1 | 121 | 0.879 (0.677, 1.142) | 179 | 1.180 (0.892, 1.562) | 178 | 0.952 (0.612, 1.481) | 35 | 0.089 (−0.095, 0.274) |
| *Adding to stratification (0 years lag)* | | | | | | | | | |
| Hypertension | 1 | 121 | 0.939 (0.703, 1.255) | 179 | 1.253 (0.917, 1.711) | 178 | 1.002 (0.606, 1.658) | 35 | 0.041 (−0.114, 0.196) |
| Body mass index | 1 | 121 | 0.852 (0.633, 1.146) | 179 | 1.182 (0.860, 1.626) | 178 | 1.030 (0.634, 1.673) | 35 | 0.076 (−0.104, 0.255) |
| Employment duration | 1 | 121 | 0.833 (0.626, 1.108) | 179 | 1.071 (0.789, 1.452) | 178 | 1.068 (0.670, 1.702) | 35 | 0.173 (−0.084, 0.431) |
| Restricting follow-up to Ozyorsk (0 years lag) | 1 | 117 | 0.845 (0.641, 1.115) | 170 | 1.102 (0.817, 1.485) | 164 | 1.028 (0.646, 1.635) | 30 | 0.151 (−0.084, 0.386) |
| Also adjusting for external dose (0 years lag) | 1 | 117 | 0.893 (0.660, 1.209) | 170 | 1.245 (0.892, 1.738) | 164 | 1.215 (0.701, 2.105) | 30 | 0.158 (−0.174, 0.489) |
| *Analyses (0 years lag) restricted to workers at* | | | | | | | | | |
| Reactors | – | | – | | – | | – | | – |
| Radiochemical plant | 1 | 49 | 0.878 (0.601, 1.281) | 103 | 1.126 (0.752, 1.686) | 107 | 1.071 (0.555, 2.068) | 15 | 0.008 (−0.259, 0.276) |
| Plutonium plant | 1 | 59 | 0.707 (0.456, 1.096) | 63 | 1.042 (0.664, 1.636) | 71 | 0.909 (0.484, 1.709) | 20 | 0.204 (−0.127, 0.535) |
| Males (0 years lag) | 1 | 86 | 0.854 (0.616, 1.182) | 115 | 1.224 (0.865, 1.731) | 120 | 0.922 (0.531, 1.600) | 23 | −0.056 (−0.154, 0.043) |
| Females (0 years lag) | 1 | 35 | 0.803 (0.478, 1.351) | 64 | 0.905 (0.515, 1.588) | 58 | 1.242 (0.552, 2.794) | 12 | 0.405 (−0.183, 0.994) |
| *Attained age (0 years lag)* | | | | | | | | | |
| <40 | 1 | 2 | – | 0 | – | 0 | – | 0 | – |
| 40–49 | 1 | 9 | 0.202 (0.024, 1.740) | 1 | 0.376 (0.042, 3.388) | 1 | – | 0 | −0.009 (−2.989, 2.971) |
| 50–59 | 1 | 30 | 0.851 (0.455, 1.593) | 19 | 1.695 (0.858, 3.348) | 20 | 1.305 (0.389, 4.377) | 4 | 0.346 (−0.424, 1.117) |
| 60–69 | 1 | 37 | 0.847 (0.527, 1.362) | 47 | 1.588 (0.974, 2.589) | 61 | 1.301 (0.558, 3.033) | 8 | 0.394 (−0.248, 1.036) |
| 70+ | 1 | 43 | 1.029 (0.699, 1.515) | 112 | 1.066 (0.700, 1.623) | 96 | 0.923 (0.508, 1.679) | 23 | 0.007 (−0.203, 0.218) |
| | | | | | | | | | $p = 0.327^{a}$ |

*CI* confidence interval

[a] Test for a log-linear trend in the ERR/Gy with attained age

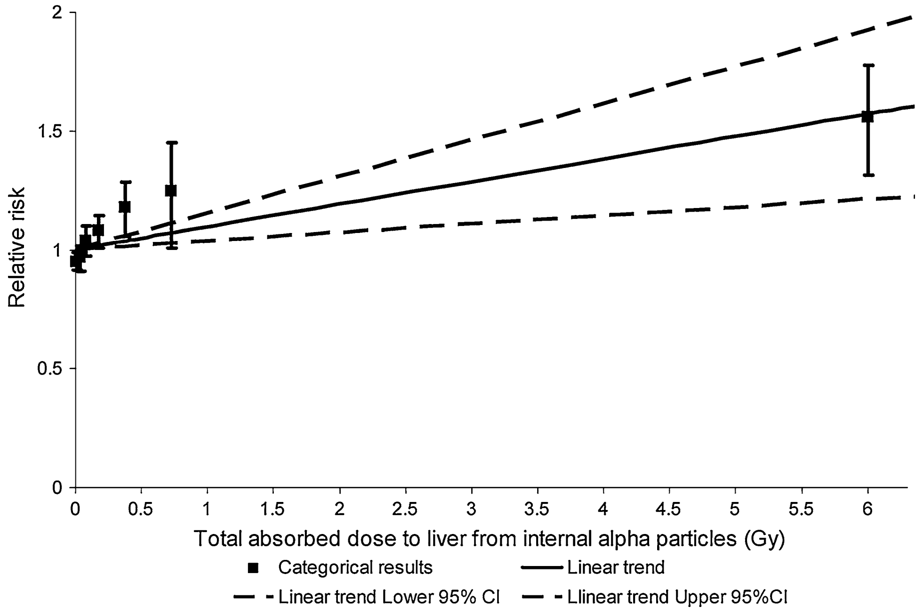

**Fig. 2** CVD incidence in relation to total absorbed dose to liver from internal alpha-particle radiation. ERR/Gy = 0.095 (95% CI 0.035, 0.154) based on 0 year lag. *CI* confidence interval

men and women as well as for workers at different plants.

Among those monitored for $^{239}$Pu body burden, statistically significantly increased risk of CVD incidence was found for workers with total absorbed dose to liver from internal alpha radiation greater than 0.025 Gy compared to those with lower doses. However, the evidence of increased risk for workers with doses of 0.025–0.1 Gy tended to be marginal when using different lag-periods or adjustment for external dose. However, in contrast to the external exposure findings, evidence for a trend in CVD incidence with internal doses related largely to men rather than women and to workers at the radiochemical plant rather than at the plutonium plant, even though these latter groups have comparable levels of exposure. It was clear that the non-linearity in the CVD incidence with internal dose seen in the first analysis was still present (Fig. 2), and this will be investigated further in a separate paper.

The evidence for associations with radiation in the present study relates mainly to CVD incidence rather than mortality, which is consistent with the first analysis of the earlier workers (Azizova et al. 2010), and the estimates of trends with either external or internal dose for CVD mortality are lower than those for CVD incidence. In our view, these apparent differences are due to the low statistical power of analyses of CVD mortality reflecting the relatively low numbers of deaths. In contrast, the analyses of CVD incidence are based on considerably larger numbers of cases and hence have much greater statistical precision. That said, the possibility of differences in radiation risk between CVD incidence and mortality cannot be ruled out. Of potential concern is whether this finding might reflect surveillance bias, which could arise if greater efforts had been made to detect these mostly non-fatal cases of CVD among workers with the highest radiation exposures. However, medical follow-up for every member of the cohort was conducted on a regular basis according to a specially developed standard program. All the workers were examined uniformly irrespective of their exposures.

Figure 3 (see also supplementary Table S2 on the website) compares risk estimates of CVD incidence and mortality from the external exposure obtained in the studies of Mayak workers with estimates obtained in other studies. There is a considerable variation between the risk estimates from these different studies, although confidence intervals generally overlap. The extension of the Mayak worker cohort and follow-up period has increased the precision of estimated trends in risk with external dose, and the central estimates of ERR/Gy both for CVD incidence and mortality are similar to those from the first study of earlier workers (Azizova et al. 2010). The ERR/Gy estimate for the CVD incidence in the expanded Mayak worker cohort is higher than that for the Japanese A-bomb survivors (Yamada et al. 2004) though it is consistent with the estimate obtained from the study of Chernobyl cleanup workers (Ivanov et al. 2006). The ERR/Gy estimate for CVD mortality in the expanded Mayak worker cohort is consistent with that for A-bomb survivors (Shimizu et al. 2010) though it is lower than estimates in the 15-countries study (Vrijheid et al. 2007) and in the cohort of British Nuclear Fuels plc (BNFL) workers (McGeoghegan et al. 2008). The latter two estimates, though statistically insignificant, are consistent with the estimate of CVD incidence in the expanded Mayak worker cohort. The central

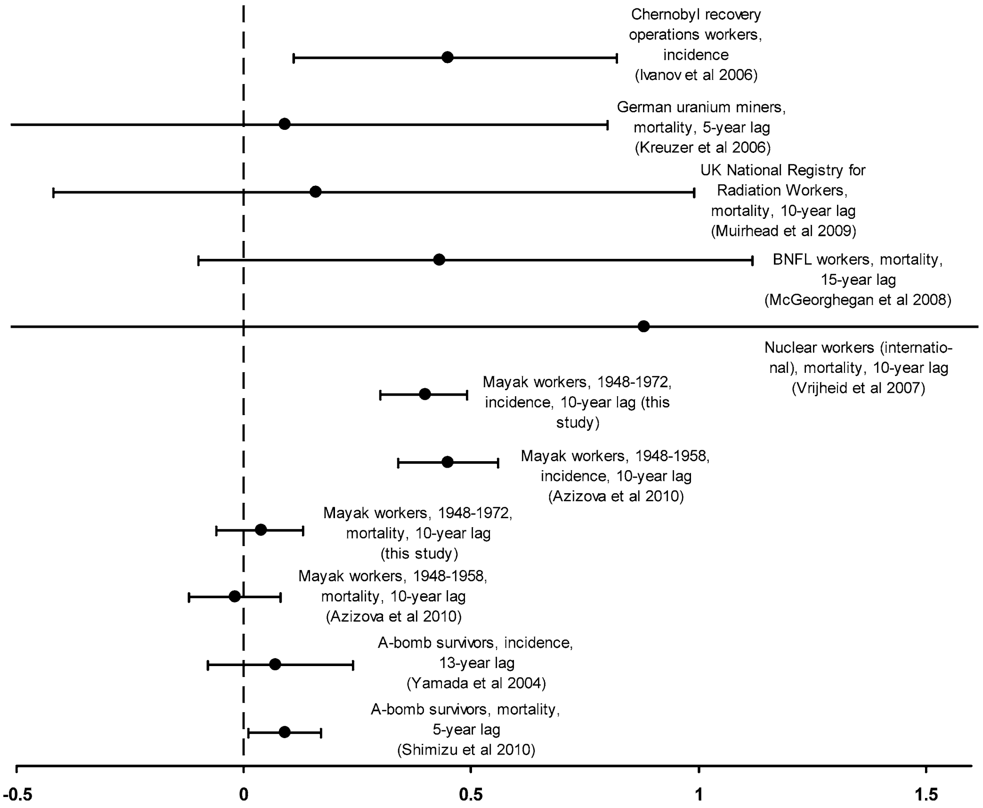

**Fig. 3** Comparison of risk estimates (ERR/Gy) of CVD incidence and mortality after external exposure from Mayak workers, various studies of radiation workers, Chernobyl recovery operation workers, German uranium miners, and the Japanese A-bomb survivors. *Bars* indicate a 95% CI for all, but the BNFL workers study, for which 90% CI is indicated. *CI* confidence interval

estimates of ERR/Gy for CVD mortality in studies of the National Registry for Radiation Workers (NRRW) in the UK (Muirhead et al. 2009) and uranium miners in Germany (Kreuzer et al. 2006) did not significantly differ from zero, but they are close to those obtained from the present study, and their confidence intervals also includes the results obtained in the present analysis for CVD incidence.

The ERR estimates obtained in this analysis of Mayak workers in relation to the internal alpha-particle radiation are also consistent with the results of the first analysis (Azizova et al. 2010). For the current analysis, liver dose has been used as a surrogate for the dose to muscle, which is likely to be similar to the dose to blood vessels and the chambers of the heart. Furthermore, the liver and muscle doses should be highly correlated with each other. However, there is uncertainty about which tissue or organ dose is appropriate for this type of analysis. A new dosimetry system for Mayak workers has been recently introduced and it is planned to examine what impact this may have on analyses of circulatory disease. At the moment, comparisons with other studies in relation to internal exposure are not possible because there is no information on risk estimates of incidence and mortality from CVD in other cohorts internally exposed to alpha-particle radiation due to incorporated $^{239}$Pu. It should be noted that whereas total absorbed dose to liver from incorporated plutonium exceeds dose to blood vessels, ERR/Gy estimated in the present study using dose to liver would be lower than that obtained using internal dose to blood vessels.

## Conclusion

The present analysis demonstrates a statistically significant dependence of incidence and mortality from CVD in the study cohort on non-radiation factors such as gender, age, calendar period, smoking, hypertension, body mass index. There are increasing trends in CVD incidence with total dose from external gamma-rays and total absorbed dose to liver from internal alpha radiation after having adjusted for non-radiation factors. CVD incidence is significantly higher among workers exposed to external gamma-rays in total dose greater than 0.2 Gy compared to those with lower doses; the obtained results are consistent with a linear trend in risk with external dose. Incidence of CVD is significantly higher among workers with total absorbed dose to liver >0.025 Gy from internal alpha radiation due to incorporated $^{239}$Pu compared to those with lower doses. An increasing trend in CVD incidence with internal dose is found primarily for workers at the radiochemical plant, while an increasing trend with external dose is observed for workers at each plant, and the findings are statistically consistent. There is no statistically significant trend in mortality from CVD either with external or internal dose; neither risk differed between categories of external and internal doses. The risk estimates obtained from the analyses of CVD incidence and mortality in relation to external gamma-rays in the cohort of Mayak worker are generally compatible with those from other large occupational studies. However, a higher risk estimate of CVD incidence is obtained in the cohort of Mayak workers in comparison with A-bomb survivors.

Various sources of ionizing radiation that contribute to human exposure (e.g., background, medical, technogenic, and occupational exposures) have become an integral part of the developed industrialized society. In addition, the threat of nuclear terrorism persists. The existing system of radiation protection based on recommendations made by the International Commission on Radiological Protection (ICRP) is generally credible. However, issues that have not been previously accounted for in development of radiation safety standards arised recently such as, for example, uncertainties in assessment of biological effects and risks of chronic exposure to low doses and low dose rates, risk assessment of non-cancer effects. Thus, on the one hand, the potential health risks associated with protracted exposure to low doses and low dose rates could be underestimated and therefore under-regulated. On the other hand, an obvious drawback of the radiation protection system for low doses and low dose rates is that it is underpinned mainly by the epidemiological evidence related to acute exposure. At the same time, there are more and more evidences that radiation risk of chronic exposure to low doses does not differ much from that of acute exposure. In addition, health risk estimates have been so far based only on cancer risk in the exposed cohorts and genetic effects in the offspring, excluding risks of non-cancer effects. Further studies of the unique cohort of Mayak workers chronically exposed to external and internal radiation will allow improving the reliability and validating the radiation safety standards for occupational and public exposure.

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