Radiation and epidemiological analysis for cancer incidence among nuclear workers who took part in recovery operations following the accident at the Chernobyl NPP

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Results of the analysis of the relationship between dose and cancer incidence among nuclear workers, liquidators of the Chernobyl accident are given in the paper. Information on this cohort of individuals is accumulated at the regional centre of Russian National Medical and Dosimetric Registry, which is operated at the RF State Research Centre - Institute of Biophysics. Medical and dosimetric information on 2,1492 persons of 18-60 years of age is used for analysis, 8,309 of them have established external radiation doses the number of person-years of follow-up of those people is 48118.5. Average age of liquidators at the time of exposure was 35.8 years. Average dose got in Chernobyl was about 0.05 Sv. For analysis of dose-effect relationship (induction of radiation-induced malignant neoplasms) method of maximal likelihood for non-stationary Poisson flow of events was used. Results of analysis showed that cancer incidence in whole does not exceed cancer incidence in relevant age groups of the Russian population. Mean value of SIR for all cancer diseases was 0.81 (0.72, 0.91, 95% CI) for the whole period of follow-up (1991-1998). Risks for induction of radiation-related cancer diseases were not statistically meaningful. Excess relative risk per 1 Sv was 0.62 (-1.55, 2.76, 95% CI).

Introduction

The large-scale epidemiological studies undertaken after the atomic bombing in Hiroshima and Nagasaki, Japan in 1945 have shown that the incidence rate of malignant neoplasms increases with radiation dose [1, 2]. In the follow-up period from 1950 to 1990, for the LSS cohort of 86,500 people exposed to radiation the expected (spontaneous) number of cancers was 7,791 cases, whereas the number of cases actually registered in this time period was 8040. The highest radiation risk was found for leukemia (except chronic leukemia) - the frequency of this pathology increased by a factor of 5-7 for those who received high radiation doses (more than 1 Sv). Based on the studies undertaken in Japan, models for radiation risk estimation were developed and these were later recommended for use by the International Commission on Radiological Protection.

There are a number of questions arising in relation to a possibility of using the radiation risks derived for Hiroshima and Nagasaki for predicting health effects of the Chernobyl accident. This is, above all, because the mean radiation dose in the Japanese cohort (about 0.3 Sv) is much higher the doses received by emergency workers and the public after the Chernobyl accident. Is it legitimate to extrapolate the radiation risk coefficients derived for the Japanese cohort to the domain of low radiation doses (less than 0.2 Sv)? This major question can be answered only on the basis of many-years radio-epidemiological studies conducted after the Chernobyl accident [3].

The possible dose response of malignant neoplasms was estimated for the Chernobyl emergency workers and nuclear workers of Russia during the period between 26.04.86 and 31.12.87 (1988-1995) and results were published earlier in [4]. The relative risk of malignant neoplasms was found to be 1.2 (0.4, 2.2; 95% confidence intervals (CI)) for the dose group 10-49 mSv and 1.4 (0.1, 3.2; 95% CI) for the dose group 50-99 mSv.

Materials and methods

Description of the cohort of emergency workers - employees of the nuclear industry

The Russian National Medical and Dosimetric Registry (RNMDR) currently contain individual data about 179923 Chernobyl emergency workers [5, 6]. There is a regional center of the RNMDR in the Institute of Biophysics where data on 21492 emergency workers are available. This cohort is of special interest from the standpoint of epidemiological studies because these are the subjects with most reliable medical and dosimetric data.

The analysis of the dose response for cancers in this cohort was performed for the follow-up period of 1991-1998. The year 1991 was chosen as the starting year of follow-up (5 years after the accident) under the assumption that by this time the system of collection and verification of medical and dosimetric data is stabilized and partially to allow for the minimal latent period of cancers.

The age range covered by the study was 18-60 years. Older age groups were not included because of limited accuracy of statistical data for these categories in Russia in general. As of 31/07/2000, the total number of emergency workers - employees of the nuclear industry subjected to medical examination (at least once during the selected follow-up period from 1991 to 1998) and selected according to the indicated criteria was 16280 people. Of them the number of emergency workers with ascertained external radiation dose is 8309 (or 51%), the number of person-years at risk for them being 48,118.

Figure 1 shows the age distribution of the emergency workers (with documented doses) at the beginning of the study period in 1991. It can be seen from the figure that most of the emergency workers were of 30-40 years old as of the beginning of 1991.

The mean age of the emergency workers at the exposure time was 35.8 years.

During the follow-up period 278 cases of solid cancers (of them 147 cases, 53% with documented doses) and 11 leukemia (8 cases, 73% with documented doses) were detected in the studied group of emergency workers. The mean dose received in Chernobyl was about 0.05 Sv.

The distribution density for the emergency workers (with documented doses) with respect to the duration of stay in Chernobyl is presented in Figure 2. The distribution shows two well defined peaks corresponding to the duration of stay of one and two months.

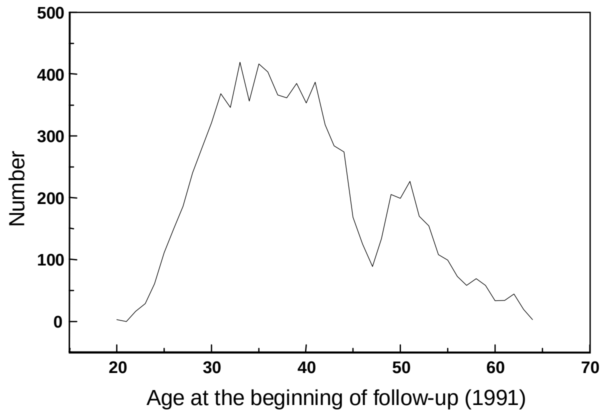

Fig. 1. Age distribution of the emergency workers at the beginning of the selected follow-up period (1991).

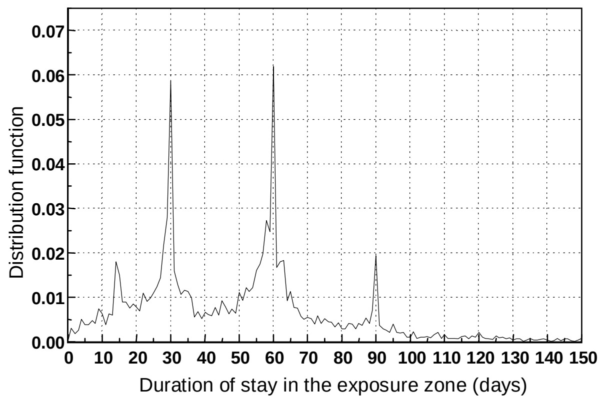

Fig. 2. Distribution of the emergency workers by the duration of stay in the exposure zone.

Statistical methods

For estimation of risk coefficients the method of maximum likelihood is used. The performed analysis is based on individual information about external radiation doses, number of follow-up person-years and age at exposure.

The authors believe that using individual information for risk estimation is preferable so that the influence of subjective factor be minimized and loss of information be avoided in data grouping and stratification.

Let us consider the non-stationary Poisson process with intensity $\lambda(t)$ in the follow-up interval [0, T). The events of the process are cases of registration of the vital status of cohort members (healthy or ill). The status «ill» is determined by the date of diagnosis of cancer, whereas the status «healthy» by the date of the last medical check-up. Let the events of the process occur at time moments

$t_i, \ldots, t_M$, where M is the number of the cohort members who were subjected to medical examination at least once in the follow-up period under study. The choice of non-stationary process is explained by changes in incidence as a function of attained age and by the time trend of spontaneous incidence rate in Russia and in the cohort of emergency workers.

The likelihood function for the given process is written as [7]:

$$L\{\lambda(t), t_1, \ldots, t_M\} = \prod_{i=1}^{n} \lambda_i(fp_i) \cdot exp(-\int_0^{fp_i} \lambda_i(\tau)d\tau) \cdot \prod_{j=1}^{N} exp(-\int_0^{fp_j} \lambda_j(\tau)d\tau) \quad (1)$$

where λ is the incidence rate, the vector dependent on sex, age at exposure, time since exposure and ionizing radiation dose; n is the number of cases in the follow-up period [0, T); N is the number of «healthy» (not diagnosed cancer) members of the cohort considered in the analysis for the follow-up period $n+N=M$; fp_i is the follow-up period for the i-th member of the cohort: for cases - starting from the beginning of follow-up to date of diagnosis and for healthy members of the cohort - from the beginning of follow-up period to date of the last medical examination.

The first term represents the contribution of cases to the likelihood function and second - the contribution of healthy members of the cohort. Let us divide the follow-up period for each cohort member into $k=1,\ldots,fp_i$ of annual intervals, substitute integration by summation and transfer to the logarithm of the likelihood function. Then we get:

$$ln\,L = \sum_{i=1}^{n}(ln(\lambda_{i,fp_i}) - \sum_{k=1}^{fp_i}\lambda_{i,k}) - \sum_{j=1}^{N}\sum_{k=1}^{fp_j}\lambda_{j,k} \quad (2)$$

For estimation of risk coefficients the following linear model is used:

$$\lambda_{i,k} = \lambda^o_{i,k} \cdot f \cdot (1 + \beta \cdot d_i)\,. \quad (3)$$

Here $\lambda^o_{i,k}$ is the spontaneous incidence rate in Russia for the attained age of the i-th cohort member at time moment k; d_i is the external radiation dose for the i-th member of the cohort; β is the excess relative risk per 1 Gy (ERR_{1Gy}). By definition the excess relative risk is equal to the ratio of incidence rates in the exposed and unexposed cohorts minus 1; $f = \lambda^s_{i,k} / \lambda^o_{i,k}$ is the ratio of the spontaneous incidence rates $\lambda^s_{i,k}$ (at zero dose) for attained age of the i-th cohort member at time moment k to the corresponding rate in Russia as a whole. Within this model the coefficient f for the whole cohort is a standardized incidence ratio (SIR). The difference of the coefficient f from unity can be due to completeness and reliability of incidence information in the Registry and also due to a possible «healthy workers effect», since the emergency workers were screened more thoroughly before dispatch to the exposure zone.

The value f is the ratio of age-specific spontaneous cancer incidence rates; this value does not vary much with attained age, which was demonstrated by comparison of age-specific cancer incidence rates in Russia to the rates in other countries (USA, UK, Belarus and Finland). Therefore, the value of f in this paper was taken to be the same for all age groups.

The advantages of the chosen risk model in distinction to the conventional regression approaches are obvious as far as it makes possible estimating the dose response coefficient and the difference in spontaneous incidence rates in the followed up cohort and in the country - wide population (Russia as a whole). Moreover, the statistical model uses reliable posterior information, which is known to improve the accuracy of statistical methods.

Thus, the parameters of the model in question (3) are coefficients β and f that were determined by solving the system of equations:

$$\partial\,ln\,L / \partial\beta = \partial\,ln\,L / \partial f = 0\,.$$

The confidence intervals for the estimation parameters were determined using asymptotic properties of the likelihood function [8].

Estimates of the parameters of risk model (3) β and f are used for prediction of cumulative cancer incidence rate in the nearest 5-10 years. This estimate can be useful for decision making with respect to optimizing medical consequences of the Chernobyl accident and determining the statistical power of similar studies in the future.

The number of expected cases (deaths) E_k at time moment t_k was estimated from the equation:

$$E_k = \sum_{i=1}^{M}\lambda_i(t_k) \cdot exp(-\int_0^{t_k}\lambda_i^{tot}(t_0 + \tau)d\tau)\,. \quad (4)$$

Here $\lambda_i^{tot}(t_k)$ is the all-cause mortality rate for person i at time moment t_k. The second term in (4) is the probability of avoiding death due to all causes in the study period. The value of $\lambda_i(t_k)$ was determined according to (3).

The number of spontaneous cases were calculated assuming that d_i=0.

The projection is based on the assumption that the Russian spontaneous mortality rates in the forthcoming time period will be equal to those in 1998.

In determination of the SIR dynamics for all members of the cohort (with and without documented doses) the expected number of cases was estimated by the following expression:

$$E_k = \sum_{i=1}^{M} PY_{i,k} \cdot \lambda^0_{i,k}\,, \quad (5)$$

where $PY_{i,k}$ is the number of person-years at risk for the i-th cohort member in the time interval k.

The confidence intervals for SIR in this case were estimated by [9].

Results of analysis of cancer incidence in the cohort of emergency workers - employees of the nuclear industry

Figure 3 shows results of estimation of the SIR for all cancers in the cohort of emergency workers (both with and without documented doses) calculated using formula (4). The value of SIR is mostly below the control (the control is the incidence rate in corresponding age groups in Russia in general) and is consistent with the control within 95% CI. The mean value of SIR for all cancers with 95% CI among all emergency workers over the whole follow-up period (with and without dose) is 0.81 (0.72, 0.91).

Table 1 includes results of estimating risk coefficients for all cancers.

As can be seen from Table 1, the values ERR/Gy for cancers of all localizations are not statistically significant. The value of SIR in model (3) is consistent with the control (the cancer incidence rate in Russia in general) within 95% CI.

For illustration of the dose response of cancer incidence in general, all data were divided into 4 dose intervals with close values of person-years at risk. The main characteristics of the dose groups are presented in Table 2.

Figure 4 shows a dose response for the overall cancer incidence rate and the linear regression.

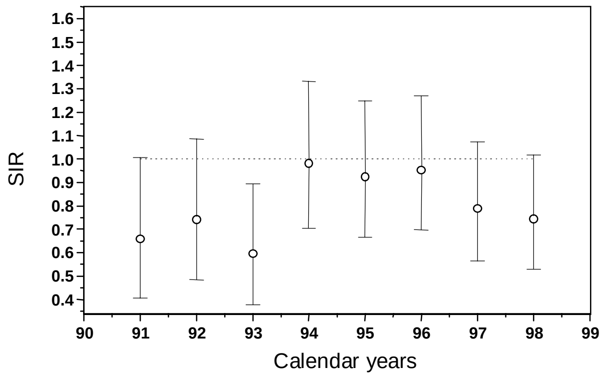

Fig. 3. Standardized incidence ratio for cancer in emergency workers (with and without dose).

Table 1

Results of estimating risk coefficients for malignant neoplasms among the emergency workers with ascertained doses

Number of cases	147
ERR/Gy* (95% CI) SIR (95% CI) (coeff. ***f***)	0.62 (-1.55, 2.76) 0.96 (0.80, 1.11)

* ERR/Gy is excess relative risk per 1 Gy.

Table 2

Main characteristics of the cohort of emergency workers by dose groups

Dose interval (mGy)	[1-5)	[5-20)	[20-80)	[80-250)
Number of cases	30	41	34	42
Person-years at risk	11,535	12,741	11,844	11,996
Mean dose (mGy)*	2.22	10.16	42.41	149.71
Mean dose rate (mGy/day)*	0.05	0.19	0.67	2.44
Cancer incidence rate (number of cases per person-year)	0.0026	0.0031	0.0029	0.0035

* Person-year weighted averages.

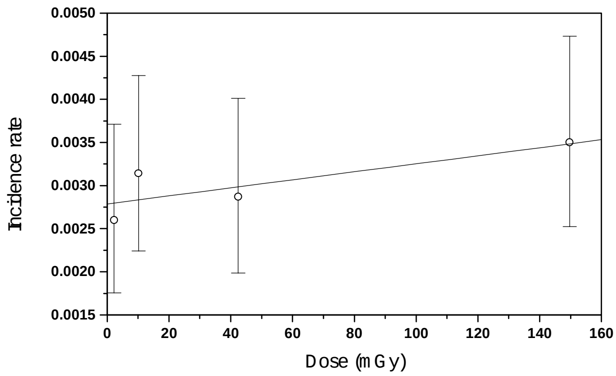

Fig. 4. Dose response for cancer incidence rate.

Results of prediction of the cumulative incidence rate for cancers of all localizations are presented in Figure 5. This projection is based on using model (4). As can be seen modeling results fit well with the actual data.

The projection is that about 380 cancer cases are to be expected by 2005.

Conclusions

The analysis of the cancer incidence rate in the cohort of emergency workers-employees of the nuclear industry shows that:

- The cancer incidence rate in general does not exceed that in the respective age groups of the population of Russia as a whole. The mean value of SIR for all cancers with 95% CI is estimated to be 0.81 (0.72, 0.91).
- The risks of induction of radiogenic cancers for all cancers are found not to be statistically significant. The excess relative risk at 1 Sv with 95% CI is 0.62 (-1.55, 2.76).
- It is projected that by the end of 2005 about 380 cancer cases will occur in the cohort of emergency workers-employees of the nuclear industry and these are due to the spontaneous dynamics of malignant neoplasms in the male population of Russia.

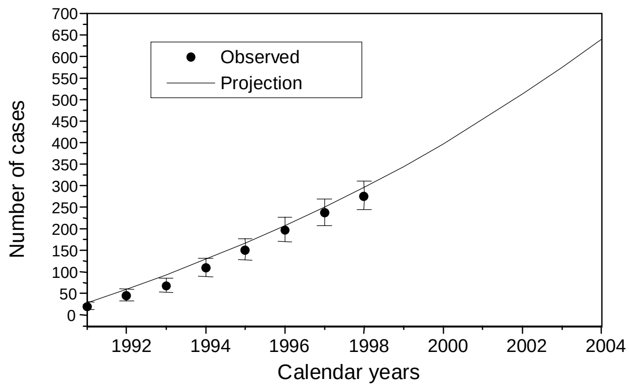

Fig. 5. Observed and predicted number of cases in the cohort of emergency workers - employees of the nuclear industry.

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