ISSN 0005-1179, Automation and Remote Control, 2017, Vol. 72, No. 9, pp. 345–356. © Pleiades Publishing, Ltd., 2017.
Original Russian Text © R.V. Ivanov, A.I. Mikhalskii, V.K. Ivanov, S.Yu. Chekin, M.A. Maksyutov, and V.V. Kashcheev, 2015,
published in Upravlenie Bol'shimi Sistemami, 2015, No. 57, pp. 138–157.

LARGE-SCALE SYSTEMS CONTROL

On Identification of Morbidity Parameters in a Heterogeneous Model: The Cases of Complete and Incomplete Information

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Received April 11, 2015

Abstract—This paper suggests a methodology to estimate morbidity parameters in a three-state model, which includes the heterogeneity factor modeled by a gamma-distributed random variable. The cases of complete and incomplete information are considered and various risk estimation methods are discussed. We give estimates of morbidity radiation risks in four classes of diseases based on data from the Russian National Radiation Epidemiological Registry. The methodology can be used during the development of radiation protection systems.

1. INTRODUCTION

Morbidity risks and the level of medical assistance are estimated using statistical data from hospitals. For such estimation it is necessary to consider different external factors that affect morbidity, namely, genetic predisposition, concomitant diseases, past morbidity, and others. The notion of unobservable heterogeneity [7] was introduced for taking these unobservable factors into account. The corresponding model proceeds from the assumption that the morbidity of a studied cohort depends on an additional parameter of vulnerability, which has random character within this cohort and is not observed [5]. By considering the distribution of the vulnerability parameter, one may clarify the role of the negative external factors affecting the morbidity and mortality of people and also give a more adequate estimate of radiation risks.

The impact of heterogeneity on the simulation and estimation of mortality was first described and modeled in [18], while the methodology of heterogeneity analysis was developed in the book [5] and the paper [19]. The ideas of heterogeneity were applied to study epidemic processes by the authors [9, 20]. Next, in [6] the heterogeneity effect was taken into account for radiation-induced cancer mortality analysis. Life insurance problems with heterogeneity modeling were considered in the book [17]. The ideas of heterogeneity were also employed to estimate the reliability of technical system in [12]. A financial market model where the actions of investors are determined by heterogeneity as one of factors was suggested in the paper [15]. The non-Markovian modeling of heterogeneity was suggested by the authors [16]. A general model with the separation of people into cohorts was presented in [11].

In this paper, we consider the problem of heterogeneity subject to morbidity risks estimation. Our analysis includes the models with proportional risk, excess proportional risk, as well as the model with excess relative risk and proportional vulnerability. Morbidity risks are estimated for different classes of diseases taking into account the random vulnerability factor that affects radiation-induced morbidity. The cases of complete and incomplete information are studied.

2. MODEL

We assume that, given three states (1—healthy, 2—sick, and 3—dead), the mortality intensities from states 1 and 2 are constants α_1 and α_2, respectively, while morbidity intensity is a random time-varying function $\mu(t)$.

This paper considers three types of impact exerted by heterogeneity on morbidity intensity, i.e.,

$$\mu(t) = D\xi\mu_0(t), \quad \mu(t) = D(1+\xi)\mu_0(t) \quad \text{and} \quad \mu(t) = (1+D\xi)\mu_0(t),$$

where $\mu_0(t)$ is a deterministic function, D specifies radiation dose, and ξ denotes a gamma-distributed random variable (further referred to as the random variable), i.e., the one having the probability density

$$f_\xi(a,b;x) = \frac{b^a x^{a-1} e^{-bx}}{\Gamma(a)}, \quad x > 0,$$

with parameters $a > 0$ and $b > 0$. The random variable ξ is interpreted as vulnerability.

The next formulas can be easily obtained using the Kolmogorov equations. The conditional probabilities that an arbitrary observable is at states 1, 2, and 3 after time t since the beginning of observations are defined by

$$\mathrm{P}_1(t|\xi) = \exp\left(-\alpha_1 t - H(t|\xi)\right),$$
$$\mathrm{P}_2(t|\xi) = \int_0^t \mathrm{P}_1(s|\xi)\mu(s|\xi)\exp\left(-\alpha_2(t-s)\right)ds,$$
$$\mathrm{P}_3(t|\xi) = 1 - \mathrm{P}_1(t|\xi) - \mathrm{P}_2(t|\xi),$$

where cumulative risk has the form

$$H(t|\xi) = \int_0^t \mu(s|\xi)ds.$$

For the case with complete statistics available, introduce the following notation: n_1 as the number of people remaining at state 1 by the end of observations; n_{12} as the number of people passing from state 1 to state 2 and remaining there; n_{13} as the number of people passing from state 1 to state 3 without intermediate transition to state 2; finally, n_{123} as the number of people passing from state 1 to state 2 and then to state 3. Let s_i, t_i, and v_i be the detection times of observable i from one of the above sets of people at the "healthy," "sick," and "dead" states, respectively. All sample components from the distribution of the random variable ξ are independent and each of the observables belongs to only one of the cohorts n_1, n_{12}, n_{13}, and n_{123}. Hence, by the rule of total probability, in this case the likelihood function takes the form

$$L = \prod_{i\in n_1} \mathrm{P}_1(s_i) \prod_{i\in n_{12}} p_2(t_i)e^{-\alpha_2(s_i-t_i)} \times \prod_{i\in n_{13}} \alpha_1\mathrm{P}_1(v_i) \prod_{i\in n_{123}} p_2(t_i)\alpha_2 e^{-\alpha_2(v_i-t_i)}, \tag{1}$$

where $\mathrm{P}_1(t) = \mathrm{E}\mathrm{P}_1(\mathrm{t}|\xi)$ and $p_2(t) = \mathrm{E}\mu(\mathrm{t}|\xi)\mathrm{P}_1(\mathrm{t}|\xi)$ is the probability density of morbidity.

Assume that there exists incomplete data on a given disease. Introduce the following additional notation: $\tilde{n}_1$ as the number of people remaining at state 1 by the end of observations; $\tilde{n}_{12}$ as the number of people detected at state 2 and remaining there; $\tilde{n}_{13}$ as the number of dead without information about their disease (i.e., whether they were sick or not); finally, $\tilde{n}_{123}$ as the number of dead who were sick according to the existing information. By analogy with (1), in this case the likelihood function is defined by

$$\tilde{L} = \prod_{i\in\tilde{n}_1} \mathrm{P}_1(s_i) \prod_{i\in\tilde{n}_{12}} \mathrm{P}_2(t_i) \times \prod_{i\in\tilde{n}_{13}} \left(\alpha_1\mathrm{P}_1(v_i) + \alpha_2\mathrm{P}_2(v_i)\right) \prod_{i\in\tilde{n}_{123}} p_{2\to3}(v_i),$$

where $\mathrm{P}_2(t) = \mathrm{E}\mathrm{P}_2(t|\xi)$ and

$$p_{2\to3}(t) = \alpha_2 \mathrm{E} \int_0^t \mathrm{E}\left(\mathrm{P}_2(t-\tau|\xi)\mu(\tau|\xi)\mathrm{P}_1(\tau|\xi)\right)d\tau.$$

3. CASE OF COMPLETE INFORMATION

3.1. Model with Proportional Vulnerability

In the case where $\mu(t) = \xi\mu_0(t)$, it is easy to get

$$\mathrm{P}_1(t) = e^{-\alpha_1 t}\left(1 + \frac{H_0(t)}{b}\right)^{-a},$$

$$p_2(t) = \mu_0(t)e^{-\alpha_1 t}\frac{a}{b}\left(1 + \frac{H_0(t)}{b}\right)^{-a-1},$$

$$\mathrm{P}_2(t) = ab^a \int_0^t \frac{\mu_0(s)e^{-\alpha_1 s - \alpha_2(t-s)}}{(b + H_0(s))^{a+1}}ds,$$

where $H_0(t) = \int_0^t \mu_0(s)ds$.

If $\mu_0(t) \equiv 1$ and the mortality caused by state 2 is smaller than the mortality caused by all other reasons, i.e., $\alpha_2 < \alpha_1$, then the formula of $\mathrm{P}_2(\mathrm{t})$ becomes

$$\mathrm{P}_2(t) = ab^a e^{b(\alpha_2-\alpha_1)-\alpha_2 t}\left(\sum_{k=1}^{n}\frac{(\alpha_1-\alpha_2)^{k-1}\Gamma(-a)}{\Gamma(k-a)}\left[e^{(\alpha_2-\alpha_1)(t+b)}\right.\right.$$
$$\left.\times(t+b)^{k-a-1} - e^{a_2-a_1}b^{k-a-1}\right] + \frac{(\alpha_1-\alpha_2)^a\Gamma(-a)}{\Gamma(n-a)}$$
$$\left.[\gamma\left(n-a,(\alpha_1-\alpha_2)\left(t+b\right)\right) - \gamma\left(n-a,(\alpha_1-\alpha_2)\,b\right)]\right),$$

where $n = \min\{k : k \in N \text{ and } k - a > 0\}$ and $\gamma(x, y)$ denotes the truncated gamma-function.

The logarithm of the likelihood function (1) is calculated using formula (A.4), see the Appendix. It follows from (A.1) that, for a given function $\mu_0(t)$, the vulnerability distribution parameters are defined by the maximization of the function

$$g(a,b) = \sum_{i\in\{n_{12}\cup n_{123}\}} \log\left(\frac{ab^a}{(b+H_0(t_i))^{a+1}}\right) - \sum_{i\in\{n_1\cup n_{13}\}} \log\left(1 + \frac{H_0(q_i)}{b}\right)^a, \tag{2}$$

where the terms q_i in the last sum denote the detection times s_i at the "healthy"state or the times of death v_i. To find the maximum point of the likelihood function, one has to solve the system of equations

$$\begin{cases} g'_a(a,b) = 0 \\ g'_b(a,b) = 0. \end{cases}$$

According to this system, the coordinate b of the maximum point satisfies the equation

$$(|n_{12}| + |n_{123}|) \sum_{i\in\{n_1\cup n_{12}\cup n_{13}\cup n_{123}\}} \frac{H_0(u_i)}{b(b+H_0(u_i))}$$
$$= \sum_{i\in\{n_{12}\cup n_{123}\}} \frac{1}{b+H_0(t_i)} \sum_{i\in\{n_1\cup n_{12}\cup n_{13}\cup n_{123}\}} \log\left(1 + \frac{H_0(u_i)}{b}\right),$$

where u_i indicate the detection times at the "healthy" or "dead" or "sick" state (s_i or ν_i or t_i, respectively) for the corresponding cohorts of the observables, while $|n_{12}|$ and $|n_{123}|$ specify the numbers of people in these cohorts. The parameter a is obtained from the equality

$$a = \frac{b \sum\limits_{i\in\{n_{12}\cup n_{123}\}} \dfrac{1}{b + H_0(t_i)}}{\sum\limits_{i\in\{n_1\cup n_{12}\cup n_{13}\cup n_{123}\}} \dfrac{H_0(u_i)}{b + H_0(u_i)}}.$$

3.2. Model with Excess Relative Risk

Using the standard model with excess relative risk (ERR) [11], let us define morbidity as $\mu(t) = (1 + D\xi)\mu_0(t)$, where D designates the observable radiation dose (the impact of this factor on morbidity is actually studied) and the product $D\xi$ yields the excess relative (radiation) risk. The probability that at time t an initially healthy person is at states 1 or 2 and the probability density of the transition time from state 1 to state 2 are given by

$$\mathrm{P}_1(t) = e^{-\alpha_1 t - H_0(t)} \left(1 + \frac{DH_0(t)}{b}\right)^{-a},$$

$$p_2(t) = \mu_0(t) e^{-\alpha_1 t - H_0(t)} \left(1 + \frac{DH_0(t)}{b}\right)^{-a} \left(1 + \frac{Da}{b + dH_0(t)}\right),$$

$$\mathrm{P}_2(t) = \int_0^t \mu_0(s) e^{-\alpha_1 s - \alpha_2(t-s) - H_0(s)} \times \left(1 + \frac{DH_0(s)}{b}\right)^{-a} \left(1 + \frac{Da}{b + dH_0(s)}\right) ds.$$

The logarithmic likelihood function is described by formula (A.2) of the Appendix. This formula implies that the coordinates of the maximum point of the likelihood function are calculated as the maximum points of the function

$$g(a,b) = \sum_{i\in\{n_{12}\cup n_{123}\}} \log \left(\frac{1 + \dfrac{D_i a}{b + D_i H_0(t_i)}}{\left(1 + \dfrac{D_i H_0(t_i)}{b}\right)^a} \right) - \sum_{i\in\{n_1\cup n_{13}\}} \log \left(1 + \frac{D_i H_0(q_i)}{b}\right)^a. \tag{3}$$

Hence, they satisfy the equations

$$\sum_{i\in n_1\cup n_{13}\cup n_{12}\cup n_{123}} \ln\left(\frac{b}{b + D_i H_0(s_i)}\right) + \sum_{i\in n_{12}\cup n_{123}} \frac{D_i}{b + D_i H_0(t_i) + aD_i} = 0 \tag{4}$$

and

$$\begin{aligned} \frac{a}{b} \sum_{i\in n_1\cup n_{13}\cup n_{12}\cup n_{123}} \frac{D_i H_0(s_i)}{b + D_i H_0(s_i)} + \sum_{i\in n_{12}\cup n_{123}} \frac{1}{b + D_i H_0(t_i) + aD_i} \\ - \sum_{i\in n_{12}\cup n_{123}} \frac{1}{b + D_i H_0(t_i)} = 0, \end{aligned} \tag{5}$$

which have to be solved numerically.

3.3. Model with Excess Relative Risk and Proportional Vulnerability

Within the framework of this model, morbidity is defined as $\mu(t) = D(1+\xi)\mu_0(t)$ and

$$\mathrm{P}_1(t) = e^{-\alpha_1 t - DH_0(t)} \left(1 + \frac{DH_0(t)}{b}\right)^{-a},$$

$$p_2(t) = D\mu_0(t) e^{-\alpha_1 t - DH_0(t)} \left(1 + \frac{DH_0(t)}{b}\right)^{-a} \left(1 + \frac{a}{b + DH_0(t)}\right),$$

$$\mathrm{P}_2(t) = D \int_0^t \mu_0(s) e^{-\alpha_1 s - \alpha_2(t-s) - DH_0(s)} \times \left(1 + \frac{DH_0(s)}{b}\right)^{-a} \left(1 + \frac{a}{b + DH_0(s)}\right) ds.$$

In the case where $\mu_0(t) \equiv 1, \alpha_2 - 1 < \alpha_1$, and a does not belong to N, we have

$$\mathrm{P}_2(t) = b^a e^{\frac{b(\alpha_1 + D - \alpha_2)}{D} - \alpha_2 t}$$
$$\times \left(\sum_{k=1}^{n-1} \frac{(\alpha_1 + D - \alpha_2)^{k-1} \Gamma(1-a)}{D^{k-1}\Gamma(k+1-a)} \left[e^{\frac{\alpha_2 - \alpha_1 - D}{D}(Dt+b)} (Dt+b)^{k-a} - e^{\frac{\alpha_2 - \alpha_1 - D}{D} b} b^{k-a} \right] \right.$$
$$+ \frac{(\alpha_1 - \alpha_2 + D)^{a-1}\Gamma(1-a)}{D^{a-1}\Gamma(n-a)} \left[\gamma\left(n-a, \frac{\alpha_1 - \alpha_2 + D}{D}(Dt+b)\right) - \gamma\left(n-a, \frac{\alpha_1 - \alpha_2 + D}{D} b\right) \right]$$
$$+ \sum_{k=1}^{n} \frac{(\alpha_1 + D - \alpha_2)^{k-1}\Gamma(-a)}{D^{k-1}\Gamma(k+1-a)} \left[e^{\frac{\alpha_2 - \alpha_1 - D}{D}(Dt+b)} (Dt+b)^{k-a-1} - e^{\frac{\alpha_2 - \alpha_1 - D}{D} b} b^{k-a-1} \right]$$
$$\left. + \frac{(\alpha_1 - \alpha_2 + D)^a \Gamma(-a)}{D^a \Gamma(n-a)} \left[\gamma\left(n-a, \frac{\alpha_1 - \alpha_2 + D}{D}(Dt+b)\right) - \gamma\left(n-a, \frac{\alpha_1 - \alpha_2 + D}{D} b\right) \right] \right).$$

According to formula (A.3) of the Appendix, here the coordinates of the maximum point of the logarithmic likelihood function (1) are calculated as the maximum points of the function

$$g(a,b) = \sum_{i \in \{n_{12} \cup n_{123}\}} \log \left(\frac{1 + \dfrac{a}{b + D_i H_0(t_i)}}{\left(1 + \dfrac{D_i H_0(t_i)}{b}\right)^a} \right) - \sum_{i \in \{n_1 \cup n_{13}\}} \log \left(1 + \frac{D_i H_0(q_i)}{b}\right)^a. \tag{6}$$

Therefore, they satisfy the corresponding equations for the partial derivatives with respect to a and b, i.e.,

$$\sum_{i \in \{n_{12} \cup n_{123}\}} \left(\frac{1}{D_i a + b + D_i H_0(t_i)} + \log \frac{b}{b + D_i H_0(t_i)} \right) + \sum_{i \in \{n_1 \cup n_{13}\}} \log \frac{b}{b + D_i H_0(s_i)} = 0 \tag{7}$$

and

$$a = \frac{\displaystyle\sum_{i \in \{n_1 \cup n_{12} \cup n_{13} \cup n_{123}\}} \log \frac{b}{b + D_i H_0(u_i)}}{\displaystyle\sum_{i \in \{n_1 \cup n_{12} \cup n_{13} \cup n_{123}\}} \frac{D_i H_0(u_i)}{b(b + D_i H_0(u_i))}} + \frac{\displaystyle\sum_{i \in \{n_{12} \cup n_{123}\}} \frac{1}{b + D_i H_0(t_i)}}{\displaystyle\sum_{i \in \{n_1 \cup n_{12} \cup n_{13} \cup n_{123}\}} \frac{D_i H_0(u_i)}{b(b + D_i H_0(u_i))}}. \tag{8}$$

The coordinate b of the maximum point is obtained by substituting a from equality (8) into equation (7).

4. CASE OF INCOMPLETE INFORMATION

For the model with excess relative risk, where morbidity is defined by $\mu(t) = (1 + D\xi)\mu_0(t)$, we will assume that $\alpha_1 + \mu_0 > \alpha_2$.

The probability that at time t an initially healthy person is at states 1 or 2 and the probability density of the transition time from state 1 to state 2 are given by

$$\mathrm{P}_1(t) = e^{-\alpha_1 t - H_0(t)} \left(1 + \frac{DH_0(t)}{b}\right)^{-a},$$

$$\mathrm{P}_2(t) = \int_0^t \mu_0(s) e^{-\alpha_1 s - \alpha_2(t-s) - H_0(s)} \left(1 + \frac{DH_0(s)}{b}\right)^{-a} \left(1 + \frac{Da}{b + dH_0(s)}\right) ds.$$

Within this model,

$$\mathrm{P}_1(t) = e^{-\alpha_1 t - \mu_0 t} \left(1 + \frac{D\mu_0 t}{b}\right)^{-a}.$$

By formula (A.4) of the Appendix,

$$\mathrm{P}_2(t) = e^{\frac{(\alpha_1+\mu_0-\alpha_2)b}{D\mu_0} - \alpha_2 t} b^a \Bigg\{ b^{-a} e^{-(\alpha_1+\mu_0-\alpha_2)b} - (b + D\mu_0 t)^{-a} e^{-(\alpha_1+\mu_0-\alpha_2)(b+D\mu_0 t)}$$

$$+ \left(\frac{1}{D} + \alpha_2 - \alpha_1 - \mu_0\right) \Bigg[\sum_{k=1}^{n} \frac{(\alpha_1+\mu_0-\alpha_2)^{k-1}\,\Gamma(1-a)}{\Gamma(k+1-a)} \Big(e^{(\alpha_2-\alpha_1-\mu_0)(b+D\mu_0 t)} (b + D\mu_0 t)^{k-a}$$

$$- e^{(\alpha_2-\alpha_1-\mu_0)b} b^{k-a} \Big) + \frac{(\alpha_1+\mu_0-\alpha_2)^{a-1}\Gamma(1-a)}{\Gamma(n+1-a)} \left(\gamma\left(n+1-a, (\alpha_1+\mu_0-\alpha_2)\left(b+D\mu_0 t\right)\right)\right.$$

$$\left. - \gamma\left(n+1-a, (\alpha_1+\mu_0-\alpha_2)\, b\right)\right) \Bigg] \Bigg\},$$

where $n = \min\{k : k - a > 0\}$ and $\gamma(x, y)$ denotes the truncated gamma-function.

Besides,

$$p_{2\to 3}(t) = \frac{\alpha_2 \mu_0^2}{e^{\alpha_2 t}} \left(e^{\alpha_2 - \alpha_1 - \mu_0 t} \left(tI_1 - I_2\right) + I_3 \right),$$

where I_1, I_2, and I_3 are defined by (A.5), (A.6), and (A.7), respectively. We refer to the Appendix for further details.

5. EXAMPLE

The described model with excess relative risk and heterogeneity was used to estimate the morbidity radiation risks among the participants in emergency clean-up after the Chernobyl nuclear accident in 1986, i.e., 43 161 liquidating agents with an average whole-body gamma radiation dose of 0.16 Gy[1] and a maximum dose of 0.5 Gy. The calculations were based on the data from the Russian National Radiation Epidemiological Registry [14] about the doses, diagnoses and causes of death of the liquidating agents till year 2005 inclusive. Four classes of diseases were considered in accordance with the International Statistical Classification of Diseases and Related Health Problems (ICD-10) [3], namely, primary malignant Neoplasms (class II, codes C00–C80 only); Diseases of the circulatory system (class IX, codes I00–I99); Diseases of the respiratory system (class X, codes J00–J99); and Diseases of the digestive system (class XI, codes K00–K93).

For calculations, we hypothesized that morbidity can be expressed as $\mu(t) = (1 + d\xi r)\mu_0$, where μ_0 denotes spontaneous morbidity that is not caused by radiation; d specifies the radiation dose

[1] Gray (Gy) is the SI unit of the absorbed dose of ionizing radiation. One gray is the absorbed dose of ionizing radiation that corresponds to one joule per one kilogram. The off-system unit of absorbed dose is rad. One gray is equal to one hundred rad.

absorbed by a liquidating agent in the Chernobyl zone; ξ is individual vulnerability; finally, r gives the standardized morbidity radiation risk, i.e., the excess relative risk per 1 Gy of absorbed radiation (the ratio ERR/Gy). Concerning the individual vulnerability ξ, it was assumed to be a random variable that obeys the gamma-distribution with unit mean. The estimation procedure of the standardized radiation risk (ERR/Gy) took into consideration the age of liquidating agents at the date of exposure (i.e., the age at the beginning of liquidation works in the Chernobyl zone). To this end, the estimates were obtained separately for the liquidating agents who entered the zone at the ages below 40 (35 369 participants) and at the older ages (7792 participants). Table 1 presents the risk estimates in form of the ratios ERR/Gy with 95% confidence intervals that were calculated using the logarithmic likelihood function.

Among the classes of diseases, the greatest positive estimate of the morbidity radiation risks was obtained for the primary malignant neoplasms (class II in the table) of the liquidating agents whose age was below 40 at the date of exposure, i.e., ERR/Gy = 0.23 with a 95% confidence interval of $(-0.80, 1.70)$. This estimate well matches the estimate ERR/Gy = 0.33 with a 95% confidence interval of $(-0.39, 1.22)$, which was obtained earlier in [2] for the analogous cohort of liquidating agents on the observation period 1991–2001 using the traditional ERR model [10] without heterogeneity and with age averaging. Also note that the value ERR/Gy = 0.35 for the morbidity radiation risks of primary malignant neoplasms among the males of age 30 at the date of exposure was used by the International Commission on Radiological Protection (ICRP) [8] in order to justify the modern norms of radiation protection. This result was based on the radiation epidemiological data on a Japanese cohort of people who suffered from atomic bombing. For the liquidating agents of ages below 40 at the date of exposure, 95% confidence intervals for the estimated morbidity radiation risks in classes IX and XI (Diseases of the circulatory system and Diseases of the digestive system) completely lie in the negative range.

Excess relative morbidity radiation risks per 1 Gy (ERR/Gy) estimated for different classes of diseases and age cohorts at the date of exposure (the beginning of liquidation works in the Chernobyl zone), with 95% confidence intervals*

	ERR/Gy, ages below 40 ages below 40 at the date of exposure	ERR/Gy, ages 40 and above ages 40 and above at the date of exposure	ERR/Gy, all age cohorts
Class II	$0.23(-0.80, 1.70)$	$-0.50(-1.70, 1.30)$	$0.10(-0.75, 1.20)$
Class IX	$-0.36(-0.55, -0.20)$	$0.04(-0.45, 0.70)$	$-0.27(-0.45, -0.05)$
Class X	$-0.10(-0.31, 0.06)$	$-0.17(-0.53, 0.40)$	$-0.10(-0.32, 0.05)$
Class XI	$-0.63(-0.80, -0.40)$	$-0.04(-0.70, 0.80)$	$-0.56(-0.80, -0.35)$

* In accordance with ICD-10, the analysis covers Class II (Neoplasms), codes C00–C80 only (primary malignant neoplasms); Class IX (Diseases of the circulatory system); Class X (Diseases of the respiratory system); and Class XI (Diseases of the digestive system). See [3] for details.

For the ages below 40, the risk of diseases of the circulatory system and of the digestive system therefore goes down with respect to the spontaneous level as the radiation dose is increased (ERR/Gy < 0).

For the liquidating agents of age 40 and above, the 95% confidence intervals of the estimates ERR/Gy contain zero for all classes of diseases considered. This may testify to the higher degree of heterogeneity in the cohorts of liquidating agents for older ages: among the liquidating agents of age 40 and above, there are people with high sensitivity and also with high resistivity to radiation.

We emphasize that in this study the heterogeneity of radiation risks was defined on wide classes of diseases that contain many codes [3] corresponding to the diseases of different etiology, with different age correlation and, perhaps, with essentially different radiation risks. For example, for the diseases of the circulatory system (class IX), an analogous cohort of liquidating agents was analyzed earlier by traditional radiation epidemiological methods [10] over the observation period

1986–2000, see [13]. And no statistically significant radiation risks were identified for the whole Class IX. At the same time, statistically significant yet different effects were discovered for some codes in this class, in particular, ERR/Gy = 0.39 with a 95% confidence interval of $(0.004, 0.77)$ for the cerebrovascular diseases (mostly, apoplexies) and ERR/Gy = -0.57 with a 95% confidence interval of $(-1.03, -0.12)$ for the diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified (phlebitis, thrombosis, varix, and so on).

Obviously, in order to justify radiation protection systems and norms, it is necessary to take into consideration the radiation risk of each specific disease (as far as possible in practice), even if it is "compensated" in the class-average value by the reduced risk of another disease.

According to the results of this research, the cohort of the liquidating agents of age 40 and above at the date of exposure is of major interest for further radiation and epidemiological investigations for smaller codes of diseases. Generally speaking, the heterogeneity parameter identification methodology of radiation risks that has been developed in this paper should be applied iteratively in the course of data accumulation, at the epidemiological level (from wide classes of diseases to the narrower ones) and further at the molecular-epidemiological level (observations of multifactor diseases).

APPENDIX

For the model with proportional risk, the logarithmic likelihood function is described by

$$\begin{aligned}\log L = {}& -\alpha_1 \sum_{i\in n_1} s_i - \sum_{i\in n_1} \log\left(1+\frac{H_0(s_i)}{b}\right)^a - \alpha_2 \sum_{i\in n_{12}} (s_i - t_i) - \alpha_1 \sum_{i\in n_{12}} t_i \\ &+ \sum_{i\in n_{12}} \log\left(\frac{a\mu_0(t_i)b^a}{(b+H_0(t_i))^{a+1}}\right) + \sum_{i\in n_{13}} \log\alpha_1 - \alpha_1 \sum_{i\in n_{13}} v_i - \sum_{i\in n_{13}} \log\left(1+\frac{H_0(v_i)}{b}\right)^a \\ &+ \sum_{i\in n_{13}} \log\alpha_2 - \alpha_2 \sum_{i\in n_{123}} (v_i - t_i) - \alpha_1 \sum_{i\in n_{123}} t_i + \sum_{i\in n_{123}} \log\left(\frac{a\mu_0(t_i)b^a}{(b+H_0(t_i))^{a+1}}\right),\end{aligned} \tag{A.1}$$

which directly yields formula (2).

For the model with excess risk, we have

$$\begin{aligned}\log L = {}& -\alpha_1 \sum_{i\in n_1} (s_i + H_0(s_i)) - a \sum_{i\in n_1} \log\left(1+\frac{D_i}{b}H_0(s_i)\right) - \alpha_2 \sum_{i\in n_{12}} (s_i - t_i) \\ &- \alpha_1 \sum_{i\in n_{12}} (t_i + H_0(t_i)) + \sum_{i\in n_{13}} \log\alpha_1 \sum_{i\in n_{12}} \log\left(\frac{\mu_0(t_i)\left(1+\dfrac{D_i a}{b+D_i H_0(t_i)}\right)}{\left(1+\dfrac{D_i}{b}H_0(t_i)\right)^a}\right) \\ &- \alpha_1 \sum_{i\in n_{13}} (v_i + H_0(v_i)) - a \sum_{i\in n_{13}} \log\left(1+\frac{D_i}{b}H_0(v_i)\right) + \sum_{i\in n_{123}} \log\alpha_2 \\ &- \alpha_2 \sum_{i\in n_{123}} (v_i - t_i) - \alpha_1 \sum_{i\in n_{123}} (t_i + H_0(t_i)) + \sum_{i\in n_{123}} \log\left(\frac{\mu_0(t_i)\left(1+\dfrac{D_i a}{b+D_i H_0(t_i)}\right)}{\left(1+\dfrac{D_i}{b}H_0(t_i)\right)^a}\right).\end{aligned} \tag{A.2}$$

And formula (3) is obtained by straightforward calculations.

For the model with excess relative risk and proportional vulnerability,

$$\begin{gathered}\log L=-\alpha_1\sum_{i\in n_1}(s_i+D_iH_0(s_i))-\sum_{i\in n_1}\log\left(1+\frac{D_iH_0(s_i)}{b}\right)^a-\alpha_2\sum_{i\in n_{12}}(s_i-t_i)\\ -\alpha_1\sum_{i\in n_{12}}(t_i+D_iH_0(t_i))+\sum_{i\in n_{13}}\log\alpha_1\sum_{i\in n_{12}}\log\left(\frac{D_i\mu_0(t_i)\left(1+\dfrac{a}{b+D_iH_0(t_i)}\right)}{\left(1+\dfrac{DH_0(t_i)}{b}\right)^a}\right)\\ -\alpha_1\sum_{i\in n_{13}}(v_i+D_iH_0(v_i))-\sum_{i\in n_{13}}\log\left(1+\frac{D_iH_0(v_i)}{b}\right)^a+\sum_{i\in n_{13}}\log\alpha_2\\ -\alpha_2\sum_{i\in n_{123}}(v_i-t_i)-\alpha_1\sum_{i\in n_{123}}(t_i+D_iH_0(t_i))+\sum_{i\in n_{123}}\log\left(\frac{D_i\mu_0(t_i)\left(1+\dfrac{a}{b+D_iH_0(t_i)}\right)}{\left(1+\dfrac{D_iH_0(t_i)}{b}\right)^a}\right).\end{gathered}\tag{A.3}$$

This expression immediately leads to formula (6).
In the case of incomplete information,

$$\begin{gathered}\mathrm{P}_2(t)=\mu_0e^{-\alpha_2t}\int_0^t e^{-(\alpha_1+\mu_0-\alpha_2)s}\left(1+\frac{D\mu_0s}{b}\right)^{-a}\left(1+\frac{Da}{b+D\mu_0s}\right)ds\\ =\mu_0e^{-\alpha_2t}b^a\left(\int_0^t e^{-(\alpha_1+\mu_0-\alpha_2)s}\left(b+D\mu_0s\right)^{-a}ds\right.\\ \left.+Da\int_0^t e^{-(\alpha_1+\mu_0-\alpha_2)s}\left(b+D\mu_0s\right)^{-(a+1)}ds\right)\\ =e^{\frac{(\alpha_1+\mu_0-\alpha_2)b}{D\mu_0}-\alpha_2t}b^a\left(\frac{1}{d}\int_b^{b+D\mu_0t}e^{-(\alpha_1+\mu_0-\alpha_2)u}u^{-a}du-\int_b^{b+D\mu_0t}e^{-(\alpha_1+\mu_0-\alpha_2)u}du^{-a}\right)\\ =e^{\frac{(\alpha_1+\mu_0-\alpha_2)b}{D\mu_0}-\alpha_2t}b^a\left(b^{-a}e^{-(\alpha_1+\mu_0-\alpha_2)b}-(b+D\mu_0t)^{-a}e^{-(\alpha_1+\mu_0-\alpha_2)(b+D\mu_0t)}\right)\\ \left(\frac{1}{D}+\alpha_2-\alpha_1-\mu_0\right)\int_b^{b+D\mu_0t}e^{-(\alpha_1+\mu_0-\alpha_2)u}u^{-a}du\Bigg).\end{gathered}\tag{A.4}$$

For obtaining $p_{2\to3}(t)$, we observe that

$$\begin{gathered}\mathrm{P}_1(t|\xi)=\exp\left(-\alpha_1t-(1+D\xi)\mu_0t\right),\\ \mathrm{P}_2(t|\xi)=\mu_0(1+D\xi)\exp\left(-\alpha_2t\right)\int_0^t\exp\left(s\left(\alpha_2-\alpha_1-(1+D\xi)\mu_0\right)\right)ds\\ =\frac{\mu_0(1+D\xi)\exp\left(-\alpha_2t\right)}{\alpha_2-\alpha_1-\mu_0(1+D\xi)}\left(\exp\left(\left(\alpha_2-\alpha_1-(1+D\xi)\mu_0\right)t\right)-1\right).\end{gathered}$$

Hence, it appears that

$$p_{2\to3}(t|\xi)=\frac{\alpha_2\mu_0^2(1+d\xi)^2e^{-\alpha_2 t}}{\alpha_2-\alpha_1-\mu_0(1+D\xi)}\int\limits_0^t e^{(\alpha_2-\alpha_1-\mu_0(1+D\xi))s}\left(e^{(\alpha_2-\alpha_1-(1+D\xi)\mu_0)(t-s)}-1\right)ds$$
$$=\frac{\alpha_2\mu_0^2(1+D\xi)^2e^{-\alpha_2 t}}{\alpha_2-\alpha_1-\mu_0(1+D\xi)}\left(e^{(\alpha_2-\alpha_1-(1+D\xi)\mu_0)t}t-\int\limits_0^t e^{(\alpha_2-\alpha_1-\mu_0(1+D\xi))s}ds\right)$$
$$=\frac{\alpha_2\mu_0^2(1+D\xi)^2e^{-\alpha_2 t}}{\alpha_2-\alpha_1-\mu_0(1+D\xi)}\left(e^{(\alpha_2-\alpha_1-(1+D\xi)\mu_0)t}t-\frac{e^{(\alpha_2-\alpha_1-(1+D\xi)\mu_0)t}-1}{\alpha_2-\alpha_1-\mu_0(1+D\xi)}\right).$$

Consequently, to calculate $p_{2\to3}(t)$, it is necessary to find

$$I_1=\mathrm{E}\frac{(1+D\xi)^2e^{-D\mu_0 t\xi}}{\alpha_2-\alpha_1-\mu_0(1+D\xi)},$$

$$I_2=\mathrm{E}\frac{(1+D\xi)^2e^{-D\mu_0 t\xi}}{(\alpha_2-\alpha_1-\mu_0(1+D\xi))^2},$$

$$I_3=\mathrm{E}\frac{(1+D\xi)^2}{(\alpha_2-\alpha_1-\mu_0(1+D\xi))^2}.$$

Calculating the expected value gives

$$I_1=\frac{b^a}{D^a\Gamma(a)}\int\limits_0^\infty\frac{(1+u)^2u^{a-1}e^{-\frac{(D\mu_0t+b)}{D}u}}{\alpha_2-\alpha_1-\mu_0-\mu_0u}du=\frac{b^a}{D^a\Gamma(a)\mu_0}\left(\int\limits_0^\infty\frac{u^{a-1}e^{-\frac{(D\mu_0t+b)}{D}u}}{\frac{\alpha_2-\alpha_1}{\mu_0}-1-u}du\right.$$
$$\left.+2\int\limits_0^\infty\frac{u^ae^{-\frac{(D\mu_0t+b)}{d}u}}{\frac{\alpha_2-\alpha_1}{\mu_0}-1-u}du+\int\limits_0^\infty\frac{u^{a+1}e^{-\frac{(D\mu_0t+b)}{D}u}}{\frac{\alpha_2-\alpha_1}{\mu_0}-1-u}du\right).$$

Using formula (3.383.10) from [1], we get

$$\begin{aligned}I_1=-\frac{b^a}{D^a\Gamma(a)\mu_0}\Bigg(&\left(1+\frac{\alpha_1-\alpha_2}{\mu_0}\right)^{a-1}e^{\left(1+\frac{\alpha_1-\alpha_2}{\mu_0}\right)\left(\frac{D\mu_0t+b}{D}\right)}\Gamma(a)\\&\times\Gamma\left(1-a,\left(1+\frac{\alpha_1-\alpha_2}{\mu_0}\right)\left(\frac{D\mu_0t+b}{D}\right)\right)\\&+2\left(1+\frac{\alpha_1-\alpha_2}{\mu_0}\right)^{a}e^{\left(1+\frac{\alpha_1-\alpha_2}{\mu_0}\right)\left(\frac{D\mu_0t+b}{D}\right)}\Gamma(a+1)\\&\times\Gamma\left(-a,\left(1+\frac{\alpha_1-\alpha_2}{\mu_0}\right)\left(\frac{D\mu_0t+b}{D}\right)\right)\\&+\left(1+\frac{\alpha_1-\alpha_2}{\mu_0}\right)^{a+1}\times e^{\left(1+\frac{\alpha_1-\alpha_2}{\mu_0}\right)\left(\frac{D\mu_0t+b}{D}\right)}\Gamma(a+2)\\&\times\Gamma\left(-a-1,\left(1+\frac{\alpha_1-\alpha_2}{\mu_0}\right)\left(\frac{D\mu_0t+b}{D}\right)\right)\Bigg),\end{aligned}\tag{A.5}$$

where $\Gamma(x,y)$ is the additional truncated gamma-function.

Analogously, by formula (3.383.8) from [1],

$$
\begin{aligned}
I_2 = \frac{b^a}{D^a\Gamma(a)\mu_0^2}\Bigg(&\left(1+\frac{\alpha_1-\alpha_2}{\mu_0}\right)^{\frac{a-3}{2}}\left(\frac{D\mu_0 t+b}{D}\right)^{\frac{1-a}{2}} e^{\frac{1}{2}\left(1+\frac{\alpha_1-\alpha_2}{\mu_0}\right)\left(\frac{D\mu_0 t+b}{D}\right)}\\
&\times\Gamma(a)\Psi_{\frac{-1-a}{2},\frac{a-2}{2}}\left(\left(1+\frac{\alpha_1-\alpha_2}{\mu_0}\right)\left(\frac{D\mu_0 t+b}{D}\right)\right)\\
&+2\left(1+\frac{\alpha_1-\alpha_2}{\mu_0}\right)^{\frac{a-2}{2}}\left(\frac{D\mu_0 t+b}{D}\right)^{\frac{-a}{2}} e^{\frac{1}{2}\left(1+\frac{\alpha_1-\alpha_2}{\mu_0}\right)\left(\frac{D\mu_0 t+b}{D}\right)}\\
&\times\Gamma(a+1)\Psi_{\frac{-2-a}{2},\frac{a-1}{2}}\left(\left(1+\frac{\alpha_1-\alpha_2}{\mu_0}\right)\left(\frac{D\mu_0 t+b}{D}\right)\right)\\
&+\left(1+\frac{\alpha_1-\alpha_2}{\mu_0}\right)^{\frac{a-1}{2}}\left(\frac{D\mu_0 t+b}{D}\right)^{\frac{-a-1}{2}} e^{\frac{1}{2}\left(1+\frac{\alpha_1-\alpha_2}{\mu_0}\right)\left(\frac{D\mu_0 t+b}{D}\right)}\\
&\times\Gamma(a+2)\Psi_{\frac{-3-a}{2},\frac{a}{2}}\left(\left(1+\frac{\alpha_1-\alpha_2}{\mu_0}\right)\left(\frac{D\mu_0 t+b}{D}\right)\right)\Bigg)
\end{aligned}
\tag{A.6}
$$

and

$$
\begin{aligned}
I_3 = \frac{b^a}{D^a\Gamma(a)\mu_0^2}\Bigg(&\left(1+\frac{\alpha_1-\alpha_2}{\mu_0}\right)^{\frac{a-3}{2}}\left(\frac{b}{D}\right)^{\frac{1-a}{2}} e^{\frac{b}{2D}\left(1+\frac{\alpha_1-\alpha_2}{\mu_0}\right)}\Gamma(a)\\
&\times\Psi_{\frac{-1-a}{2},\frac{a-2}{2}}\left(\frac{b}{D}\left(1+\frac{\alpha_1-\alpha_2}{\mu_0}\right)\right)\\
&+2\left(1+\frac{\alpha_1-\alpha_2}{\mu_0}\right)^{\frac{a-2}{2}}\left(\frac{b}{D}\right)^{\frac{-a}{2}} e^{\frac{b}{2D}\left(1+\frac{\alpha_1-\alpha_2}{\mu_0}\right)}\Gamma(a+1)\\
&\times\Psi_{\frac{-2-a}{2},\frac{a-1}{2}}\left(\frac{b}{D}\left(1+\frac{\alpha_1-\alpha_2}{\mu_0}\right)\right)\\
&+\left(1+\frac{\alpha_1-\alpha_2}{\mu_0}\right)^{\frac{a-1}{2}}\left(\frac{b}{D}\right)^{\frac{-a-1}{2}} e^{\frac{b}{2D}\left(1+\frac{\alpha_1-\alpha_2}{\mu_0}\right)}\Gamma(a+2)\Psi_{\frac{-3-a}{2},\frac{a}{2}}\left(\frac{b}{D}\left(1+\frac{\alpha_1-\alpha_2}{\mu_0}\right)\right)\Bigg),
\end{aligned}
\tag{A.7}
$$

where $\Psi_{\lambda,\mu}(z)$ denotes the Whittaker function.

REFERENCES

1. Gradshtein, I.S. and Ryzhik, I.M., *Tablitsy integralov, summ, ryadov i proizvedenii* (Tables of Integrals, Sums, Series, and Products), Moscow: Fizmatlit, 1963.
2. Ivanov, V.K., Tsyb, A.F., Gorsky, A.I, et al., Cancer Morbidity and Mortality among Chernobyl Emergency Workers: Estimation of Radiation Risks, *Radiats. Biol. Radioekol.*, 2006, vol. 46, no. 2, pp. 159–166.
3. *International Statistical Classification of Diseases and Related Health Problems*, Geneva: IHO, 1995.
4. Miller, B.M. and Pankov, A.R., *Teoriya sluchainykh protsessov* (Theory of Random Processes), Moscow: Fizmatlit, 2002.
5. Mikhalskii, A.I., *Metody analiza geterogennykh struktur i populyatsii* (Analysis Methods for Heterogeneous Structures and Populations), Moscow: Inst. Probl. Upravlen., 2002.
6. Mikhalskii, A.I. et al., Accounting of Heterogeneity in the Estimation of Radiation Risks, *Autom. Remote Control*, 2008, vol. 69, no. 6, pp. 1045–1050.
7. Mikhalskii, A.I., Petrovskii, A.M., and Yashin, A.I., *Teoriya otsenivaniya neodnorodnykh populyatsii* (Theory of Estimation of Heterogeneous Populations), Moscow: Nauka, 1989.

8. *Annals of the ICRP. ICRP Publication 103. The 2007 Recommendations of the International Commission on Radiological Protection*, 2007, vol. 37, nos. 2–4. Translated under the title *Publikatsiya 103 Mezhdunarodnoi komissii po radiatsionnoi zashchite*, Moscow: Alana, 2009.

9. Brauer, F., Epidemic Models with Heterogeneous Mixing and Treatment, *Bull. Mathem. Biol.*, 2008, vol. 70, pp. 1869–1885.

10. *Statistical Methods in Cancer Research*, vol. 2: *The Design and Analysis of Cohort Studies*, Breslow, N.E. and Day, N.E., Eds., Lyon: IARC, 1987.

11. Cook, R.J. and Lawless, J.F., Statistical Issues in Modeling Chrohic Disease in Cohort Studies, *Stat. Biosci.*, 2014, no. 6, pp. 127–221.

12. Finkelstein, M. and Cha, J.H., *Stochastic Modeling for Reliability*, Springer Series in Reliability Engineering, London: Springer-Verlag, 2013.

13. Ivanov, V.K., Maksioutov, M.A., Chekin, S.Y., et al., The Risk of Radiation-Induced Cerebrovascular Disease in Chernobyl Emergency Workers, *Health Phys.*, 2006, vol. 90, no. 3, pp. 199–207.

14. Ivanov, V.K., Tsyb, A.F., Ivanov, S.I., et al., *Medical Radiological Consequences of the Chernobyl Catastrophe in Russia: Estimation of Radiation Risks*, St. Petersburg: Nauka, 2004.

15. Madan, D., Bakshi, G., and Panayotov, G., Heterogeneity in Beliefs and Volatility Tail Behavior, *J. Finan. Quantit. Anal.*, 2015, vol. 50, no. 6, pp. 1389–1414.

16. Meira-Machado, L., de Una-Alvarez, J., and Datta, S., Nonparametric Estimation of Conditional Transition Probabilities in a Non-Markov Illness-Death Model, *Comput. Stat.*, 2015, vol. 30, no. 2, pp. 377–397.

17. Norberg, R., *Life Insurance Mathematics. Encyclopedia of Actuarial Science*, New York: Wiley, 2004.

18. Vaupel, J.W., Manton, K.G., and Stallard, E., The Impact of Heterogeneity in Individual Frailty on the Dynamics of Mortality, *Demography*, 1979, vol. 16, pp. 439–454.

19. Vaupel, J.W. and Yashin, A.I., Heterogeneity's Ruses: Some Surprising Effects of Selection on Population Dynamics, *Am. Stat.*, 1985, vol. 39, pp. 176–182.

20. Yashin, A.I., Akushevich, I., Arbeev, K., et al. Studying Health Histories of Cancer: A New Model Connecting Cancer Incidence and Survival, *Math. Biosci.*, 2009, vol. 218, no. 2, pp. 88–97.