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COMPARISON OF TIME RISKS BASED ON A MULTINOMIAL LOGISTIC RESPONSE MODEL IN LONGITUDINAL STUDIES

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Summary

The multinomial logistic response model has been used in the analysis of data from longitudinal studies of RERF's mortality cohort population. The model was restricted to linear and quadratic dose-responses for practical as well as biological reasons. The advantages and disadvantages of the multinomial logistic model are pointed out. Numerical comparison is made of the maximum likelihood (ML) estimates of parameters obtained by binomial and multinomial logistic procedures. The dose-response difference between two independent "same age" groups is evaluated from the ML estimates of parameters under a linear logistic response model. A significant dose-response difference between two independent "same age" groups in the years 1950–1959 and 1960–1969 is noted only for the 15–24 age group for all cancers other than leukemia.

1. Introduction

Let a $c\times k\times s$ contingency table be denoted for $t=1, 2, \cdots, s$ by

(1.1)

Stratum (Age)	Category (Dose) $1 \cdots j \cdots k$	
1	d_{ij1}^t	Specific causes of death at t-th time period
$\vdots$	$\vdots$	
i	d_{ijr}^t	
$\vdots$	$n_{ij}^{t-1}-\sum_{l=1}^{r} d_{ijl}^t$	Survivors at t-th time period
c	n_{ij}^{t-1}	Cases alive at $(t-1)$-th time period

We shall assume that the observations, $d_{ij1}^t, \cdots, d_{ijr}^t$, are independently and multinomially distributed with parameters n_{ij}^{t-1} and $P_{ij1}^t, \cdots, P_{ijr}^t$ $\left(0<\sum_{l=1}^{r} P_{ijl}^t<1\right)$ (see Appendix 1). When $r=1$, we have the ordinary binomial distribution. Let us suppose that the parameters $P_{ij1}^t, \cdots, P_{ijr}^t$ have the multinomial logistic response (Cox [6], Bock [4], Kudo and Ito [14]).

We have applied this approach to RERF's cohort mortality experience from 1950 to 1969 (Jablon and Kato [12]). The reasons for using this multinomial logistic response approach in the analysis of these data are several in number; they include 1) evaluation of the dose-response after eliminating the effects of nuisance parameters (Fleiss [8]); 2) assessment of the dose-response difference between two time periods by classifying the cohort data into the same time intervals, say age groups; 3) examination of competing risks in a given population (Chiang [5], Havid [11]), and 4) evaluation of the characteristics, convergence, and computability of maximum likelihood estimates of parameters based on the logistic response model (see Berkson [3], Cox [7], Ashton [2]).

The purposes of this paper are, first, to apply a multinomial response procedure to longitudinal data arising in epidemiologic studies, especially to the mortality risks in a complete cohort, and second, to evaluate the dose-response difference between two independent age groups from the maximum likelihood estimates of parameters obtained by a multinomial response procedure.

Recently Koch et al. [13], Stanish et al. [16] and Woolson et al. [17] have proposed methods of analyzing longitudinal studies with incomplete or missing data. Their approaches differ from the one set out here.

2. Multinomial logistic response model

The two multinomial logistic response models applied here are defined as follows:

$$\begin{aligned}&\text{Model I:}\quad \log\left[P_{ijl}^t\Big/\left(1-\sum_{l=1}^{r} P_{ijl}^t\right)\right]=\lambda_{ijl}^t=\alpha_{il}^t+\beta_{il}^t D_{ij}\\ &\text{Model II:}\quad \log\left[P_{ijl}^t\Big/\left(1-\sum_{l=1}^{r} P_{ijl}^t\right)\right]=\lambda_{ijl}^t=\alpha_{il}^t+\beta_{il}^t D_{ij}+\gamma_{il}^t D_{ij}^2\end{aligned} \tag{2.1}$$

where α_{il}^t denotes the age effect of the t-th time period for specific causes of death of the l-th kind and β_{il}^t and γ_{il}^t are the radiation effects, that is, the increase in the probability of death with increase in exposure (D_{ij}).

3. Estimation of parameters

The joint multinomial logistic response distribution in (2.1) is given by

$$(3.1)\qquad L=\prod_{i=1}^{c}\prod_{j=1}^{k}\prod_{t=1}^{s}\text{const.}\left[1+\sum_{l=1}^{r}\exp(\lambda_{ijl}^{t})\right]^{-n_{ij}^{t-1}}\prod_{l=1}^{r}\left[\exp(\lambda_{ijl}^{t})\right]^{d_{ijl}^{t}}.$$

We assume the deaths to be mutually exclusive events among the s time periods. The maximum likelihood (ML) estimates of $(\alpha_{i1}^{t}, \cdots, \alpha_{ir}^{t}, \beta_{i1}^{t}, \cdots, \beta_{ir}^{t}$ or $\gamma_{i1}^{t}, \cdots, \gamma_{ir}^{t})$ can be easily obtained by the Newton-Raphson iteration procedure. The ML estimates of $(\alpha_{i1}^{t}, \cdots, \alpha_{ir}^{t}, \beta_{i1}^{t}, \cdots, \beta_{ir}^{t})$ for the linear response model, for instance, are obtained by the $(\nu+1)$-th iteration, i.e.,

$$\begin{aligned}&[\alpha_{i1}^{t}(\nu+1), \cdots, \alpha_{ir}^{t}(\nu+1), \beta_{i1}^{t}(\nu+1), \cdots, \beta_{ir}^{t}(\nu+1)]\\&=[\alpha_{i1}^{t}(\nu), \cdots, \alpha_{ir}^{t}(\nu), \beta_{i1}^{t}(\nu), \cdots, \beta_{ir}^{t}(\nu)]\\&\quad-\begin{pmatrix}\dfrac{\partial^2\log L}{\partial\alpha_{i1}^{t}\partial\alpha_{i'1}^{t'}}\Big|_{(\nu)} & \cdots & \dfrac{\partial^2\log L}{\partial\alpha_{i1}^{t}\partial\alpha_{i'r}^{t'}}\Big|_{(\nu)} & \dfrac{\partial^2\log L}{\partial\alpha_{i1}^{t}\partial\beta_{i'1}^{t'}}\Big|_{(\nu)} & \cdots & \dfrac{\partial^2\log L}{\partial\alpha_{i1}^{t}\partial\beta_{i'r}^{t'}}\Big|_{(\nu)}\\ \ddots & & \vdots & \vdots & & \vdots\\ & & \dfrac{\partial^2\log L}{\partial\alpha_{ir}^{t}\partial\alpha_{i'r}^{t'}}\Big|_{(\nu)} & \dfrac{\partial^2\log L}{\partial\alpha_{ir}^{t}\partial\beta_{i'1}^{t'}}\Big|_{(\nu)} & \cdots & \dfrac{\partial^2\log L}{\partial\alpha_{ir}^{t}\partial\beta_{i'r}^{t'}}\Big|_{(\nu)}\\ & & & \dfrac{\partial^2\log L}{\partial\beta_{i1}^{t}\partial\beta_{i'1}^{t'}}\Big|_{(\nu)} & \cdots & \dfrac{\partial^2\log L}{\partial\beta_{i1}^{t}\partial\beta_{i'r}^{t'}}\Big|_{(\nu)}\\ & & & \ddots & & \vdots\\ & & & & & \dfrac{\partial^2\log L}{\partial\beta_{ir}^{t}\partial\beta_{i'r}^{t'}}\Big|_{(\nu)}\end{pmatrix}^{-1}\\&\quad\times\begin{pmatrix}\dfrac{\partial\log L}{\partial\alpha_{i1}^{t}}\Big|_{(\nu)}\\ \vdots\\ \dfrac{\partial\log L}{\partial\alpha_{ir}^{t}}\Big|_{(\nu)}\\ \dfrac{\partial\log L}{\partial\beta_{i1}^{t}}\Big|_{(\nu)}\\ \vdots\\ \dfrac{\partial\log L}{\partial\beta_{ir}^{t}}\Big|_{(\nu)}\end{pmatrix}\end{aligned}$$

where $\dfrac{\partial^2\log L}{\partial\alpha_{il}^{t}\partial\alpha_{i'l}^{t'}}=0$ when $t\neq t'$ or $i\neq i'$ for $l=1, 2, \cdots, r$.

The inverse of this matrix of second derivatives is a matrix whose elements are the asymptotic variances and covariances of the ML

estimates. These latter estimates in the multinomial logistic model are asymptotically equivalent to those of the binomial logistic model when the sample size is large. The multinomial logistic model is applicable here because the ultimate categories of the underlying quantitative response are the result of a nesting of several mutually exclusive classifications of the same subjects, n_{ij}^{t-1}, in the independent (i, j, t)-th cell.

Ashford [1] has examined the use of a series of mutually exclusive intervals, i.e., a quantitative response scale, to approximate the normal distribution and has shown that the parameters associated with the underlying probability may be estimated from the semi-quantal response. He also noted that this statement holds good only if it is known what parameters there are to be estimated and that the method of analysis depends on the validity of the relatively large number of assumptions which must necessarily be made. Gurland et al. [9], Cox [6] and Haberman [10] discuss various aspects of this issue.

Death is not a repetitive event and it is usually attributed to a single cause; however, various risks competing for the life of an individual must be considered in cause-specific studies. To do so, Chiang [5] introduced the use of risks based upon a multinomial approach with the conditional distribution of the numbers of deaths and the number of survivors, i.e., d_{ijl}^t and $n_{ij}^{t-1}-\sum_{l=1}^{r} d_{ijl}^t$, given n_{ij}^{t-1} individuals alive at time $t-1$, which is the probability distribution of (3.1). The advantages of the multinomial logistic response model were pointed out as the main reasons to use this approach in the Introduction. There are disadvantages also; they include 1) that it is somewhat more troublesome to determine different dose-responses by cause of death, 2) that it is inconvenient in that a large information matrix is required, and 3) that much computing time is required for the numerical convergence of the ML estimates. The numerical procedure continues until $\Delta\alpha_{i1}^t, \cdots, \Delta\alpha_{ir}^t$, $\Delta\beta_{i1}^t, \cdots, \Delta\beta_{ir}^t$ or $\Delta\gamma_{i1}^t, \cdots, \Delta\gamma_{ir}^t$ in (3.1) each become less than 10^{-5}.

We have computed the approximate values of the ML estimates of parameters in the binomial logistic model, and then in the multinomial logistic model. With regard to the solution of the ML equations of the binomial model, a computational procedure based on a fixed l-level and t-period was employed. The first values estimated by minimizing the sum of the weighted squares

$$\sum_{i=1}^{c}\sum_{j=1}^{k}\{n_{ij}^{t-1}/\hat{P}_{ijl}^t(1-\hat{P}_{ijl}^t)\}\{\log[P_{ijl}^t/(1-P_{ijl}^t)]-\log[\hat{P}_{ijl}^t/(1-\hat{P}_{ijl}^t)]\}^2$$

for each of the (l, t)-th classes were used as the initial values of the iteration for computing the approximate values of the ML estimates.

Table 1 ML estimates of parameters between binomial and multinomial models, 1950-1969

Age at 1950		Leukemia		All cancers except leukemia		Other causes	
		$\hat{\alpha}_i^*$	$\hat{\beta}_i^* \times 10^{-3}$	$\hat{\alpha}_i^*$	$\hat{\beta}_i^* \times 10^{-3}$	$\hat{\alpha}_i^*$	$\hat{\beta}_i^* \times 10^{-4}$
				Binomial Logistic Model			
5-14	Est.	-7.16	10.50***	-8.00	10.34***	-4.01	8.89N.S.
	SE	.29	1.20	.44	1.84	.06	8.96
15-24	Est.	-7.36	7.52***	-5.67	1.65 N.S.	-3.15	-2.34N.S.
	SE	.31	1.40	.14	1.27	.04	4.88
25-34	Est.	-7.11	8.34***	-4.47	2.63**	-2.85	-5.67N.S.
	SE	.35	1.50	.10	.83	.05	5.97
35-44	Est.	-8.04	11.87***	-3.31	.37N.S.	-2.40	4.30N.S.
	SE	.50	1.80	.05	.69	.04	4.63
45-54	Est.	-6.29	5.59***	-2.59	.68N.S.	-1.39	3.24N.S.
	SE	.21	1.41	.04	.48	.02	3.23
55-64	Est.	-6.80	9.16***	-2.12	.67N.S.	-.21	4.28N.S.
	SE	.33	1.60	.04	.55	.02	3.65
65+	Est.	-7.44	7.88*	-2.42	.98N.S.	1.43	-1.49N.S.
	SE	.60	3.64	.06	.88	.04	6.79
Homogenity test: χ^2 value with 7 d.f.			233.10***		48.39***		5.41N.S.
($H_0 : \beta_1^* = \beta_2^* = \ldots = \beta_7^* = 0$)							
χ^2 value of goodness of fit under the model = 85.56 with 84 d.f.N.S.							
				Multinomial Logistic Model			
5-14	Est.	-7.14	10.56***	-7.98	10.45***	-4.01	9.98N.S.
	SE	.29	1.20	.44	1.84	.06	8.97
15-24	Est.	-7.31	7.52***	-5.62	1.66N.S.	-3.14	-2.04N.S.
	SE	.31	1.40	.14	1.27	.04	4.88
25-34	Est.	-7.04	8.36**	-4.41	2.65**	-2.84	-4.80N.S.
	SE	.35	1.50	.10	.83	.05	5.98
35-44	Est.	-7.91	11.94***	-3.22	.47N.S.	-2.36	5.05N.S.
	SE	.50	1.80	.05	.70	.04	4.65
45-54	Est.	-5.98	5.75***	-2.34	.81N.S.	-1.30	4.42N.S.
	SE	.22	1.41	.04	.49	.02	3.28
55-64	Est.	-5.99	9.69***	-1.42	1.18*	.01	8.17*
	SE	.33	1.61	.04	.59	.03	3.98
65+	Est.	-5.24	8.69*	-.30	1.72N.S.	1.99	8.00N.S.
	SE	.60	3.74	.07	1.24	.05	9.66
Homogenity test: χ^2 value with 7 d.f.			239.10***		53.26***		9.95N.S.
($H_0 : \beta_1^* = \beta_2^* = \ldots = \beta_7^* = 0$)							
χ^2 value of goodness of fit under the model = 82.49 with 84 d.f.N.S.							

Significant levels: N.S. $P>.05$; *$P<.05$; **$P<.01$; ***$P<.001$.
Data in 1950-1969 are shown in Appendix 2.

Table 2 ML estimates of parameters for the multinomial quadratic response model, 1950-1969

Age at 1950		Leukemia			All cancers except leuk.			Other causes		
		$\hat{\alpha}_i^*$	$\hat{\beta}_i^* \times 10^{-2}$	$\hat{\gamma}_i^* \times 10^{-5}$	$\hat{\alpha}_i^*$	$\hat{\beta}_i^* \times 10^{-3}$	$\hat{\gamma}_i^* \times 10^{-5}$	$\hat{\alpha}_i^*$	$\hat{\beta}_i^* \times 10^{-3}$	$\hat{\gamma}_i^* \times 10^{-6}$
5-14	Est.	-7.39	2.35**	-3.56 N.S.	-7.91	5.33 N.S.	1.42 N.S.	-4.03	2.87 N.S.	-5.91 N.S.
	SE	.35	.73	1.96	.48	16.65	4.62	.07	3.12	9.50
15-24	Est.	-7.56	1.97**	-3.38 N.S.	-5.58	-2.40 N.S.	1.21 N.S.	-3.13	-1.53 N.S.	4.10 N.S.
	SE	.37	.73	1.98	.15	6.15	1.78	.04	1.86	5.55
25-34	Est.	-7.14	1.40 N.S.	1.56 N.S.	-4.48	8.10*	-1.63 N.S.	-2.84	-.00 N.S.	-1.51 N.S.
	SE	.40	.95	2.59	.11	3.45	1.01	.05	2.10	6.37
35-44	Est.	-8.18	2.31*	-3.00 N.S.	-3.19	-2.80 N.S.	1.01 N.S.	-2.36	.45 N.S.	.16 N.S.
	SE	.63	1.17	3.07	.06	2.69	.80	.04	1.67	5.03
45-54	Est.	-5.85	-.61 N.S.	3.38 N.S.	-2.35	1.43 N.S.	-.19 N.S.	-1.29	.10 N.S.	1.10 N.S.
	SE	.23	1.06	2.98	.04	1.68	.51	.03	1.12	3.40
55-64	Est.	-6.25	2.29**	-3.73 N.S.	-1.43	2.37 N.S.	-.39 N.S.	-4.56	2.06 N.S.	-4.11 N.S.
	SE	.40	.84	2.29	.04	1.89	.58	.03	1.22	3.81
65+	Est.	-4.84	-6.93 N.S.	22.11 N.S.	-.32	4.08 N.S.	-.78 N.S.	1.99	1.39 N.S.	-2.03 N.S.
	SE	.63	10.48	29.84	.08	3.65	1.15	.05	2.71	8.63
Homogenity test; χ^2 value with 7 d.f.			31.89***	12.04 N.S.		10.39 N.S.	5.82 N.S.		4.71 N.S.	2.32 N.S.

$(H_0 : \beta_1^* = \beta_2^* = \ldots = \beta_7^* = 0)$ or $(H_0 : \gamma_1^* = \gamma_2^* = \ldots = \gamma_7^* = 0)$

χ^2 value of goodness of fit under the model = 63.23 with 63 d.f. N.S.

Significant levels are the same as those described in Table 1.

The desired degree of accuracy (stable fifth decimal) was obtained after the 3rd to the 5th iteration. The ML solution of the multinomial model was obtained using the ML estimates of the binomial parameters as the initial values. The convergence had the desired degree of accuracy (less than 10^{-5}) after the 4th or 5th iteration. Numerically, the sum of the estimated probabilities, $\sum_{l=1}^{r+1}\hat{P}_{ijl}$, in the binomial model satisfies approximately the probability 1 for each of the (i, j) cells even when the sample size is not large where $\sum_{l=1}^{r+1}\hat{P}_{ijl}$ denotes the estimated probability of survivors when $l=r+1$ (Appendix 2). The expected values obtained by the binomial model are almost the same as those of the multinomial logistic model. However, the ML estimates of the parameters associated with the two response models differ more, particularly as the number of deaths increases as is shown in Table 1. For this reason, the ML estimates were computed under a quadratic response model for the same cohort data in 1950–1969, but Table 2 shows the results of the multinomial logistic response model only. The equality of marginal totals of observed and estimated frequencies in the i-th rows is supported in the binomial logistic model or multinomial logistic model, but not guaranteed in the j-th column.

4. Approximate relative risk

Let P_{ijl}^{t} be the mortality rate from specific causes $(l=1, \cdots, t)$ among atomic bomb survivors with the deaths classified by age $(i=1, \cdots, c)$, dose $(j=1, \cdots, k)$ and time period $(t=1, \cdots, s)$. The mortality rates among the exposed survivors with these independent characteristics are defined by $P_{ijl}^{t}=\exp(\lambda_{ijl}^{t})\Big/\Big[1+\sum_{l=1}^{r}\exp(\lambda_{ijl}^{t})\Big]$ where $\lambda_{ijl}^{t}=\alpha_{il}^{t}+\beta_{il}^{t}D_{ij}$ or $\lambda_{ijl}^{t}=\alpha_{il}^{t}+\beta_{il}^{t}D_{ij}+\gamma_{il}^{t}D_{ij}^{2}$ in the simple linear or quadratic form, respectively, for $j=2, \cdots, k$. Similarly, the mortality rates among the control survivors are given by $P_{i1l}^{t}=\exp(\lambda_{i1l}^{t})\Big/\Big[1+\sum_{l=1}^{r}\exp(\lambda_{i1l}^{t})\Big]$ where $\lambda_{i1l}^{t}=\alpha_{il}^{t}$.

We shall consider now the odds that the exposed survivors will die of a specific cause of death. These odds are expressed by

$$\Omega_1=P_{ijl}^{t}\Big/\Big(1-\sum_{l=1}^{r}P_{ijl}^{t}\Big)=\exp(\alpha_{il}^{t}+\beta_{il}^{t}D_{ij}), \quad \text{or} \quad =\exp(\alpha_{il}^{t}+\beta_{il}^{t}D_{ij}+\gamma_{il}^{t}D_{ij}^{2}) \tag{4.1}$$

in the simple linear and quadratic forms, respectively. The odds that an individual in the control group will die of a specific cause of death are given by

$$\Omega_2=P^t_{i1l}\Big/\Big(1-\sum_{l=1}^{r}P^t_{i1l}\Big)=\exp(\alpha^t_{il})\,. \tag{4.2}$$

Thus the ratio defined by (4.1) and (4.2) becomes

$$\begin{aligned}\Omega_1/\Omega_2&=\exp(\beta^t_{il}D_{ij})\,,\\ \text{or}\quad&=\exp(\beta^t_{il}D_{ij}+\gamma^t_{il}D^2_{ij})\end{aligned} \tag{4.3}$$

and is a function of the dose-response alone. The odds ratio (4.3) is well known as an approximate relative risk. Using the asymptotic normality of the maximum likelihood estimates, we can easily calculate the asymptotic $100(1-\alpha)\%$ confidence intervals (Otake [15]).

5. Comparison of approximate relative risk between time periods with the same age group

From (4.3), let $\exp(\beta^1_iD_{ij})$, $\cdots$, $\exp(\beta^s_iD_{ij})$ for a fixed l-level be the respective approximate relative risks estimated for $t=1, 2, \cdots, s$, where D_{ij} denotes the mean dose in (i, j)-th cell. We shall consider the simplest case where $s=2$, i.e.,

$t=1$ $(R.R^1_i)$	$t=2$ $(R.R^2_i)$
$\exp(\hat\beta^1_1D_{1j})$	—
$\exp(\hat\beta^1_2D_{2j})$	$\exp(\hat\beta^2_2D_{2j})$
$\vdots$	$\vdots$
$\exp(\hat\beta^1_cD_{cj})$	$\exp(\hat\beta^2_cD_{cj})$

(5.1)

where the successive age intervals must be of equal length. Thus, comparison of relative risks between two periods involves the dose-response difference after eliminating the effects of the control levels. That is, the dose-response difference from (4.1) is defined by

$$R.R^2_i/R.R^1_i=\exp(\hat\beta^2_i-\hat\beta^1_i)D_{ij}\,. \tag{5.2}$$

The significance of the dose-response difference under the hypothesis H_0: $\exp(\beta^2_i-\beta^1_i)=1$ can be tested by the statistic $(\hat\beta^2_i-\hat\beta^1_i)^2/\mathrm{V}(\hat\beta^2_i-\hat\beta^1_i)$ which is distributed as χ^2 with 1 degree of freedom, where $\mathrm{V}(\hat\beta^2_i-\hat\beta^1_i)$ is the estimate of the asymptotic variance for the dose-response difference between two periods. The inequalities for the asymptotic $100(1-\alpha)\%$ confidence intervals of (5.2) are

$$\begin{aligned}\exp[(\hat\beta^2_i-\hat\beta^1_i)-t_\alpha\sqrt{\mathrm{V}(\hat\beta^2_i-\hat\beta^1_i)}\,]&\leqq\exp(\beta^2_i-\beta^1_i)\\ &\leqq\exp[(\hat\beta^2_i-\hat\beta^1_i)+t_\alpha\sqrt{\mathrm{V}(\hat\beta^2_i-\hat\beta^1_i)}\,]\end{aligned} \tag{5.3}$$

where t_α denotes the $100\alpha\%$ value of a normal deviate.

6. Statistical test of the dose-response relationship

The significance of the difference in dose-responses among the c age groups can be evaluated by χ^2 under the hypothesis H_0: $\beta_1^t=\beta_2^t=\cdots=\beta_c^t=0$ for each of $t=1, 2, \cdots, s$ under a fixed l-level. The test statistic is

$$\chi^2=\hat{\boldsymbol{\beta}}'\Sigma^{-1}\hat{\boldsymbol{\beta}} \tag{6.1}$$

which has approximately a χ^2 distribution with c degrees of freedom, where $\hat{\boldsymbol{\beta}}'=(\hat{\beta}_1^t, \hat{\beta}_2^t, \cdots, \hat{\beta}_c^t)$ are the ML estimates of the parameters and $\overset{(c\times c)}{\Sigma^{-1}}$ a matrix whose diagonal elements are asymptotic variances and whose off-diagonal elements are zero under the model proposed by (3.1) since the stratum of the c age groups are assumed to be mutually independent. If no dose-response relationship among the c age groups is noted in a cross-sectional analysis for all periods combined from 1950 to 1969, we conclude that the data satisfy the hypothesis H_0: $\beta_i^t=\beta_2^t=\cdots=\beta_c^t=0$ for all time periods of $t=1, 2, \cdots, s$ under a fixed l-level. If a significant difference for all periods is noted, it is of interest to test the dose-response relationship for each time period under the hypothesis H_0: $\beta_1^t=\beta_2^t=\cdots=\beta_c^t=0$, and to evaluate the dose-response within each age group. The test statistic is now

$$\chi^2=(\hat{\beta}_i^t)^2/\mathrm{V}(\hat{\beta}_i^t) \tag{6.2}$$

which has a χ^2 distribution with one degree of freedom under the hypothesis H_0: $\beta_i^t=0$, where $\mathrm{V}(\hat{\beta}_i^t)$ denotes the asymptotic variance of the ML estimate $\hat{\beta}_i^t$ of β_i^t.

7. Numerical evaluation

The data from 1950 to 1969 in the RERF Life Span Study Extended [12] are the basis of this numerical evaluation of the multinomial logistic response model; four alternative states are considered, namely, death from leukemia, from cancers other than leukemia, from other causes and still living. The mean doses used here are 0, 3.7, 21.7, 70.3, 141.6 and 349.1 for each of the six dose groups based on all ages combined. Table 3 shows the observed and expected values of the data classified into the above three types of deaths for the period from 1950 to 1959 and the number of survivors in 1950 by age and dose. Table 4 gives the observed and expected numbers of deaths for the period from 1960 to 1969, and the number of survivors in 1960 by age and dose. The data for the two periods combined, namely 1950–1969, are shown in

Table 3 Relationship between observed and expected values by age and dose, 1950-1959

Age at 1950	Deaths		Total	Radiation Dose in rad											
				0		1-9		10-49		50-99		100-199		200+	
				Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.
5-14	Leukemia	(d^1_{1j1})	14	3	2.61	1	1.66	0	1.48	1	.59	3	.77	6	6.89
	All cancers other than leuk.	(d^1_{1j2})	2	1	.40	0	.25	0	.23	0	.09	0	.11	1	.92
	Other causes	(d^1_{1j3})	141	48	57.57	41	35.55	28	27.30	11	7.19	6	5.19	7	8.20
	Subjects	(n^0_{1j})	15286	6675	-	4084	-	2998	-	700	-	423	-	406	-
15-24	Leukemia	(d^1_{2j1})	15	0	2.93	2	2.01	3	1.32	1	.62	3	1.22	6	6.90
	All cancers other than leuk.	(d^1_{2j2})	13	6	5.45	4	3.62	2	2.03	0	.63	0	.66	1	.61
	Other causes	(d^1_{2j3})	392	195	166.21	101	110.14	46	61.55	10	18.63	22	19.09	18	16.38
	Subjects	(n^0_{2j})	17109	7099	-	4716	-	2668	-	835	-	898	-	893	-
25-34	Leukemia	(d^1_{3j1})	10	2	1.82	2	1.13	0	.92	0	.45	1	.69	5	4.99
	All cancers other than leuk.	(d^1_{3j2})	27	9	10.93	9	6.57	4	4.65	2	1.55	1	1.37	2	1.93
	Other causes	(d^1_{3j3})	290	122	126.21	80	75.23	52	51.19	15	15.40	10	11.61	11	10.37
	Subjects	(n^0_{3j})	10424	4425	-	2646	-	1828	-	573	-	459	-	493	-
35-44	Leukemia	(d^1_{4j1})	8	0	.89	0	.51	1	.50	1	.25	1	.44	5	5.41
	All cancers other than leuk.	(d^1_{4j2})	114	55	48.85	30	26.87	17	21.55	2	6.14	2	4.81	8	5.78
	Other causes	(d^1_{4j3})	418	179	177.66	99	97.83	76	78.82	20	22.70	22	18.12	22	22.87
	Subjects	(n^0_{4j})	11571	5122	-	2806	-	2205	-	594	-	430	-	414	-
45-54	Leukemia	(d^1_{5j1})	20	9	6.25	3	3.50	2	3.13	0	1.19	1	1.41	5	4.52
	All cancers other than leuk.	(d^1_{5j2})	328	127	140.75	81	77.17	73	62.52	21	18.19	11	14.55	15	14.82
	Other causes	(d^1_{5j3})	990	452	442.29	229	241.15	197	190.25	48	51.50	35	37.05	29	27.75
	Subjects	(n^0_{5j})	12472	5499	-	3004	-	2392	-	664	-	496	-	417	-
55-64	Leukemia	(d^1_{6j1})	10	2	2.53	0	1.47	2	1.28	2	.58	1	.71	3	3.43
	All cancers other than leuk.	(d^1_{6j2})	371	187	166.35	80	93.44	57	69.22	22	19.95	17	12.85	8	9.19
	Other causes	(d^1_{6j3})	1403	635	623.13	362	350.55	256	261.61	53	76.92	53	51.03	44	39.76
	Subjects	(n^0_{6j})	8012	3578	-	2011	-	1494	-	434	-	283	-	212	-
65+	Leukemia	(d^1_{7j1})	3	1	.86	1	.49	0	.44	0	.17	0	.17	1	.87
	All cancers other than leuk.	(d^1_{7j2})	256	119	114.64	59	63.41	48	49.31	13	13.14	10	7.74	7	7.76
	Other causes	(d^1_{7j3})	2264	1039	1047.32	604	575.97	418	435.42	99	107.59	63	56.64	41	41.06
	Subjects	(n^0_{7j})	4862	2245	-	1235	-	935	-	232	-	123	-	92	-
Total	Leukemia	$(d^1_{\cdot j1})$	80	17	17.89	9	10.77	8	9.07	5	3.85	10	5.41	31	33.01
	All cancers other than leuk.	$(d^1_{\cdot j2})$	1111	504	487.37	263	271.33	201	209.51	60	59.69	41	42.09	42	41.01
	Other causes	$(d^1_{\cdot j3})$	5898	2670	2640.39	1516	1486.42	1073	1106.14	256	299.93	211	198.73	172	166.39
	Subjects	$(n^0_{\cdot j})$	79736	34643	-	20502	-	14520	-	4032	-	3112	-	2927	-

Note: $\mathrm{E}(\hat{d}^1_{ijl}) = n^0_{ij} * \hat{P}_{ijl} = n^0_{ij} \exp(\hat{\lambda}^1_{ijl}) \Big/ \Big[1 + \sum_{l=1}^{3} \exp(\hat{\lambda}^1_{ijl})\Big]$, where $\hat{\lambda}^1_{ijl} = \hat{\alpha}^1_{il} + \hat{\beta}^1_{il} D_{ij}$, d^1_{ijl}= the number of deaths in the (i, j, l)-th cell for 1950-1959 and n^0_{ij}=the number of alive subjects in the (i, j)-th cell in 1950 for $i=1, 2, \cdots, 7$ (age) and $j=1, 2, \cdots, 6$ (dose).

Table 4 Relationship between observed and expected values by age and dose, 1960-1969

Age at 1960	Deaths		Total	Radiation Dose in Rad											
				0		1-9		10-49		50-99		100-199		200+	
				Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.
15-24	Leukemia	(d^2_{2j1})	12	2	2.58	1	1.64	3	1.44	0	.55	1	.68	5	5.11
	All cancers other than leuk.	(d^2_{2j2})	9	3	1.84	1	1.17	0	1.03	0	.40	1	.50	4	4.06
	Other causes	(d^2_{2j3})	136	65	61.70	38	37.39	22	26.54	6	5.60	3	2.94	2	1.83
	Subjects	(n^2_{2j})	15129	6623	-	4042	-	2970	-	688	-	414	-	392	-
25-34	Leukemia	(d^2_{3j1})	5	1	1.64	0	1.11	3	.68	0	.27	0	.38	1	.92
	All cancers other than leuk.	(d^2_{3j2})	50	15	18.99	17	12.79	8	7.53	2	2.62	3	3.21	5	4.86
	Other causes	(d^2_{3j3})	309	114	126.37	93	84.53	51	48.27	17	15.43	17	16.71	17	17.69
	Subjects	(n^2_{3j})	16689	6898	-	4609	-	2617	-	824	-	873	-	868	-
35-44	Leukemia	(d^2_{4j1})	7	2	1.81	0	1.11	1	.87	1	.38	1	.51	2	2.32
	All cancers other than leuk.	(d^2_{4j2})	104	32	39.12	26	23.54	18	17.20	9	6.21	9	6.14	10	11.80
	Other causes	(d^2_{4j3})	272	107	116.34	78	69.20	47	47.84	15	14.87	14	11.79	11	11.96
	Subjects	(n^2_{4j})	10097	4292	-	2555	-	1772	-	556	-	447	-	475	-
45-54	Leukemia	(d^2_{5j1})	5	0	.76	1	.44	1	.42	0	.19	0	.31	3	2.88
	All cancers other than leuk.	(d^2_{5j2})	299	132	131.98	64	72.33	64	57.19	21	15.59	7	11.18	11	10.73
	Other causes	(d^2_{5j3})	557	244	249.28	148	136.33	99	106.76	30	28.33	19	19.54	17	16.76
	Subjects	(n^2_{5j})	11031	4888	-	2677	-	2111	-	571	-	405	-	379	-
55-64	Leukemia	(d^2_{6j1})	10	3	3.95	3	2.19	2	1.83	1	.60	0	.56	1	.87
	All cancers other than leuk.	(d^2_{6j2})	561	231	244.41	137	134.16	120	106.58	28	30.59	24	23.85	21	21.40
	Other causes	(d^2_{6j3})	1515	647	654.95	386	359.86	261	287.28	93	83.54	65	66.38	63	62.99
	Subjects	(n^2_{6j})	11134	4911	-	2691	-	2120	-	595	-	449	-	368	-
65+	Leukemia	(d^2_{7j1})	7	0	1.89	3	1.09	1	.98	0	.44	1	.45	2	2.16
	All cancers other than leuk.	(d^2_{7j2})	653	282	285.63	163	159.81	127	125.46	36	38.24	24	22.63	21	21.23
	Other causes	(d^2_{7j3})	3862	1676	1727.24	996	963.02	749	743.27	232	216.37	121	119.73	88	92.37
	Subjects	(n^2_{7j})	8567	3840	-	2140	-	1648	-	477	-	262	-	200	-
Total	Leukemia	$(d^2_{.j1})$	46	8	12.63	8	7.58	11	6.22	2	2.43	3	2.89	14	14.26
	All cancers other than leuk.	$(d^2_{.j2})$	1676	695	721.97	408	403.80	337	314.99	96	93.65	68	67.51	72	74.08
	Other causes	$(d^2_{.j3})$	6651	2853	2935.88	1739	1650.33	1229	1259.96	393	364.14	239	237.09	198	203.60
	Subjects	$(n^2_{.j})$	72647	31452	-	18714	-	13238	-	3711	-	2850	-	2682	-

Note: $E(\hat{d}^2_{ijl}) = n^1_{ij} * \hat{P}^2_{ijl} = n^1_{ij} \exp(\hat{\lambda}^2_{ijl}) \Big/ \left[1 + \sum_{l=1}^{3} \exp(\hat{\lambda}^2_{ijl})\right]$, where $\hat{\lambda}^2_{ijl} = \hat{\alpha}^2_{il} + \hat{\beta}^2_{il} D_{ij}$, d^2_{ijl}= the number of deaths in the (i, j, l)-th cell for 1960-1969 and n^1_{ij}=the number of alive subjects in the (i, j)-th cell in 1960 for $i=2, \cdots, 7$ (age) and $j=1, 2, \cdots, 6$ (dose).

Table 5 Mortality data in 1950-1969

Cause of death	1950-1959	%	1960-1969	%	1950-1969	%
Leukemia	80	.1	46	.1	126	.2
All cancers without leukemia	1111	1.4	1676	2.3	2787	3.5
Other deaths	5898	7.4	6651	9.2	12549	15.7
Survivors	72647	91.1	64274	88.5	64274	80.6
Total	79647	100.0	72647	100.0	79736	100.0

Appendix 2. Table 5 shows the total mortality rate by cause and time period.

The dose-response relationship among the c age groups obtained from (6.1) can be shown to be significant at less than the 0.1% level for leukemia and all cancers other than leukemia but not significant for other causes of death (Table 1). The linear response model introduced here gives a good fit to the data ($\chi^2=82.49$ with 84 d.f. N.S.). No quadratic response relationships among the c age groups were noted for any of the three causes of death (Table 2). Thus, these mortality data can be adequately represented by a linear response relationship.

Table 6 shows the linear dose-response relationship between 1950–1959 and 1960–1969 by age and cause of death. There is a good fit of the model to the observed deaths (see Tables 3 and 4). As is evident from Table 6, the dose-response relationship in the leukemia data for the period 1950–1959 is significant for all age groups, but this is not true for the period 1960–1969. The dose-response relationship among the seven age groups was found to be significant only for all cancers other than leukemia in 1960–1969.

It is of interest to compare the dose-response difference in the same age group between 1950–1959 and 1960–1969 when the risks in the control level are eliminated. These results computed by (5.2) and (5.3) are shown in Table 7. A significant positive dose-response difference was observed only between the two 15–24 age groups and then only for all cancers other than leukemia. In the leukemia data, the hypothesis that the dose-response between the two time periods is not different was satisfied in all comparisons between the same age groups. We conclude, therefore, that no significant difference in leukemia has been noted for any age group between the two time periods, i.e., 1950–1959 and 1960–1969. The competing risks in the cohort mortality data for the period from 1950 to 1969 used here appear to be negligible for the ML estimates based on a semi-quantal response which are

Table 6 ML estimates of parameters for multinomial model, 1950-1959 and 1960-1969

Age at 1950 or at 1960		Leukemia $\hat{\alpha}_1^t$	Leukemia $\hat{\beta}_1^t \times 10^{-3}$	All cancers except leukemia $\hat{\alpha}_2^t$	All cancers except leukemia $\hat{\beta}_2^t \times 10^{-3}$	Other causes $\hat{\alpha}_3^t$	Other causes $\hat{\beta}_3^t \times 10^{-4}$
				1950-1959 (t=1)			
5-14	Est.	-7.84	10.09***	-9.71	10.49*	-4.73	25.25
	SE	.40	1.63	1.03	4.31	.09	10.16
15-24	Est.	-7.77	8.40***	-7.15	-.34 N.S.	-3.73	-6.93
	SE	.38	1.59	.30	3.57	.06	6.86
25-34	Est.	-7.76	9.18***	-5.97	1.32 N.S.	-3.53	-8.62
	SE	.40	1.95	.21	2.10	.06	8.58
35-44	Est.	-8.61	12.48***	-4.61	1.21 N.S.	-3.32	14.48
	SE	.68	2.37	.10	1.19	.05	6.12
45-54	Est.	-6.67	6.48***	-3.55	.96 N.S.	-2.41	-5.24
	SE	.27	1.59	.06	.74	.04	5.25
55-64	Est.	-7.01	9.07***	-2.82	-.10 N.S.	-1.50	3.08
	SE	.42	2.02	.06	.89	.03	4.72
65+	Est.	-7.14	9.34*	-2.25	.16 N.S.	-.03	.09
	SE	.73	3.82	.70	.11	.03	6.67
Homogenity test; χ^2 value with 7 d.f.			164.99***		11.30 N.S.		-
($H_0 : \beta_1^1 = \beta_2^1 = \ldots = \beta_7^1 = 0$)							
χ^2 value of goodness of fit under the model = 101.64 with 84 d.f. N.S.							
				1960-1969 (t=2)			
15-24	Est.	-7.84	10.10***	-8.18	10.41***	-4.67	-19.26
	SE	.41	1.77	.48	2.04	.09	18.68
25-34	Est.	-8.32	4.32 N.S.	-5.87	2.05 N.S.	-3.98	3.23
	SE	.53	3.38	.16	1.36	.06	6.81
35-44	Est.	-7.73	7.07**	-4.66	2.93**	-3.57	-1.56
	SE	.50	2.42	.11	.90	.07	8.15
45-54	Est.	-8.68	11.13***	-3.53	.14 N.S.	-2.89	-4.03
	SE	.75	2.80	.06	.85	.05	6.75
55-65	Est.	-6.92	3.27 N.S.	-2.80	.62 N.S.	-1.81	8.88
	SE	.35	3.18	.05	.61	.03	3.84
65+	Est.	-6.87	9.19***	-1.85	1.37*	-5.52	4.22
	SE	.49	2.48	.05	.66	.02	3.95
Homogenity test; value with 6 d.f.			73.33***		44.44***		-
(H_0: $\beta_2^2 = \beta_3^2 = \ldots = \beta_7^2 = 0$)							
χ^2 value of goodness of fit under the model=66.39 with 72 d.f. N.S.							

See the significant levels in Table 1.

Table 7 Dose-response difference with the 95% confidence intervals of same age groups between 1950-1959 and 1960-1969

Age at 1950	Age at 1960	Leukemia			All cancers other than leukemia		
		Low limit	$\exp(\hat{\beta}_i^2-\hat{\beta}_i^1)$	Upper limit	Low limit	$\exp(\hat{\beta}_i^2-\hat{\beta}_i^1)$	Upper limit
5-14	-	-	-	-	-	-	-
15-24	15-24	.997	1.002	1.006	1.003	1.011**	1.019
25-34	25-34	.988	.995	1.003	.996	1.001	1.006
35-44	35-44	.988	.995	1.001	.999	1.002	1.005
45-54	45-54	.998	1.005	1.011	.997	.999	1.001
55-64	55-64	.987	.994	1.002	.999	1.001	1.003
65+	65+	.991	1.000	1.009	.998	1.000	1.002

Note: $^{**}P<.01$ and all other differences are not significant.
The numerical evaluation showed the same values in the dose response difference of parameters estimated between the binomial and multinomial logistic models.

almost identical with those based on a multi-quantal response. This may be natural because both mortality rates between two time periods are small.

Finally, it is expected that this approach will give more definitive results when the additional cohort data from 1970–1979 are used.

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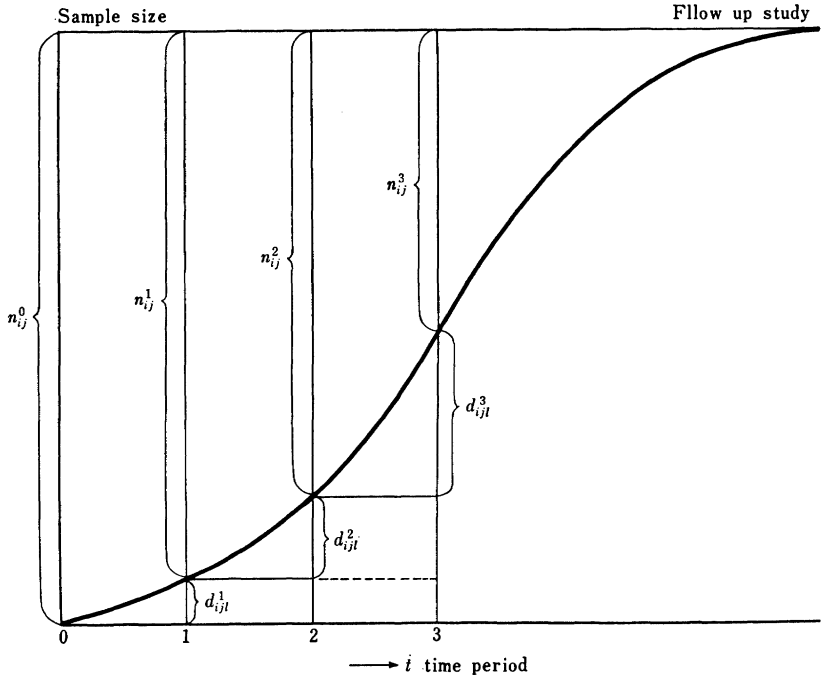
Appendix

Appendix 1 Illustration of cohort mortality data for t time period



where n_{ij}^t is equivalent to $n_{ij}^{t-1} - \sum_{l=1}^{r} d_{ijl}^t$ of (1.1) for $t=1, 2, \cdots, s$.

Appendix 2 Relationship between observed and expected values in

Age at 1950 (I)	Dose (J)	Total (n^0_{ij})	Sum of estimated probabilities (Bi.)	(Multi.)	Leukemia (ℓ=1) Observed ($d^{\cdot}_{ijl}$)	Expected (Bi.)	(Multi.)
1	1	6675	1.000	1.000	5	5.19	5.19
1	2	4084	1.000	1.000	2	3.30	3.30
1	3	2998	1.000	1.000	3	2.93	2.93
1	4	700	.998	1.000	1	1.14	1.14
1	5	423	.995	1.000	4	1.45	1.46
1	6	406	1.003	1.000	11	12.00	11.99
2	1	7099	1.000	1.000	1	4.53	4.53
2	2	4716	1.000	1.000	2	3.10	3.10
2	3	2668	1.000	1.000	6	2.01	2.01
2	4	835	.999	1.000	1	.90	.90
2	5	898	.998	1.000	3	1.66	1.66
2	6	893	1.001	1.000	7	7.80	7.80
3	1	4425	1.000	1.000	4	3.62	3.62
3	2	2646	1.000	1.000	2	2.23	2.23
3	3	1828	1.000	1.000	1	1.79	1.79
3	4	573	.998	1.000	1	.84	.84
3	5	459	.996	1.000	2	1.22	1.22
3	6	493	1.002	1.000	7	7.30	7.30
4	1	5122	1.000	1.000	0	1.66	1.66
4	2	2806	1.000	1.000	1	.95	.95
4	3	2205	1.000	1.000	2	.92	.92
4	4	594	.998	1.000	1	.44	.44
4	5	430	.995	1.000	1	.75	.75
4	6	414	1.003	1.000	8	8.28	8.28
5	1	5499	1.000	1.000	12	10.15	10.15
5	2	3004	1.000	1.000	6	5.66	5.66
5	3	2392	1.000	1.000	4	4.98	4.99
5	4	664	.999	1.000	1	1.82	1.82
5	5	496	.998	1.000	1	2.02	2.02
5	6	417	1.001	1.000	6	5.36	5.36
6	1	3578	1.001	1.000	2	3.98	3.97
6	2	2011	1.000	1.000	2	2.31	2.31
6	3	1494	.999	1.000	3	2.03	2.03
6	4	434	.997	1.000	2	.92	.92
6	5	283	.994	1.000	2	1.15	1.15
6	6	212	1.005	1.000	5	5.62	5.62
7	1	2245	1.000	1.000	1	1.31	1.31
7	2	1235	1.000	1.000	2	.74	.74
7	3	935	1.000	1.000	0	.65	.65
7	4	232	.998	1.000	0	.24	.24
7	5	123	.997	1.000	0	.22	.22
7	6	92	1.003	1.000	1	.84	.84
Total		79736	-		126	126.01	126.00

Note: $E(\hat{d}^{\cdot}_{ijl})=n^0_{ij} * \hat{P}_{ijl}=n^0_{ij}/[1+\exp -(\hat{\lambda}_{ijl})]$ in a binomial model and $E(\hat{d}^{\cdot}_{ijl})=n^0_{ij} *$ the number of deaths in the (i, j, l)-th cell for 1950-1969 and n^0_{ij}=the number

binomial and multinomial response models by age and dose, 1950-1969

All cancers other than leukemia (ℓ=2)			Other causes (ℓ=3)			Survivors (ℓ=4)	
Observed $(d_{ij2}^{\cdot})$	Expected (Bi.)	Expected (Multi.)	Observed $(d_{ij3}^{\cdot})$	Expected (Bi.)	Expected (Multi.)	Observed $(d_{ij4}^{\cdot})$	Expected (Bi.)
4	2.24	2.24	113	118.52	118.40	6553	6551.89
1	1.42	1.42	79	72.75	72.70	4002	4007.68
0	1.26	1.26	50	54.25	54.31	2945	2938.27
0	.49	.49	17	13.22	13.29	682	683.43
1	.61	.62	9	8.50	8.59	409	410.12
5	4.98	4.97	9	9.77	9.71	381	380.62
21	24.49	24.48	309	293.02	292.96	6768	6778.32
21	16.37	16.37	194	194.49	194.47	4499	4502.64
10	9.54	9.54	97	109.59	109.61	2555	2546.40
2	3.23	3.24	27	33.92	33.96	805	796.18
3	3.91	3.91	39	35.90	35.97	853	855.01
6	5.46	5.46	35	34.07	34.04	845	846.46
41	49.98	49.96	229	242.42	242.31	4151	4131.02
35	30.18	30.17	158	144.67	144.63	2451	2469.73
22	21.85	21.86	99	98.99	99.04	1706	1704.58
11	7.77	7.78	30	30.23	30.30	531	532.89
10	7.49	7.51	24	23.30	23.40	423	425.13
12	13.73	13.72	22	22.38	22.32	452	450.64
187	181.06	180.96	423	426.98	426.75	4512	4514.54
94	99.32	99.28	247	234.26	234.17	2464	2472.30
81	78.55	78.59	175	185.39	185.48	1947	1939.25
23	21.53	21.59	50	50.91	51.04	520	519.80
9	15.98	16.07	41	37.90	38.10	379	373.40
19	16.56	16.51	39	39.57	39.45	348	350.71
358	385.20	385.10	1099	1096.90	1096.60	4030	4007.82
218	210.92	210.89	615	599.79	599.69	2165	2188.01
193	169.88	169.92	458	479.83	479.97	1737	1736.83
49	48.63	48.69	141	134.88	135.06	473	478.03
35	37.99	38.07	100	102.62	102.85	360	352.52
36	36.37	36.33	92	90.97	90.83	283	284.79
398	384.74	384.43	1557	1601.17	1599.91	1621	1590.45
212	216.72	216.61	941	900.72	900.27	856	892.09
147	162.75	162.88	674	872.01	672.57	670	656.19
55	48.67	48.86	193	197.45	198.24	184	185.50
35	33.11	33.35	141	130.90	131.83	105	116.10
27	28.01	27.87	99	102.75	102.18	81	76.67
190	184.15	184.10	1793	1812.86	1812.28	261	247.35
90	101.64	101.63	1021	997.17	996.99	122	135.66
85	78.21	78.23	749	754.55	754.88	101	101.21
16	20.27	20.30	191	186.96	187.31	25	24.13
16	11.45	11.48	96	98.92	99.21	11	12.06
9	10.28	10.27	74	73.54	73.33	8	7.59
2787	2786.99	2787.01	12549	12548.99	12549.00	64274	64274.01

$\hat{P}_{ijl}=n_{ij}^{0}\exp(\hat{\lambda}_{ijl})\Big/\Big[1+\sum_{l=1}^{3}\exp(\hat{\lambda}_{ijl})\Big]$ in a multinomial model, where $\hat{\lambda}_{ijl}=\hat{\alpha}_{il}+\hat{\beta}_{il}D_{ij}$, $d_{ijl}=$ of alive subjects in the (i, j)-th cell in 1950.

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