Radiation Epidemiological Studies in Russian National Medical and Dosimetric Registry: Estimation of Cancer and Non-cancer Consequences Observed among Chernobyl Liquidators

Marat M. MAKSIOUTOV

Medical Radiological Research Center, Russian Academy of Medical Sciences,
National Radiation and Epidemiology Registry
Koroleva st. 4, Obninsk, 249020, Russia: nrer@obninsk.com

Abstract

In June 1986 the USSR Ministry of Health Care initiated a large-scale program to establish All-Union Distributed Registry of persons exposed to radiation. The Research Institute of Medical Radiology of Russian Academy of Medical Sciences in Obninsk (currently Medical Radiological Research Center of RAMS) was appointed as the leading organization to create and manage the Registry. Two tasks were set before the Registry: first, assessment of health effects due to the Chernobyl accident with a view to develop an optimal strategy for alleviating the accident consequences for human health and, second, organization of many-years epidemiological studies primarily directed to estimating the actual radiation risks. By 1 December 2001, the Russian National Medical and Dosimetric Registry (RNMDR) included medical and dosimetric data for 585,121 persons exposed to radiation as a result of the Chernobyl accident and residing in the territory of Russian Federation. At present the Registry includes 187,596 liquidators (32.1% of total number of registered).

This article presents comprehensive radiological and epidemiological analysis of individual medical and dosimetric data for the cohort of liquidators available in the RNMDR. Particular emphasis is placed on the issue of estimating radiation risks in induction of cancer and non-cancer diseases. This is due to the fact that the coefficients recommended by ICRP are primarily based on the Japanese epidemiological studies of 1945 atomic bomb survivors of Hiroshima and Nagasaki (the LSS cohort). Statistically significant estimates of radiation risk coefficients for the Japanese cohort, however, were received in the individual dose range above 0.3 Sv. For low doses (up to 0.2 Sv), only extrapolation models without direct epidemiological ascertainment were used. Therefore, the RNMDR is the first to estimate radiation risks for low radiation doses using individual medical and dosimetric information available for the liquidators cohort.

The article consists of five parts. Chapter 1 describes the organizational structure and basic principles of operation of the Russian National Medical and Dosimetric Registry, and provides characterization of the liquidators cohort in the RNMDR. Chapters 2-4 deal with direct radiation-epidemiological studies aimed at estimating and predicting radiation risks using the actual data of the Registry. Radiation risk estimates derived from incidence data on leukemias, solid cancers and noncancer diseases among the liquidators are discussed. The last chapter 5 deals with estimating mortality rate among the Chernobyl liquidators and establishing a possible dose response relationship for mortality. The submitted material is based on scientific papers prepared by the experts of the Registry and published in the famous Russian and international scientific magazines.

1. The short description of the Registry

In 1986 the USSR Ministry of Health Care initiated a program to establish All-Union Distributed Registry (UDR) of persons exposed to radiation due to the Chernobyl accident. The computer center of Research Institute of Medical Radiology of USSR RAMS (Obninsk) became the core of the Registry. The UDR was formed with contributions from all republics of the former Soviet Union, many scientific research

institutions and practical organizations [1]. Information to the UDR was mainly supplied by republican information computer centers of Ministries of Health Care of Belarus, Russian Federation and Ukraine. In 1992 after the disintegration of USSR, on the base of the UDR the Russian National Medical and Dosimetric Registry (RNMDR) was set up in Medical Radiological Research Center of RAMS (former Research Institute of Medical Radiology). The principal objective of the Registry was organization of long-term automated individual recording of persons exposed to radiation effects of the Chernobyl accident, their children and subsequent generations as well as assessment of their vital status.

1.1. Organizational structure and tasks of the Registry

The Registry is a multilevel information system covering all regions of Russian Federation. The Registry provides for four levels: federal, regional, province and district.

In each of the 11 administrative and economic regions of Russia a regional center of the RNMDR was set up to collect individual medical and dosimetric information supplied from districts and provinces and to pass it on to the national level (Fig. 1.1). In addition to regional centers established by the territorial principle, the RNMDR has affiliation centers in Ministry of Defense, Ministry of Internal Affairs, Ministry of Railways, Ministry of Atomic Energy and Federal Security Service. Affiliations with the same status as regional centers were also set up in the regional cities the population of which was worst exposed to radiation as a result of the Chernobyl accident, namely Bryansk, Kaluga, Tula and Oryol.

The Registry is designed to provide information support and to improve the quality and effectiveness of the following:

- clinical examination of the population;
- treatment and health promotion activities;
- studies of the incidence pattern, dynamics and trends of health outcomes in the monitored contingent;
- recommendations on improving prevention, diagnosis and treatment of diseases, conducting protection measures and perfecting the health care system;
- special scientific studies on the health effects of the Chernobyl accident and other radiation disasters and incidents.

The tasks of the Registry include:

- automated recording of passport and registration data for persons exposed to radiation as a result of the Chernobyl accident and other radiation disasters and incidents;
- automated recording and determination of individual radiation doses among the population;
- automated recording of chronic diseases in the monitored cohort before the accident and automated

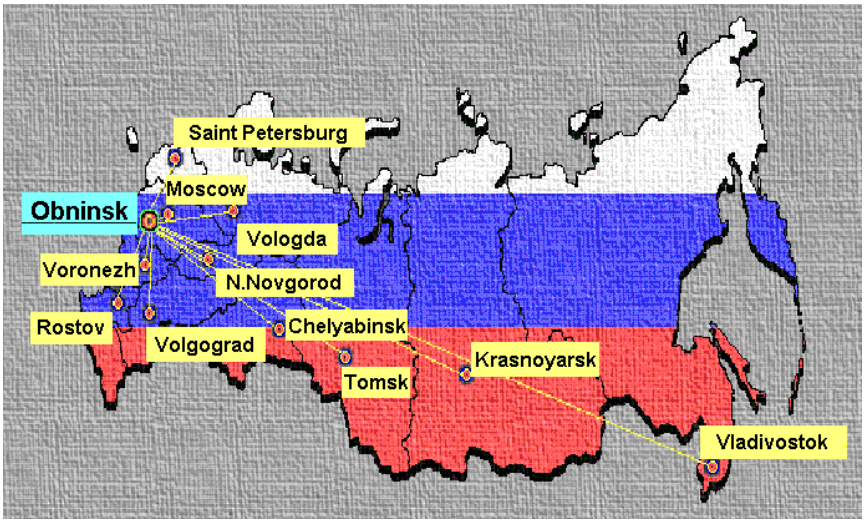

Fig. 1.1. Distribution of regional centers of the Registry across the territory of Russia.

recording of health status after the accident;

- retrieval of data on request of users;
- quality control for data completeness and medical follow-up.

The users of the Registry are Ministry of Health Care of Russian Federation and Ministry of Emergency of Russian Federation. Other organizations are entitled to get access to materials of the Registry with permission of appropriate health care authorities.

The structure of the Registry was devised with allowance for the experience of similar registries in the world, in particular, the Japanese Registry of atomic bomb survivors in Hiroshima and Nagasaki as well as registries in other countries [2].

1.2. Monitored groups and operational procedures in the Registry

By 1 December 2001, the Registry included medical and dosimetric data for 585,121 persons exposed to radiation as a result of the Chernobyl accident and residing in the territory of Russian Federation. The contingent of the registered persons consists of four groups:

1st group - persons involved in clean up works at the Chernobyl NPP (liquidators). These include:

- persons who were involved in mitigation of the Chernobyl accident consequences in the exclusion zone in 1986-1990 (including temporary workers and those on a mission), persons dealing with public and cattle evacuation or working at the Chernobyl NPP, military servicemen including air force staff irrespective of where they were stationed and what works involved, and senior and junior militia personnel servicing in the exclusion zone in 1986-1990. These include specialists, servicemen and reservists called up for mitigation works and having a certificate of Chernobyl liquidator of established format. At present the Registry included 187,596 liquidators (32.1% of total registered in the Registry).

2nd group - persons evacuated (among them volunteers) from the exclusion zone in 1986 (areas from which the population was evacuated in 1986 by the radiation safety regulation) including children, among them prenatal at the evacuation time (1.7 %).

3rd group - persons living in the monitored territories (relocation zone) or having lived there immediately after the accident (later moved to another area) (61.1%).

4th group - children born to parents in 1st group involved in mitigation of the accident consequences in 1986-1987 (5.1%).

1.3. Doses for liquidators in the Registry

Let us consider the density $f(D)$ of the distribution of absorbed dose D for liquidators. In what follows, we give a step-by-step approximation to $f(D)$, which by the definition for the dose interval $(D, D+\Delta D)$ is equal to:

$$f(D) = \frac{\Delta N(D)}{\Delta D \cdot N}, \qquad (1.1)$$

where: $\Delta N(D)$ is the number of liquidators with a dose between $(D,D+\Delta D)$;

N is the total number of liquidators in the group analyzed.

We then form groups of liquidators depending on the date of their entry into the contamination zone: 1986; 1987; 1989 and 1990. This classification corresponds to the type of work performed (from the end of May to November 1986: the construction of the sarcophagus) and differs with regard to the radiation situation [3,4].

Fig. 1.2 shows unnormalized histograms of the density of the distribution function D-$\Delta N(D)$ for the above groups. For convenience of comparison, the interval of histograms was taken to be the same for all groups. As can be seen in Fig. 1.2, the distribution of absorbed doses for all liquidators (the group of 119,416 persons with known doses and places of accommodation and work) is rather complex and has peaks at doses

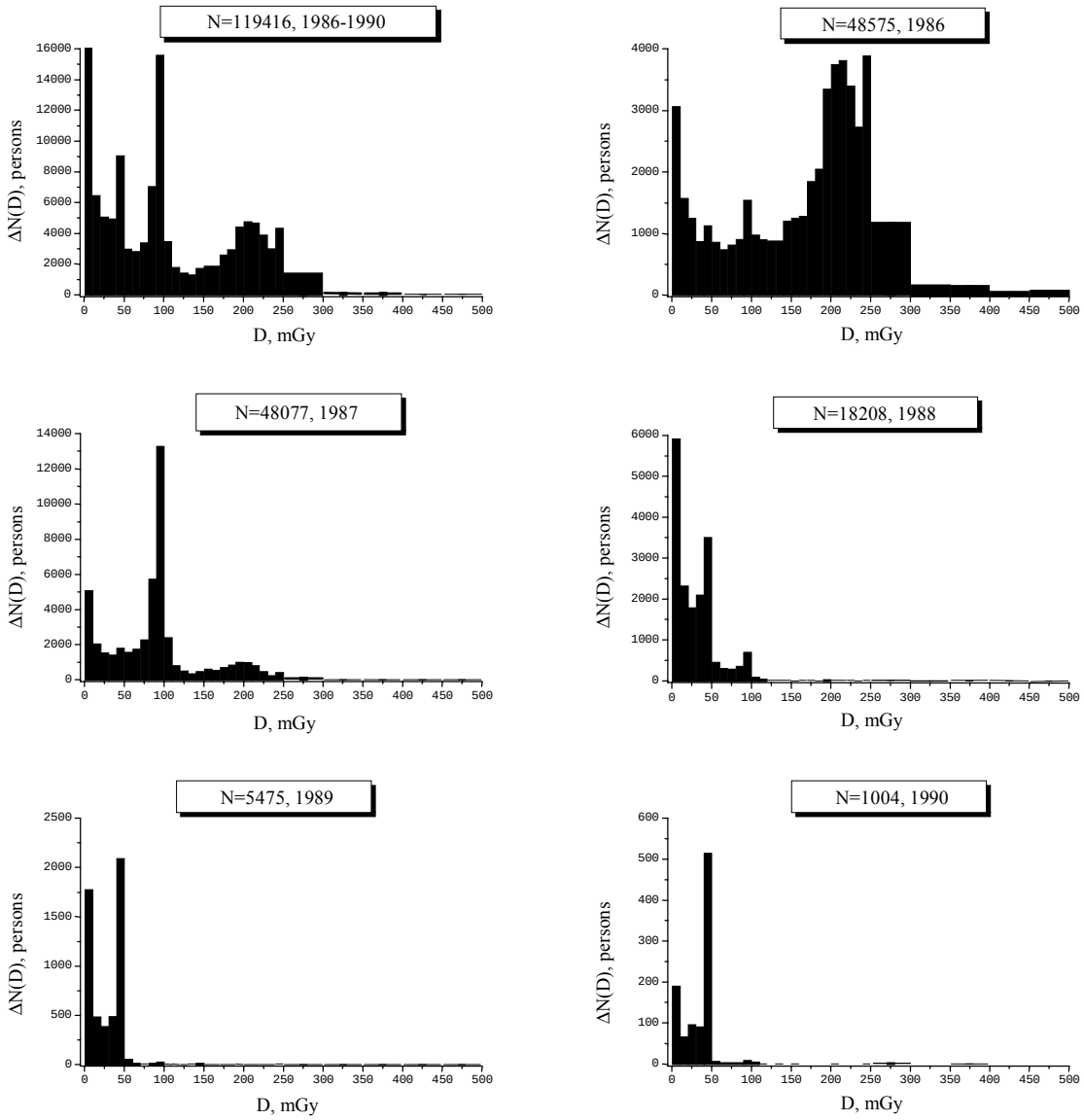

Fig. 1.2. Unnormalized density *ΔN(D)* of the distribution of absorbed doses *D* in liquidators registered in the RNMDR and densities *ΔN(D)* for liquidators with different dates of entry into the contaminated areas - 1986, 1987, 1988, 1989, 1990.

of 10, 50, 100 and 200 mGy. At doses higher than 250 mGy the distribution density decreases sharply, which suggests proper management of doses during recovery operations (preventing the excess above the dose limit of 250 mGy for most liquidators) or can be explained by other, possibly, subjective reasons.

For the liquidators of 1986 the dose distribution density has maxima in the range of low doses up to 10 mGy (these doses are most probably attributable to the liquidators who were not involved in Recovery Operations in heavily contaminated areas) and in the range of high doses of 200-250 mGy. For 1987 the indicated maxima are added with a sharp maximum at doses about 100 mGy. This is the dose limit which was established for most of the liquidators in 1987. In the following years, the dose distribution was shifted to even lower values with the maxima at about 10 and 50 mGy.

2. Prediction of long term stochastic effects for liquidators

There are currently two models of radiation risk used for prediction of the temporal trend of radiogenic cancers: the model of relative risk (multiplicative) and the model of absolute risk (additive) [5, 6]. In this

work the multiplicative model is used, since experts of the ICRP consider it to be preferable for most solid cancers.

In a simple multiplicative model for the ***i***-th disease the increment to the cancer mortality rate due to radiation is written as:

$$\Delta\lambda_i(u,t,d) = ERR^i_{1Sv}(u,t)\times\lambda_i(u,t)\times f(d),$$

ERR^i_{1Sv} is the excess relative risk of mortality for the ***i***-th disease per unit dose [1/Sv];

f(d) is the dose response function (usually linear or linear-quadratic);

$\lambda_i(u,t)$ is the spontaneous mortality rate for the ***i***-th disease in the stratum of the age group, *t* and the time period, *u*.

In the additive model:

$$\Delta\lambda_i(u,t,d) = EAR^i_{1Sv}(u,t)\times f(d),$$

EAR^i_{1Sv} is the excess absolute risk of mortality for the ***i***-th disease [10^4 person-years Sv]$^{-1}$.

Obviously, $ERR^i_{1Sv} = EAR^i_{1Sv}/\lambda_i$.

In case of rare diseases (for example, leukemia) or diseases with low survival rate and short disease time course, these models can be used to estimate additional incidence rate due to the radiation factor by substitution of mortality rates for incidence rates.

Knowing the distribution of population density for liquidators with time and dose response coefficients, frequency of radiogenic cancers for the ***i***-th disease $\Delta IM_i(t,d)$ (additional mortality due to radiation induced cancers) can be estimated:

$$\Delta IM_i(t,d) = \int_{u_{min}}^{u_{max}} n(u,t)\times\Delta\lambda_i(u,t,d)du,$$

where $n(u,t)$ is the time variations in the size and age structure of the cohort. For calculation of this value one can use survival tables or apply the approach to solve the equation accounting for variations in the population.

Additional mortality rate from all radiogenic cancers is given by

$$\Delta IM(t,d) = \sum_i \Delta IM_i(t,d).$$

For estimation of the contribution of radiogenic cancers to cancer mortality we estimate the value of attributive risk equal to the ratio of the number of radiogenic cancers to the total spontaneous and radiogenic cancers, i.e. to the detected number of cancers.

As exposure of liquidators was protracted in time (the dose rates are lower than in the LSS cohort [7]) we used the dose and dose rate effectiveness factor (DDREF) of 2 for estimating radiogenic cancers. Frequency of radiogenic cancers is calculated with allowance for the latent period (10 years for solid cancers and 2 years for leukemias).

2.1. Calculation models of excess mortality risk for solid cancers and leukemias

In calculation of additional mortality from radiogenic solid cancers and leukemias the approximants of excess relative risk given in [21] were used.

The model used for describing the risk of radiogenic solid cancers has the following form (designations are as in the original):

$$ERR(d,s,e) = \beta_s\times d\times exp(\gamma\times(e-30)).$$

Here ***s*** is the sex attribute;

d is the dose;

e is the age at exposure;

β_s is the risk coefficient dependent on sex and cancer localization (***ERR***/Sv). For all solid cancers the coefficient is equal to 0.38;

Table 2.1. Age dependence of parameters β_e and δ_e for leukemias

Age at exposure	0-19	20-39	40+
β_e	-0.553	-0.037	0.708
δ_e	-1.542	-0.688	0.173

Leukemia: In accordance with [21] the model of excess absolute risk of radiogenic leukemias for males is written as:

$$EAR(d,s,e,t) = (d + \theta \times d^2) \times exp(\beta_e + \delta_e \times log(t/25)) .$$

The parameters β_e and δ_e dependent on age at exposure account for the level and temporal trend of risk for leukemias, respectively. The values of these parameters as a function of age at exposure are given in Table 2.1. The value of θ is taken to be 1.53.

2.2.Prediction of mortality from radiogenic cancers in the liquidators

Leukemia

Effects of exposure to ionizing radiation are characterized by the increase of the leukemia incidence rate because, according to current concepts, radiation risks of leukemia are much higher than those for solid cancers. The time elapsed since the accident is now sufficient for leukemia induction (the latent period is about 2 years). A prediction of expected mortality from radiogenic leukemias in the Chernobyl liquidators is presented in Fig. 2.1. The expected life-time number of radiogenic leukemias is 32 cases (per 100,000 persons with the mean dose 0.11 Sv).

The attributive risk of radiogenic leukemias changes significantly with time since the accident. The peak in the attributive risk of 41% is expected 5 years after the accident. Such dependence of the attributive risk is due to a similar time dependence of the excess relative risk. This means that today the peak in induction of radiogenic leukemias has passed. The attributive risk is currently 35%, i.e. each third leukemia in the cohort of liquidators is radiation induced. Even 50 years after the accident the attributive risk of leukemias will exceed the risk for solid cancers and be equal to 10%.

Solid cancers

Fig. 2.2 shows occurrence of solid radiogenic cancers in the cohort of liquidators as a function of time since the accident (per 100,000 persons), the mean dose is 0.11 Sv (mean dose for liquidators). The expected life-time number of radiogenic solid cancers is 320 cases (per 100,000 persons). The peak in the incidence rate is expected to occur 30-35 years after the accident and will approximately be equal to 10 cases per year.

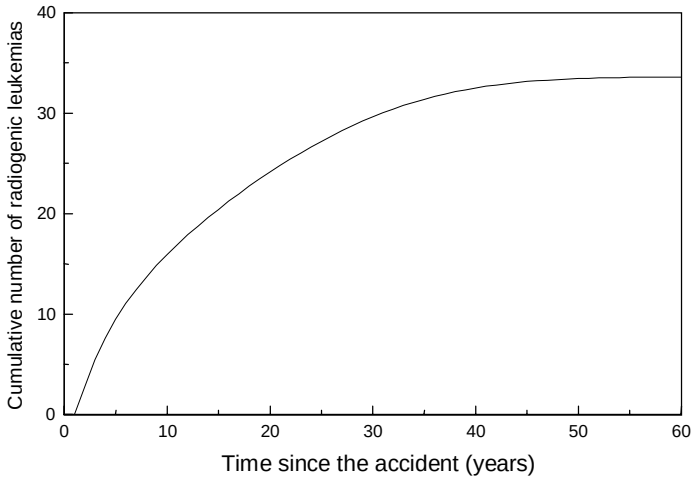

Fig. 2.1. Temporal pattern of radiogenic leukemias in the cohort of liquidators (per 100,000 persons).

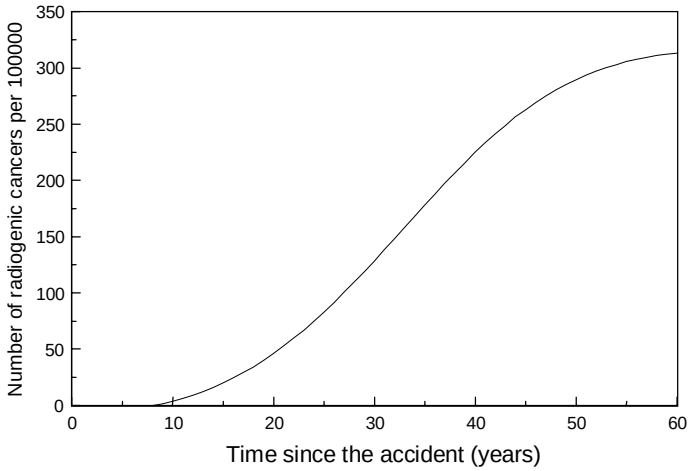

Fig. 2.2. Temporal pattern of radiogenic solid cancers in the liquidators. (per 100,000 persons).

Table 2.2. Temporal pattern of the attributive risk of radiogenic cancers (%).

Malignant neoplasms	Time since the accident (years)			
	5	10	20	50
Solid cancers	-	1.5	1.6	2.4
Leukemias	40.5	34.4	23.3	10.1
Digestive system diseases	-	1.5	1.7	2.3
Respiratory system diseases	-	8.4	3.3	0.9

The attributive risk increases with time and reaches 2.4% 50 years after the accident. The growth of the attributive risk with time is due to a greater contribution from liquidators exposed at younger age because the radiation risk of solid cancers increases as the age at exposure decreases.

Table 2.2 contains the values of the attributive risks for solid cancers, leukemia and malignant neoplasms for the digestive and respiratory systems.

The presented results of predicting the excess cancer mortality due to radiation in liquidators are preliminary. As was indicated, the estimates are rather approximate because of uncertainties in parameters used in predictions. This is, first of all, the uncertainty in the risk coefficients which were obtained for different exposure conditions (doses and dose rates) and for other populations. All this lets us assume that the projection based on the models currently accepted in the world radiation epidemiology and discussed in this chapter may be underestimation. As a consequence, the expected stochastic effects can, in fact, be more pronounced. Optimization of measures to minimize health effects of the Chernobyl accident becomes of even more social significance. Solutions to these problems can be sought in many-years radiation-epidemiological studies in the RNMDR system based on the Chernobyl data.

3. Trends of cancer incidence among liquidators: estimation of radiation risks

One of the issues related to radiation effects on liquidators that has not been adequately covered in the literature is how frequency of malignant diseases can be modified by risk factors. At the same time, malignant neoplasms are known to be radiogenic [8], as confirmed by both clinical and radiation-epidemiological studies [5].

The long-term study of the 1945 atomic bomb survivors in Hiroshima and Nagasaki has revealed an increase in risk of malignant diseases and corresponding mortality with increase in radiation dose [2].

This chapter deals with calculating cancer incidence rates and assessing radiation risks for the liquidators in the period from 1986 to 1997-1998. The analysis is based on the data available in the RNMDR about radiation risks of leukemia (ICD-9: 204-208) and solid tumors (ICD-9: 140-165, 170-195). The

incidence of leukemia and solid tumors was analyzed using the cohort methodologies [9,10]. Particular attention was attached to deriving a relationship between incidence rates and different risk factors. The incidence rates are primarily dependent on age of liquidators, external radiation dose and time of entry into the zone. The absolute values of incidence rates tend to increase with time since the Chernobyl accident.

3.1. Analytical method for radiation risk assessment

In cohort epidemiological studies long-term systematic surveillance of a group of persons is carried out to collect individual information on their health status.

For each person the time at risk to develop a disease of a particular class is calculated as a difference of dates T_1 and T_0, where T_0 is time of arrival to the 30-km zone and T_1 is one of the following dates: the date of the first diagnosis for the class of diseases under study, the date of the latest medical examination or the date of death. The incidence rate used in this study is defined as a ratio of the total cases to the total times at risk measured in person-years.

At first, in order to estimate the difference in cancer incidence between liquidators and the population of Russia as a whole, Standardized incidence ratio (SIR) is calculated. Age-specific incidence rates for the male population of Russia were used in SIR calculations.

Secondly, to derive the dependence of incidence rates on dose, the individual data about liquidators have been grouped in a multidimensional table. In the present study the data are grouped into 10 strata by age ([18-20), [20-25), [25-30), [30-35), [35-40), [40-45), [45-50), [50-55), [55-60), [60+) years), into 6 groups according to dose ([0-50), [50-100), [100-150), [150-200), [200-250), [250+) mGy) and groups by calendar year (from 1986 to last year of surveillance).

Let i be the index of age-time group and j be the index of dose group.

Let Y_{ij} be the number of cases, P_{ij} is person-years and M_{ij} is the incidence rate in stratum ij. In these terms M_{ij} for a given class of diseases can defined as:

$$M_{ij} = Y_{ij} / P_{ij} . \quad (3.1)$$

It is reasonable to assume [11,12] that Y_{ij} values are independent Poisson random variables with mathematical expectation $E(Y_{ij}) = P_{ij}M_{ij}$. To determine the dose dependence of M_{ij} it is necessary to present M_{ij} in the form of parametric function and determine its parameters using the maximization of likelihood function:

$$l = \Sigma\{Y_{ij} \ln(P_{ij}M_{ij}) - P_{ij}M_{ij}\}, \quad (3.2)$$

where $M_{ij} = f(D_{ij})$ where D_{ij} is the average dose in stratum ij.

Simple functions are used in this work:

$$f(D_{ij}) = M_{i0} \exp(ad_{ij}), \quad (3.3)$$

$d_{ij} = 0$ for $j = 0$ and $d_{ij} = 1$ for $j > 0$.

$$f(D_{ij}) = M_{i0} (1 + bD_{ij}). \quad (3.4)$$

$$f(D_{ij}) = M_{i0} + yD_{ij}. \quad (3.5)$$

Equation (3.3) is used to determine the relative risk $RR = \exp(a)$, and equation (3.4) is used to determine the significance of dependence of relative risk on dose. The statistical test applied for these purposes is the test of ratios of likelihood maxima at null hypothesis b=0. The 0-50 mGy group is used as baseline dose group (j=0, internal control).

Estimation of parameters of equations (3.3-3.4), statistical tests and determination of confidence intervals are performed on the software AMFIT [12].

For calculation of the dose dependence of leukemia incidence rates, equation (3.5) was used with stratification solely by age.

3.2. Results of radiation risk assessment

Leukemia

The cohorts of liquidators in this study total 99,024 people [13]. All worked within the 30-km zone.

Members of the cohort reside in the European part of Russia. In 1986, 44,057 individuals served, and their mean dose from external penetrating radiation was 0.168 Gy. In 1987, 35,689 people served; their mean dose was 0.093 Gy. For the three-year period 1988-1990 inclusive, additional 19,278 persons, with a mean dose of 0.033 Gy, from the Russian Federation were involved in recovery operations related to the Chernobyl accident.

The incidence of leukemia in these liquidators has been followed up to the end of 1997. Standardized incidence ratios (SIR) together with related information are provided in Table 3.1 for all leukemia, chronic lymphocytic leukemia, and chronic myeloid leukemia in the liquidators. The results have been tabulated separately for the early period (April 1986-1990), the later period (1991-1997) and for the entire period of follow-up. The SIR values are relative to the comparable age-, sex- and period-specific rates for the Russian Federation as a whole.

The SIR for all leukaemia was elevated for both periods, but slightly more for 1991-1997. The question is to what extent these elevated values may reflect the effect of differential case ascertainment for the liquidators compared to that for the general population of Russia. Table 3.1 provides the standardized incidence ratios for chronic lymphocytic leukemia (deemed a subtype not increased by radiation exposure) and chronic myeloid leukemia (a subtype for which incidence can be increased by radiation exposure) for these same periods. The elevated standardized incidence ratio for chronic lymphocytic leukemia indicates that a substantial effect of screening exists. However, the standardized incidence ratio for chronic myeloid leukemia is some two-fold higher than that for chronic lymphocytic leukemia in the same 1991-1997 period,

Table 3.1 Standardized incidence ratio for various types of leukemia in Russian liquidators.

Period	*Person-years*	*Number of cases*		*Standardized incidence ratio* [a] *(SIR)*
		Observed	*Expected*	
Leukaemia (ICD-9: 204-208)				
1986-1990	398 630	17	8.6	1.98 (1.15-3.17)
1991-1997	613 203	48	17.7	2.71 (2.00-3.59)
1986-1997	1 011 833	65	26.3	2.47 (1.91-3.15)
Chronic lymphocytic leukaemia (ICD-9: 204.1)				
1986-1990	398 630	4	1.7	2.33 (0.62-5.96)
1991-1997	613 203	14	4.5	3.10 (1.70-5.20)
1986-1997	1 011 833	18	6.2	2.89 (1.71-4.56)
Chronic myelogenous leukaemia (ICD-9: 205.1)				
1986-1990	398 630	4	1.3	3.01 (0.81-7.72)
1991-1997	613 203	21	2.7	7.76 (4.81-11.9)
1986-1997	1 011 833	25	4.0	6.20 (4.01-9.16)

a 95% CI in parentheses.

Table 3.2. Standardized incidence ratio and excess relative risk for leukemia among Russian liquidators with documented individual doses.

Period	*Person-years*	*Number of cases*		*Standardized incidence ratio* [a] *(SIR)*	*Excess relative risk* [a] *$(Gy)^{-1}$*
		Observed	*Expected*		
Leukaemia (ICD-9: 204-208)					
1986-1990	288 917	16	6.1	2.63 (1.15-4.28)	n.a.
1991-1997	454 867	36	12.6	2.85 (1.99-3.94)	0.83 (-1.62-3.31)
1986-1997	743 784	52	18.7	2.78 (2.07-3.64)	1.16 (-1.17-3.52)
Leukaemia excluding chronic lymphocytic leukaemia (ICD-9: 204-208 excluding 204.1)					
1986-1990	288 917	13	4.9	2.55 (1.41-4.54)	n.a.
1991-1997	454 867	27	9.5	2.84 (1.88-4.14)	2.93 (-0.83-6.72)
1986-1997	743 784	40	14.4	2.78 (1.99-3.79)	4.58 (0.51-8.60)

a 95% CI in parentheses.

Table 3.3. Incidence of solid cancers among Russian liquidators.

Period	*Person-years of follow-up*	*Number of cases*		*Standardized incidence ratio (SIR)* [a]
		Observed	*Expected*	
Nuclear workers				
1991-1998	107 133	278	293	0.95 (0.84-1.07)
Previously not nuclear workers				
1991-1998	704 375	1 152	1 259	0.91 (0.86-0.97)

a 95% CI in parentheses.

Table 3.4. Standardized incidence ratio and excess relative risk of solid cancers among Russian liquidators with documented individual doses in the range of 0.001-0.3 Gy.

Period	*Person-years of follow-up*	*Number of cases*		*Standardized incidence ratio* [a] *(SIR)*	*Excess relative risk* [a] *$(Gy)^{-1}$*
		Observed	*Expected*		
Nuclear workers					
1991-1998	56 356	149	146	1.01 (0.86-1.20)	0.56 (-1.23-2.79)
Previously not nuclear workers					
1991-1998	514 101	847	898	0.94 (0.88-1.01)	0.82 (0.28-1.37)

a 95% CI in parentheses.

suggesting the possibility of radiation-related excesses.

The question whether radiation exposure from their work in the 30-km zone may have led to excess leukemia was addressed by examining the excess relative risk (ERR) per Gy in the liquidators for whom individual measurements of external dose were available. With this criterion, the number of person-years of follow-up (Table 3.2) is about three-quarters of the total in Table 3.1. The SIR for all leukemia is given in Table 3.2 for this group with documented individual doses; 2.85 (95% CI: 1.99-3.94) for the period 1991-1997, which is essentially identical to the value of 2.71 (95% CI: 2.00-3.59) in Table 3.1 for the entire cohort. The ERR per Gy for all leukaemias was not significantly associated with radiation dose. For the forms of radiogenic leukemia (all leukemia excluding chronic lymphocytic leukemia), however, a significant association with dose is observed over the entire period of follow-up (1986-1997). For the period 1991-1997, however, ERR per Gy is elevated but not significantly so.

Solid cancers

For investigation of solid cancers, Russian liquidators were divided into two different groups. The first group comprised 16,280 persons who had been nuclear workers before the accident occurred. The second group is larger (comprising 96,982 persons) and consists of those who had not been nuclear workers prior to their participation in recovery operations within the 30-km zone.

A five-year latency period was employed for the analysis of solid cancers. The SIR values for solid cancer appearing 1991-1998 are provided in Table 3.3 for the two groups of the liquidators. The control is the age-and sex-standardized rates for the whole of Russia. SIR were <1 for both groups, while for those who had not previously been nuclear workers SIR was significantly low, indicating a significant healthy worker effect.

The correlation of solid cancer incidence with dose was examined for those workers who had documented individual doses (the range 0.001-0.3 Gy was selected). This selection decreased the person-years of follow-up by about 50% for those who had been nuclear workers (comparing Table 3.3 with Table 3.4) and by about 30% for those who had not previously been nuclear workers. The SIRs for those with documented individual doses, however, were similar to those shown for the entire group. While the point estimates of ERR were greater than zero for both groups (Table 3.4), the ERR was significant only for those who had not been nuclear workers prior to their participation in recovery operations (0.82 (0.28-1.37)). The ERR was not significant in the case of those who had been nuclear workers previously (0.56 (-1.23-2.79)).

Some words about risk assessment for other solid cancer sites. Table 3.5 contains estimates of radiation

Table 3.5. Excess relative risk for malignant neoplasm of the digestive and respiratory systems.

Disease class	ICD-9 code	ERR/Gy	Significance level
Malignant neoplasm of the digestive system	150-159.9	0.85 (-0.3,2.04)	0.2
Malignant neoplasm of the respiratory system	160-165.9	1.13 (-0.24,2.4)	0.14

risks for malignant neoplasm of the digestive and respiratory systems. For both types of the solid tumors were detected non-statistically significant excesses in the incidence of malignant neoplasm.

The estimates of radiation risks for solid cancers in the previous studies of cancer incidence in liquidators [14] are consistent, within statistical errors, with the results of the present study. In our present study the ERR per Gy for solid cancers is estimated to be 0.82 (0.28-1.37), which is somewhat higher than the values previously presented [15,16]. It should be pointed out, however, that the sex and age patterns of these cohorts are different, as well are the systems of health care, methods of data collection, estimation of radiation doses etc. In order to assess the influences of all these factors, detailed long-term studies are required. Further study of the Chernobyl liquidators will serve to reduce uncertainties in interpretation of the effects of radiation on human health.

4. Radiation-epidemiological analysis of incidence of non-cancer diseases in liquidators.

Most of studies of health consequences of the Chernobyl accident and related radiation risks are concerned with dose response relationship of cancer incidence and mortality. But in the last few years a possible relationship between radiation exposure and frequency of non-cancer diseases is being discussed in scientific publications in Russia and abroad. Therefore it becomes particularly important to estimate radiation risks of non-cancer diseases from low doses within the study of the health status of liquidators. This chapter presents results of radiation-epidemiological studies of the cohort of liquidators registered in the RNMDR. This chapter discusses the dose response relationship for non-cancer incidence [17].

For this epidemiological analysis we formed a retrospective cohort consisting of 68,309 male liquidators, for each of which external gamma radiation dose was known and health information was available in the RNMDR (at least one entry from 1986 to 1996) and all were registered before 1.01.1992. For radiation risk assessment the analytical method described in chapter 3.1 was used. The 0-50 mGy group was taken as the baseline group (internal control).

4.1. Results of radiation risk assessment

All non-cancer classes

This section provides estimates of the excess relative risks (ERR) for main classes of non-cancer diseases derived from the cohort of liquidators.

As can be seen from Table 4.1, the statistically significant dose dependency with 95% confidence interval was derived for four classes of non-cancer diseases [18]:

1. endocrine diseases and metabolic disorders (ERR=0.58 with 95% CI (0.30; 0.87));
2. mental disorders (ERR=0.40 with 95% CI (0.17; 0.63));
3. diseases of the nervous system and sensory organs (ERR=0.35 with 95% CI (0.19; 0.52));
4. diseases of the digestive system (ERR=0.24 with 95% CI (0.05; 0.43)).

Two other classes of diseases have been estimated to be close to their statistical significance. These classes are:

1. diseases of the circulatory system (ERR=0.23 with 95% CI (-0.03; 0.50));
2. diseases of the genitourinary system (ERR=0.43 with 95% CI (-0.02; 0.87)).

For other classes of diseases under study no statistically significant dose dependencies were observed. We also calculated ERR for liquidators separately with different time of arrival to the emergency zone. It is only the endocrine

Table 4.1. Estimation of parameters of dose dependency of incidence rates for different non-cancer diseases among liquidators.

Disease	ICD-9 codes	P	ERR (1/Gy)
Infectious and parasitic diseases	001-139	0.152	-0.49 (-1.12; 0.15)
Endocrine and metabolic diseases	240-279	<0.001	0.58 (0.30; 0.87)
Diseases of blood and blood-forming organs	280-289	0.701	-0.17 (-1.00; 0.67)
Mental disorders	290-319	<0.001	0.40 (0.17; 0.64)
Diseases of the nervous system and sensory organs	320-389	<0.001	0.35 (0.19; 0.52)
Diseases of the circulatory system	390-459	0.077	0.23 (-0.03; 0.50)
Diseases of the respiratory system	460-519	0.893	0.11 (-0.15; 0.18)
Diseases of the digestive system	520-579	0.013	0.24 (0.05; 0.43)
Diseases of the genitourinary system	580-629	0.048	0.43 (-0.02; 0.87)
Diseases of the skin and subcutaneous tissue	680-709	0.377	-0.22 (-0.70; 0.26)
Diseases of the musculoskeletal system and connective tissue	710-739	0.319	0.09 (-0.09; 0.26)
Injuries and poisoning	800-999	0.161	0.24 (-0.11; 0.59)

and metabolic diseases for which statistically significant estimates of ERR were obtained for both 1986 and 1987. The values of ERR for the liquidators of 1986 was 0.57 with 95% CI (0.19; 1.00) and for the liquidators of 1987 the value of ERR was 0.75 with 95% CI (0.28; 1.22). Below listed are diseases for which statistically significant estimates of ERR were obtained when the group was separated according to the year of arrival to the zone:

- mental disorders, 1986 (ERR=0.53 with 95% CI (0.21, 0.85));
- diseases of the nervous system and sensory organs, 1986 (ERR=0.45 with 95% CI (0.22; 0.68));
- diseases of the digestive system, 1986 (ERR=0.27 with 95% CI (0.01, 0.52));
- diseases of the genitourinary system, 1987 (ERR=0.89 with 95% CI (0.10, 1.68)).

Thus, as a result of the radiation-epidemiological analysis of the dose dependency of non-cancer diseases a series of classes of diseases were identified which show a statistically significant growth with increase in dose. For diseases of the genitourinary system, the statistically significant relative risk was obtained only for the liquidators of 1987, whereas for all liquidators the estimate of relative risk is not statistically significant.

Cardiovascular diseases

Table 4.2 gives calculated radiation risks of the diseases of the circulatory system among liquidators. The conducted studies have revealed, first of all, a statistically significant estimate of ERR for cerebrovascular diseases (ERR=1.17 with 95% CI (0.45; 1.88) and essential hypertension (ERR=0.52 with 95% CI (0.07; 0.98)). It has also been demonstrated that for the liquidators who arrived to the zone in 1986 the value of ERR for cerebrovascular diseases was higher than for the cohort as a whole and equals 1.29 (95% CI (0.34; 2.24)) and for essential hypertension among the liquidators of 1987 the value ERR is 0.88 with 95% CI (0.10; 1.66).

Among diseases of the circulatory system attention should be paid to the class as a whole, in which the value ERR is 0.23 with 95% CI (-0.03; 0.50), and hypertension (ERR=0.35 with 95% CI (-0.05; 0.74)). The lower boundary of these two diseases is almost 0, i.e. there is a clear tendency, even though not statistically

Table 4.2. Estimated parameters of the dose dependency of incidence of diseases of the circulatory system among liquidators.

Disease	ICD-9 codes	P	ERR(1/Gy)
Diseases of the circulatory system	390-459	0.077	0.23 (-0.03; 0.50)
Hypertensive disease	401-405	0.071	0.35 (-0.05; 0.74)
essential hypertension	401	0.016	0.52 (0.07; 0.98)
hypertension with heart affection	402	0.814	-0.08 (-0.76; 0.60)
Ischaemic heart disease (IHD)	410-414	0.735	0.08 (-0.39; 0.55)
acute myocardial infarction	410	0.702	0.29 (-1.23; 1.81)
other acute IHD	411	0.642	-0.35 (-1.74; 1.05)
angina pectoris	413	0.372	0.31 (-0.40; 1.01)
other chronic forms of IHD	414	0.970	-0.04 (-0.64; 0.57)
Other heart diseases	420-429	0.927	-0.04 (-0.83; 0.90)
Cerebrovascular diseases	430-438	<0.001	1.17 (0.45; 1.88)
Diseases of arteries, arterioles and capillaries	440-448	0.167	0.56 (-0.31; 1.44)
Diseases of veins, lymphatic vessels and other diseases of the circulatory system	451-459	0.341	-0.25 (-0.75; 0.26)

significant.

We also studied robustness of radiation risk estimates depending on dose group ranges and effect of stratification by the arrival year on these estimates. The study has shown that division into smaller dose groups does not result in noticeable differences in radiation risk estimates.

It should be noted that the study did not allow for recognized risk factors such as excessive weight, hypercholesterolemia, smoking and alcoholism. Therefore, there is no way thus far to single out the radiation component in incidence of diseases of the circulatory system and other somatic diseases among liquidators. This requires in-depth studies considering all risk factors of both radiation and non-radiation nature and conducting detailed questioning of liquidators under study.

5. Mortality among the liquidators: estimation of radiation risks

This part of the article is based on the paper [19] and deals with estimating mortality rate among the Chernobyl liquidators and establishing a possible dose response relationship for mortality (radiation risks). The importance of these issues is associated with two aspects: first, from the epidemiological standpoint it is vital to study a possible dose response of mortality rate, considering low doses in the cohort under study (the mean external gamma radiation dose to liquidators is 0.1 Sv), and secondly, because mortality and its dynamics is a reflection of social, economic and political conditions in the country.

The size of the cohort of liquidators (65,905 persons) considered in the present paper is comparable to that of the above mentioned cohorts and these data may be of interest as an additional source of information about relationship of low radiation doses (<0.3 Sv) and mortality.

In the present work, the term dose implies a documented external radiation dose for a specific liquidator. In order to reduce the uncertainty in the marginal dose intervals, the analysis of dose response was based on data on liquidators with the doses from 5 to 300 mSv. A total of 65,905 liquidators with a

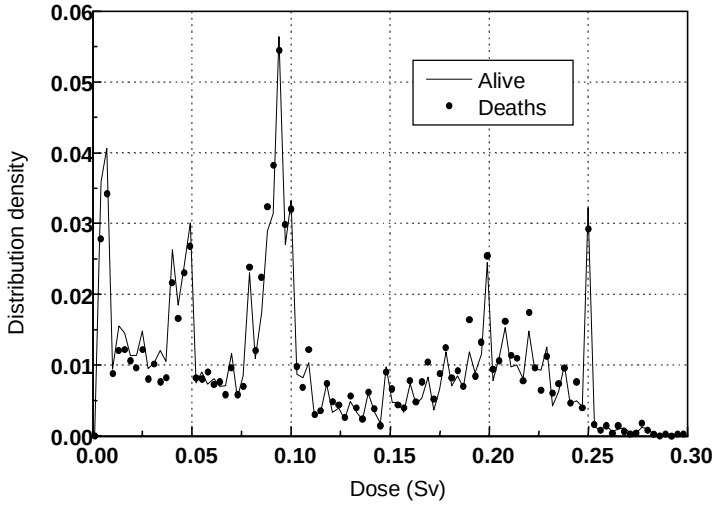

Fig. 5.1.Distribution of the alive liquidators and deaths by external radiation dose.

documented dose falling in this dose interval (follow up 1991-1998) were entered in the cohort under study. The number of follow-up person-years in 1991-1998 in this cohort was 426,304.

Distribution of liquidators by external dose is shown in Fig. 5.1. It is seen from Fig.5.1 that the distribution has four pronounced peaks. The peaks of 0.05, 0.10 and 0.25 Sv are dose limits established administratively. The limit of 0.25 Sv was set for liquidators working in the zone in 1986, 0.1 Sv - for liquidators of 1987 and 0.05 Sv - for the remainder.

The analysis included 4,995 deaths with documented cause of death and doses in the selected dose interval 5-300 mSv.

Basically, four classes of causes of death were considered as based on the International Classification of Diseases (ICD) [18]:

- malignant neoplasms: code of ICD-9 140-239.9;
- cardiovascular diseases: code of ICD-9 390-459.9;
- injuries and poisoning: code of ICD-9 800-E 999;

Table 5.1. Mean dose characteristics for death cases as a function of working time in the zone (the range 5-300 mSv).

Year of working time	Population	Mean dose (mSv)[a]	Mean length of stay (days)[a]	Mean dose rate (mSv day^{-1})[a]
1986	1978	171	68.2	2.9
1987	2169	97	74.2	1.4
1988	636	37	74.5	0.4
1989	206	40	108.5	0.5
1990	16	43	30.0	0.5
1986-1990	4995	116	72.4	1.8

[a] Person-year weighted averages.

Table 5.2. Number of deaths and SMR with 95% confidence intervals for main mortality classes.

Parameter	Malignant neoplasms	Noncancer causes of death				All causes
		Cardiovas-cular diseases	Injuries and poisoning	Other	Total	
Number of deaths	515	1728	1858	894	4480	4995
SMR (95%CI)	0.87 (0.80, 0.95)	1.07 (1.03, 1.13)	0.78 (0.74, 0.81)	0.82 (0.77, 0.88)	0.85 (0.83, 0.88)	0.85 (0.82, 0.87)

- diseases other than the above: code of ICD-9 0-139.9, 240-389.9 and 460-799.9.

Subclasses were not considered because of the short observational period and limited number of deaths.

The main dosimetric characteristics for cases of death are shown in Table 5.1.

The number of deaths included in the analysis of the mortality pattern is shown in Table 5.2.

For analysis of mortality rates and estimation of risk coefficients (using the external control), the general spontaneous mortality rate in Russia in 1991-1998 obtained from official statistics sources was used.

5.1. Analytical method for radiation risk assessment

The performed descriptive analysis of mortality is based on using the standardized mortality ratio (SMR). The expected number of deaths is calculated using the dynamics of person-years in the cohort and the age-specific mortality rate (males) for the population of Russia in the period from 1991 to 1998. The confidence intervals for SMR were calculated using the approach proposed in [11]. The projection of the mortality pattern is based on estimates of expected number of deaths.

Risk coefficients were estimated by the method of maximum likelihood, assuming that the numbers of deaths are the non-stationary Poisson series of events. We considered the non-stationary process to allow for changes in the spontaneous mortality in the considered time period.

The significance tests were derived from asymptotic properties of the likelihood ratios. The analysis is based on individual information about external radiation dose, number of observational person-years and age at exposure time.

The risk estimates were made using both the external (spontaneous mortality in Russia as a whole) and the internal control group. The logarithm of the likelihood function L for the given sample is [20]:

$$\ln L(f, ERR_{1Sv}) = \sum_{i=1}^{n} (\ln(\lambda_{i,fp_i}) - \sum_{k=0}^{fp_i} \lambda_{i,k}) - \sum_{j=1}^{N} \sum_{k=0}^{fp_i} \lambda_{j,k} \ . \qquad (5.1)$$

Risk coefficients were estimated using the linear model.

Model for the external control

In calculations using the external control group the risk model takes the form:

$$\lambda_{i,k} = \lambda^{o}_{i,k} \cdot f \cdot (1 + ERR_{1Sv} \cdot d_i). \qquad (5.2)$$

Where $\lambda_{i,k}$ is the intensity of the events series (here the mortality) for person i at the k-th time interval;

fp_i is the period of follow-up for the cohort member i (the time lapse from the start of follow up to the date of death or the period of the follow-up for an alive member of the cohort);

n is the number of deaths in the observational period;

N is the number of alive members of the cohort included in the analysis;

$\lambda^{o}_{i,k}$ is the spontaneous mortality rate in Russia corresponding to the attained age of the i-th cohort member at the k-th time interval;

d_i is the external radiation dose for the i-th cohort member;

ERR_{1Sv} is the excess relative risk per unit dose (sought parameter);

f is the coefficient (sought parameter) accounting for the difference between the spontaneous mortality in the liquidators cohort and the general population of respective age in the time period considered. In the used model this coefficient is equal to the SMR for unexposed members of the cohort. The variation of the coefficient f from unity may be explained by completeness and reliability of mortality data in the Registry or a possible «healthy workers effect», as the liquidators were subject to additional medical checks before going to work in the zone. The selected risk model has the advantage that it estimates both the dose response and the difference in spontaneous mortality in the followed up cohort and the referent Russian population.

The spontaneous mortality rate for each person was equal to the corresponding national rate for the attained age at a given time moment. We believe that individual information is preferable for risk estimation

because it makes possible to minimize the influence of subjective factor and loss of information in data grouping and stratification.

Thus, it is only the relative age distribution of spontaneous mortality rates that is used for risk estimation and this is a more robust characteristic than the absolute distribution. The value of *f* was assumed to be the same for all age groups.

The 95% likelihood intervals were determined from the likelihood function profile.

Model for the internal control

When risk coefficients were estimated using the internal control, data were stratified by attained age and calendar time, and the spontaneous mortality was determined from the balance of the observed and expected number of cases in a given stratum.

The risk model is written as:

$$\lambda_{i,k} = \lambda_{i,k}^{EW} \cdot (1 + ERR_{1Sv} \cdot d_i) \qquad (5.3)$$

Where:

$\lambda_{i,k}^{EW}$ -is the spontaneous mortality rate among liquidators in the stratum by the attained age and calendar time in which the i-th person under study falls.

The spontaneous mortality in the stratum by attained age *j*, at time moment *k* was taken to be as follows:

$$\lambda_{j,k}^{EW} = \frac{n_{j,k}}{\sum_{i \subset j} PY_{i,k} \cdot (1 + ERR_{1Sv} \cdot d_i)} \qquad (5.4)$$

5.2.Results

Fig. 5.2 shows the SMR dynamics from all causes in the studied cohort of 65,905 individuals.

The mortality from all causes is lower than the general Russian rate and is basically a reflection of the corresponding pattern in Russia as a whole in the considered period. It should be pointed out, however, that the mortality rate in the cohort of liquidators is gradually approaching the general Russian one. In 1998 the mortality from all causes was about 8 deaths per 1,000 persons.

Table 5.3 shows that for the considered dose interval (5-300 mSv) the spontaneous mortality of liquidators is lower than the general Russian one and equals about 82% of the general all-Russian mortality for the population of corresponding age. The observed difference in the spontaneous mortality (the coefficient *f*=0.82) can be either because of incomplete data on mortality in the general population or due to the «healthy workers effect» in the liquidators.

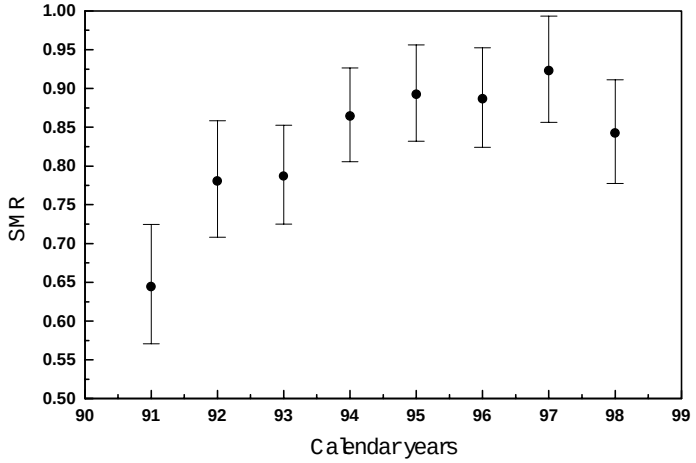

Fig. 5.2. SMR dynamics from all causes.

Table 5.3. Estimates of risk coefficients for deaths among liquidators.

Parameter	Cancer: ICD-9 140-208	Non cancer				All causes
		Non cancer: Other than ICD-9 140-208	Injuries and poisoning: ICD-9 800-E999	Cardiovascular diseases: ICD-9 390-459.9	Other than in columns 3 and 4: ICD-9 0-139.9, 240-389.9, 460-799.9	
Number of cases	515	4480	1858	1728	894	4995
Risk coefficients derived using the external control (spontaneous mortality in Russia)						
ERR Sv^{-1}	2.11 (1.31, 2.92)	0.13 (-0.09, 0.35)	-0.36 (-0.68, -0.04)	0.54 (0.18, 0.91)	0.23 (-0.26, 0.73)	0.27 (0.06, 0.48)
Coefficient *f*	0.70 (0.64, 0.76)	0.84 (0.81, 0.87)	0.81 (0.77, 0.85)	1.01 (0.97, 1.06)	0.80 (0.75, 0.85)	0.82 (0.80, 0.85)
Risk coefficients calculated using the internal control (spontaneous mortality derived from the balance of the observed and expected mortality in the strata at attained age and calendar time. In parentheses are 95% likelihood intervals						
ERR Sv^{-1}	2.04 (0.45,4.31)	0.15 (-0.24,0.60)	-0.36 (-0.89,0.26)	0.79 (0.07,1.64)	0.18 (-0.67,1.26)	0.31 (-0.08,0.74)

The mortality pattern for the considered causes of death is shown in Fig. 5.3. The observed pattern is in good agreement with the expected.

The proportion of deaths from malignant neoplasms and other causes (except the circulatory system diseases and injuries and poisoning) remains nearly constant at 10 and 20%, respectively, which is consistent with the prognosis. The percentage of the deaths due to cardiovascular diseases grows, while deaths from injuries and poisoning decrease. It is worth noting that the fraction of mortality from injuries and poisoning among liquidators in 1986-1992 was significantly higher than in the same age group in the country as a whole.

The mortality from cardiovascular diseases becomes predominant (about 42% in 1998) and corresponds to changes in the general mortality pattern for a given age group in Russia.

The SMR dynamics for cancer in Fig. 5.4 show a little lower mortality than the control (all-Russian). In 1998 the mortality rate from this cause was 110 deaths per 100,000 persons. Dynamics of SMR from cardiovascular diseases is shown in Fig. 5.5

With respect to all causes of death as a whole and separate categories, the mortality pattern in the considered cohort reflects the general trends in Russia. The mortality among liquidators is lower than in the

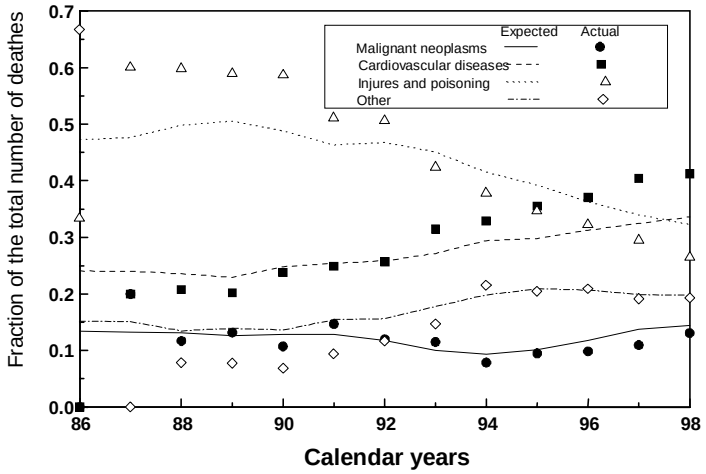

Fig. 5.3. Pattern of overall mortality by disease categories for liquidators.

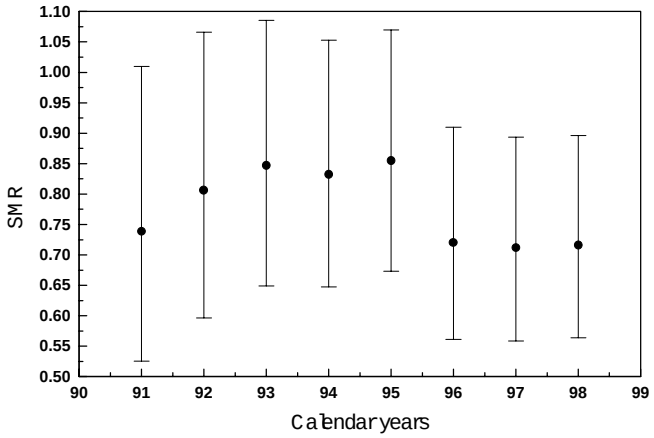

Fig. 5.4. SMR dynamics from malignant neoplasms.

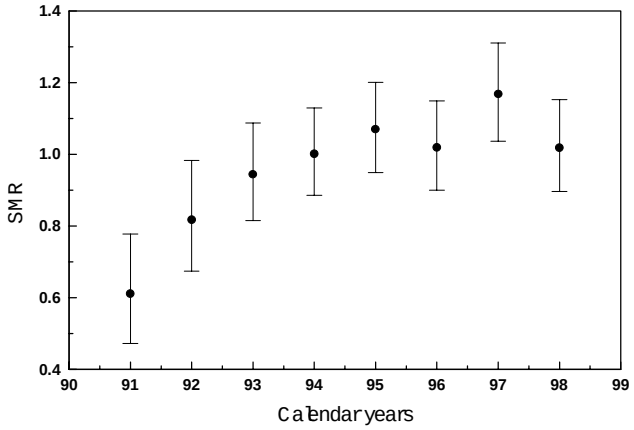

Fig. 5.5. Dynamics of SMR from noncancer diseases in liquidators (cardiovascular diseases).

corresponding age group in the country. An exception is the mortality from cardiovascular diseases for which the mortality became the same level as all-Russian by the end of the follow-up period.

Table 5.2 contains results of SMRs over the whole follow-up period. Comparing the SMR values from Table 5.2 with the values of coefficients f (SMR for non-exposed liquidators) from Table 5.3, it can be seen that the confidence intervals of these two estimates for various death causes are practically the same.

Results of estimation of the radiation risk coefficient for the mortality (ERR per Sv) are presented in Table 5.3. As follows from Table 5.3, the ERR values obtained using external and internal controls are close and the difference does not exceed, on the average, 10-15% (the greatest difference of 46% is observed for the death from cardiovascular diseases). It should be noted that the range of likelihood intervals derived using the approach proposed by the authors is very narrow, which suggests, as mentioned above, an increase in estimate accuracy.

As is seen from the presented results for all causes of death, except cancer and cardiovascular diseases, radiation risks are not statistically significant. For injuries and poisoning the dose relationship is actually inverse: the risk is decreasing with dose.

The ERR of death from malignant neoplasms of 2.11 (1.31, 2.92 95% CI) (with external control) and 2.04 (0.45, 4.31 95% LI) (with internal control) are statistically significant for the considered dose interval (0.005-0.3 Sv).

Thus, the results of the study lead us to conclude that there is a dose response relationship for mortality

from cancer in the cohort of liquidators. Given the above considerations and remembering that no account was taken of the minimal latent period (10 years) preceding the development of malignant neoplasms, the derived values of risk should be treated as preliminary.

It should be also recognized that even with reliable estimates of risk, the dose values being low, induction of radiogenic cancers will be insignificant. If the maximum risk estimate of 2.04 Sv^{-1} is adopted, the attributive risk of induction of radiogenic cancers will be 20% (with the mean dose 0.1 Sv), which corresponds to 20 annual radiation-induced deaths per 100,000 liquidators.

In conclusion we would like to point out that the approach to estimation of risk coefficients using the relative age distribution of spontaneous mortality normalized to national rates (external control) seems to be justified. The risk coefficients (ERR per Sv) estimated with the external and internal controls appear to be close each other. The values of SMR (Table 5.2) and the coefficient f (Table 5.3) and their confidence intervals for various death causes, which reflect no dose response, are also very close. We believe that the proposed approach will have an advantage for rare death causes, for example leukemia, when the accuracy of determination of spontaneous mortality in strata is not very high.

5.3. Conclusion

1. The mortality in liquidators is mostly lower than the all-Russian one and correlates with the trends in the corresponding age groups of the Russian population. The SMR for liquidators varies from 0.62 to 0.90.
2. The observed pattern of mortality is consistent with the predicted. At present the percentage of deaths from malignant neoplasms is about 10%, deaths from injuries and poisoning - 30%. Predominant are deaths from cardiovascular diseases which account for 40% of the overall mortality.
3. The values of the excess relative risk per unit dose (ERR Sv^{-1}) for malignant neoplasms and cardiovascular diseases are estimated as 2.11 (1.31, 2.92 95% CI) and 0.54 (0.18, 0.91 95% CI), (external control), and as 2.04 (0.45, 4.31 95% CI) and 0.79 (0.07, 1.64 95% CI) (internal control), respectively. The risk of death from all noncancer causes is not statistically significant and close to zero. The derived estimates of risk coefficients, however, are preliminary.

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