Modeling Survival After Diagnosis of a Specific Disease Based on Case Surveillance Data

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Abstract: Motivated by a study assessing the impact of treatments on survival of AIDS (Acquired Immune Deficiency Syndrome) patients, we developed a semi-parametric method to estimate the life expectancy after diagnosis using data from case surveillance. With the proposed method, the life expectancy is estimated based on the traditional non-parametric life table method, but the age-specific death rates are estimated using a parametric model to derive more robust estimates from limited numbers of deaths by single year of age. The uncertainties associated with the semi-parametric estimates are provided. In addition, the life expectancy among people with the disease is compared with the life expectancy among those with similar demographic characteristics in the general population. The average years of life lost is used to measure the impact of the disease or the treatment on the survival after diagnosis. The trend of impact over time can be evaluated by the annual estimates of life expectancy and average years of life lost in the past.

Keywords: AIDS, Average years of life lost, HIV, Life expectancy, Mean survival time.

1. INTRODUCTION

There are two different approaches to estimating survival of a target population: one is based on a cohort with a follow-up time long enough to observe survival until death and the other, often referred to as the life table approach, is based on a cross-sectional sample with a relatively short follow-up time (e.g., one year). It usually takes a long time to collect cohort data and a large proportion of observations may be censored (e.g., due to longevity or loss to follow-up). When there are censored survival times longer than all observed (non-censored) survival times, the necessary data are not available to estimate the survival probability at time that is longer than the maximum observed survival time. Hence, it is impossible to estimate the mean survival time of the cohort.

Cross-sectional data include all individuals who are alive at a specific time point and their survival is monitored during a relatively short follow-up time period. By dividing individuals into consecutive age groups, survival can be modeled using conditional survival probabilities from all age groups. This is the so called life table approach [1]. It has been applied to the analysis of survival of cancer patients (called period method, [2,3]). This approach provides more up-to-date survival estimates by restricting the analysis to a relatively short, recent time period. In addition, it also greatly minimizes the censoring problem and makes estimating the mean survival time possible. One problem for applying this approach is that the number of deaths in any given age group (usually a single year of age) is likely too small (e.g., when the data are stratified by too many demographic or risk covariates) to generate reliable results.

Fang *et al.* [4] estimated the life expectancy of HIV patients based on cohort data. They proposed an extrapolation approach to deriving the survival probability through regression on the survival probability ratio which is the relative survival rate defined as the survival probability among the patient population divided the survival probability among the general population [3]. In this paper, we introduce a method to estimate the life expectancy based on cross-sectional data with a relative short follow up time. We apply the method to estimating the life expectancy of AIDS patients based on data collected through the HIV case surveillance system in the United States. To overcome the limited number of observed deaths by single year of age within a short follow up time period, we use a parametric function to model the age-specific death rates, then, use the life table approach to estimate the survival function and the expected survival time or life expectancy of AIDS patients at the time of AIDS diagnosis. To measure the difference in survival between persons diagnosed with AIDS and the rest of the population, we compare the life expectancy of AIDS patients with the life expectancy of the general population and calculate the average years of life lost (AYLL, see [5]) due to the diagnosis of AIDS. Our method is applicable to any disease for which death

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data are routinely collected on a population. The method is particularly useful for diseases for which incidence and death rates are low and can be adapted to account for any age-dependent pattern of low incidence or death rates.

2. AIDS SURVEILLANCE DATA

Since the first cases of AIDS were diagnosed in 1981, all 50 U.S. states, the District of Columbia, and U.S. dependent areas have reported AIDS cases to the Centers for Disease Control and Prevention [6] in a uniform format. Reported information includes date of diagnosis, state of residence at diagnosis, demographic variables, and transmission category. Health departments report information to CDC monthly on changes in vital status of previously reported cases and additional cases that had not been reported before with personal identification information removed.

At the beginning of the HIV epidemic, survival after AIDS diagnosis was short. Without treatment, the average survival time was about 2 years [7,8]. After the introduction of antiretroviral therapy, particularly highly active antiretroviral therapy (HAART) in 1996, survival among HIV patients has greatly improved [9,10,11]. Over time the proportion of HIV patients in treatment increased, but the exact proportion was unknown since information on treatment is not routinely collected through the US HIV surveillance system. Although we do not have information on the proportion in treatment, we can use observed death rates to estimate the effect of treatment over the years on a population using the data collected in the US HIV surveillance system. Survival after HIV diagnosis depends on how long the person has been infected. Without any treatment, the expected life expectancy after HIV diagnosis can vary from few years if diagnosis late (e.g., AIDS at diagnosis) to more than ten years if diagnosis early (e.g., diagnosed right after infection) [7,8]. To reduce the impact of when HIV is diagnosed during the course of HIV infection, we consider survival after AIDS diagnosis rather than survival after HIV diagnosis. We estimate death rate by year of AIDS diagnosis and age at a specific time point. To illustrate the characteristics of the data, we provide the observed death rates in 2007 among persons diagnosed with AIDS before 2007 by year of AIDS diagnosis and age in 2007 (Figure **1**). We see that death rates are significantly higher in the first year after diagnosis. For those who have survived more than one year after AIDS diagnosis, the death rate depends on age and is relatively independent of the number of years after diagnosis. The lower death rate after one year of AIDS diagnosis is likely to be the benefit of treatment, particularly the highly active antiretroviral therapy, which delays the progress of the disease when the patient's CD4 count is not too low [12]. Also, the observed death rates for age greater than 60 are unstable because there are not many persons with AIDS in those age groups.

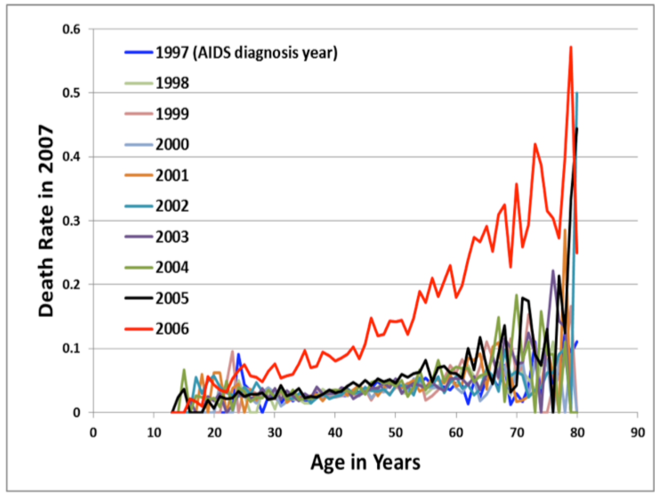

Figure 1: Observed AIDS death rate in 2007 among 303,693 persons who diagnosed with AIDS in 1997-2006 and survived to the end of 2006 by year of AIDS diagnosis and age in 2007.

3. MODELS FOR SURVIVAL AFTER DIAGNOSIS

For a person diagnosed with the disease of interest at age x, let $S_x(t)$ be the probability that the person survives t years after diagnosis. The average time that the person survives or the mean survival time after diagnosis at age x is

$$M(x)=\int_0^\infty S_x(t)dt \qquad (1)$$

Assume that T is the maximum survival age, i.e., none can survive beyond that age. Then the mean survival time after diagnosis at age x is approximately given by:

$$M(x)=1/2+S_x(1)+S_x(2)+\cdots +S_x(T-x)+(1/2)S_x(T-x+1) \qquad (2)$$

This formula is derived by dividing time into one-year intervals and using the trapezoidal rule to get the approximate integral of the survival function over the interval. Note that the last term is actually zero since it is the survival probability beyond the maximum survival age.

Generalizing from the life table method [1], survival probabilities can be computed using conditional probabilities. Let $P_x(j|i)$ be the conditional probability that a person who has survived i years after diagnosis at age x survives additional j - i years. Then, for all k > 1, we have

$$S_x(k) = P_x(1|0) \cdot P_x(2|1) \cdots P_x(k|k-1) \quad (3)$$

Replacing these probabilities in formula (2), we get an estimate of mean survival time for a person with age x at diagnosis. Finally, the average mean survival time at diagnosis for persons who were diagnosed in a calendar year can be estimated as

$$\bar{M} = \sum_x n(x) \cdot M(x) \Big/ \sum_x n(x) \quad (4)$$

where $n(x)$ is the number of cases diagnosed at age x in the calendar year considered. The summation can be specified for a specific age group, for example, $x > 0$ for all cases or $x > 12$ for adults and adolescents.

Let $P_{x,i} = P_x(i+1|i)$, we have

$$S_x(k) = P_{x,0} \cdot P_{x,1} \cdots P_{x,k-1} \quad (5)$$

Based on the data observed from persons diagnosed with AIDS, the death rate is relatively constant after the first year of diagnosis (see discussion in the previous section). More generally, we assume that the conditional survival probability $P_{x,i}$ depends on age $x+i$ and whether it is within d year(s) of diagnosis (d=1 for AIDS survival). The probability $P_{x,i}$ with $i < d$ can be estimated by the proportion of persons diagnosed at age x with a current age $x+i$ and survive to age $x+i+1$. The probability $P_{x,i}$ with $i \geq d$ can be estimated by the proportion of persons with a current age $x+i$ but diagnosed d or more year(s) and survive to age $x+i+1$.

One problem in estimating the conditional survival probabilities is that there are very few persons diagnosed with AIDS in older age groups, and hence estimates for single year age groups won't be stable. To obtain reliable estimates for these age-specific survival probabilities, one may consider using parametric models. For example, Goldstein *et al.* [13] used a polynomial function to fit age-specific hepatitis B-related cirrhosis and hepatocellular carcinoma mortality rates.

Suppose that the probability $P_{x,i}$ with $i < d$ is modeled as a probability function with a parameters $\varphi = (\varphi_1,...,\varphi_a)$ and $P_{x,i}$ with $i \geq d$ as a probability function with b parameters $\theta = (\theta_1,...,\theta_b)$. Let $\varphi = (\varphi_1,...,\varphi_a)$ be an estimate of φ with a covariance matrix Σ_φ and $\theta = (\theta_1,...,\theta_b)$ be an estimate of θ with a covariance matrix Σ_θ. Under the parametric models, the survival probabilities and the mean survival time are functions of the model parameters: φ and θ. Based on the delta method [14], we can estimate the variance of the survival probability estimator and the variance of the average mean survival time (see Appendix). Using the estimated variances, one can construct confidence intervals based on a normal approximation. In the next section, we will use a two parameter function to model each of the two probability functions and estimate the survival and life expectancy after AIDS diagnosis using US HIV surveillance data.

4. SURVIVAL AND LIFE EXPECTANCY AFTER AIDS DIAGNOSIS

In this section, we model the forms of the survival curves for AIDS. Based on the AIDS surveillance data described in section 2, AIDS death rates within one year of AIDS diagnosis are significantly different than the death rates among those diagnosed with AIDS for more than one year. So, we have d = 1 for the model described in the previous section.

Let $Q(x) = 1 - P_{x,0}$ be the probability of dying at age x in the first year after AIDS diagnosis. Based on the observed probabilities of AIDS survival in the first year after diagnosis by age, we model this probability to increase as age increases at a rate given by an exponential function:

$$Q(x) = Q(x-1) \cdot e^{\varphi_2} \text{ or } Q(x) = Q(x_0) \cdot e^{\varphi_2(x-x_0)} = e^{\varphi_1 + \varphi_2 x} \quad (6)$$

Let $G(x) = 1 - P_{x-i,i}$ be the probability of dying at age x after the first year of AIDS diagnosis. We assume that this probability is similar to the probability $Q(x)$ but with different parameter values.

$$G(x) = G(x-1) \cdot e^{\theta_2} \text{ or } G(x) = G(x_0) \cdot e^{\theta_2(x-x_0)} = e^{\theta_1 + \theta_2 x} \quad (7)$$

If the death rate estimate is less than the death rate of the general population, then it is replaced with the death rate of the general population. For both $Q(x)$ and $G(x)$, if the death rate is greater than 1, then it is set to 1. This usually happens when age is out of the normal survival range so the impact of this fix is very limited. In order to avoid this issue, one may consider using the logistic model. Unfortunately, the logistic model does not fit the AIDS mortality data well compared to the proposed model based on the goodness of fit measure,

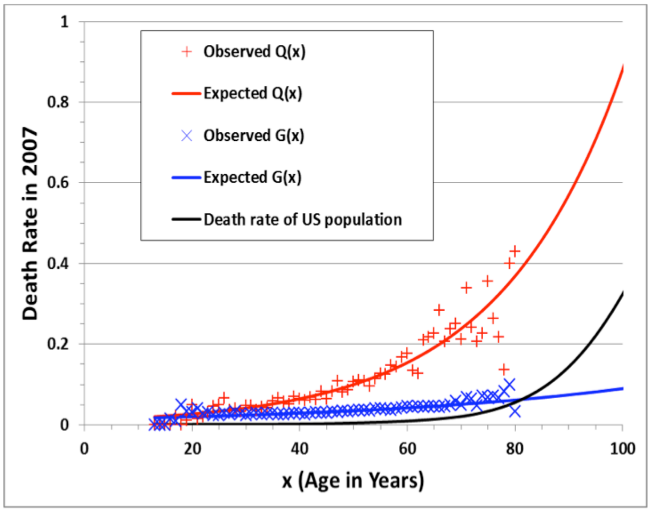

Figure 2: Observed and expected death rates based on AIDS surveillance data and US population mortality rate in 2007.

e.g., the BICs (Bayesian Information Criterion) for fitting the probability $G(x)$ using the logistic model and the proposed model are 562.6 and 559.7, respectively.

With the above models, the survival probabilities and mean survival time are functions of model parameters: θ_1, θ_2, φ_1, and φ_2. Parameters θ_1 and φ_1 are related to the baseline rates, while θ_2 and φ_2 are related to the age effects on death rates.

We estimated death rates specified in models (9) and (10) for each calendar year from 1993 to 2009 based on AIDS cases reported to CDC. Due to delays in reporting diagnosed cases and AIDS death, the numbers of diagnosed AIDS cases and deaths were adjusted for reporting delay using a weighting method [15,16,17]. As an example, AIDS death rates observed in 2007 with estimated functions $Q(x)$ and $G(x)$ are presented in Figure **2**. Observed and expected death rates within one year of AIDS diagnosis $Q(x)$ among 35,075 persons who were diagnosed with AIDS in 2006 by age at diagnosis (marked as '+' with fitted curve in red), observed and expected death rates $R(x)$ in 2007 among 397,047 persons who diagnosed with AIDS before 2006 and survived to the end of 2006 by age in 2007 (marked as 'x' with fitted curve in blue), and the death rate of US population in 2007 by age (curve in black). Model parameters by year of AIDS diagnosis are listed in Tables **1** and **2**. Estimates of life expectancy among all individuals at the time of AIDS diagnosis by year of diagnosis from 1993 to 2009 are listed in Table **3**.

Table 1: Estimates of Q Model Parameters Based on AIDS Death Rates within One Year After AIDS Diagnosis Using AIDS Surveillance Data Reported to US Centers for Disease Control and Prevention Before July of 2011

Y	N	φ_1	φ_2	se(φ_1)	se(φ_2)	cov(φ_1,φ_2)
1993	75329	-2.84	0.028	0.031	0.00070	-0.000021
1994	75063	-3.15	0.030	0.036	0.00081	-0.000028
1995	68978	-3.29	0.033	0.038	0.00085	-0.000031
1996	66350	-3.39	0.034	0.040	0.00089	-0.000034
1997	58523	-3.77	0.039	0.046	0.00100	-0.000045
1998	47766	-4.03	0.041	0.056	0.00120	-0.000065
1999	41076	-4.10	0.042	0.060	0.00128	-0.000075
2000	39383	-4.21	0.043	0.063	0.00132	-0.000080
2001	39792	-4.15	0.041	0.065	0.00137	-0.000087
2002	38752	-4.32	0.043	0.067	0.00139	-0.000090
2003	38823	-4.30	0.042	0.069	0.00145	-0.000097
2004	39507	-4.48	0.044	0.071	0.00147	-0.000102
2005	38283	-4.39	0.043	0.072	0.00147	-0.000103
2006	36529	-4.59	0.046	0.076	0.00155	-0.000114
2007	35075	-4.48	0.044	0.077	0.00155	-0.000115
2008	34258	-4.65	0.046	0.079	0.00159	-0.000123
2009	33535	-4.67	0.047	0.077	0.00153	-0.000115

Notes: N is the number of AIDS cases diagnosed in the previous calendar year of Y with age at AIDS diagnosis from 13 to 80 years old, se and cov stand for standard error and covariance of corresponding parameter estimates.

Table 2: Estimates of G Model Parameters Based on AIDS Death Rates in Each Calendar Year (Y) Among Cases Diagnosed with AIDS More than One Year (N) Using AIDS Surveillance Data Reported to US Centers for Disease Control and Prevention Before July of 2011

Y	N	θ_1	θ_2	se(θ_1)	se(θ_2)	cov(θ_1,θ_2)
1993	68287	-1.68	0.008	0.030	0.00075	-0.000022
1994	96971	-1.67	0.008	0.025	0.00062	-0.000015
1995	121810	-1.78	0.008	0.024	0.00058	-0.000014
1996	139440	-2.15	0.008	0.029	0.00069	-0.000019
1997	165999	-2.95	0.011	0.039	0.00094	-0.000036
1998	200441	-3.36	0.013	0.042	0.00099	-0.000041
1999	228811	-3.61	0.017	0.042	0.00096	-0.000039
2000	251100	-3.79	0.018	0.043	0.00096	-0.000040
2001	272303	-3.76	0.016	0.042	0.00094	-0.000039
2002	293649	-3.92	0.018	0.043	0.00093	-0.000039
2003	314359	-4.01	0.018	0.043	0.00092	-0.000039
2004	335030	-4.12	0.019	0.043	0.00092	-0.000039
2005	356862	-4.22	0.020	0.043	0.00090	-0.000038
2006	377521	-4.31	0.021	0.043	0.00089	-0.000038
2007	397047	-4.30	0.019	0.044	0.00090	-0.000039
2008	415930	-4.73	0.027	0.044	0.00088	-0.000038
2009	435128	-4.75	0.026	0.044	0.00086	-0.000037

Note: se and cov stand for standard error and covariance of corresponding parameter estimates.

Table 3: Estimated Life Expectancy (LE), Standard Error (se), and 95% Confidence Interval (L95, U95) of Life Expectancy for AIDS Patients Diagnosed in Each Year. N is the Number of Diagnosed AIDS Cases in Each Year with Age ≥ 13 Years at AIDS Diagnosis

Year	N	LE	se	L95	U95
1993	75092	3.7	0.015	3.7	3.8
1994	69001	3.9	0.013	3.8	3.9
1995	66374	4.1	0.013	4.1	4.1
1996	58548	5.7	0.023	5.7	5.8
1997	47793	10.6	0.057	10.4	10.7
1998	41115	13.4	0.067	13.3	13.6
1999	39406	14.3	0.059	14.2	14.4
2000	39835	15.3	0.058	15.2	15.4
2001	38781	16.0	0.061	15.9	16.1
2002	38849	16.8	0.058	16.7	16.9
2003	39546	17.4	0.056	17.3	17.5
2004	38317	18.2	0.054	18.1	18.3
2005	36561	18.6	0.051	18.5	18.7
2006	35126	19.2	0.049	19.1	19.3
2007	34283	19.9	0.052	19.8	20.0
2008	33573	20.5	0.043	20.4	20.6
2009	32928	20.7	0.043	20.6	20.8

We compared the life expectancy after AIDS diagnosis with the life expectancy in the general population by age in 2007 [18]. Our estimates of the average years of life lost among AIDS patients diagnosed in 2007 by age at AIDS diagnosis are shown in Figure **3**. Our estimate for the average life expectancy of the 34,283 people diagnosed AIDS in 2007 is 19.5 years. Their life expectancy would be 39.3 years if they were not infected with HIV. The average years of life loss is expected to be 19.8 years.

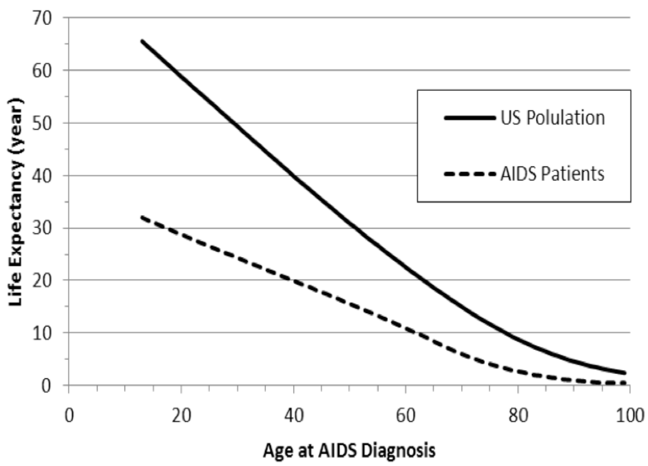

Figure 3: Life expectancy of AIDS patients diagnosed in 2007 and their average years of life lost by age at AIDS diagnosis.

5. DISCUSSION

We have proposed a method for estimating the life expectancy of persons diagnosed with a disease using data from a disease surveillance system. We have illustrated our method using HIV surveillance data and observed mortality in a calendar year. This method allows us to estimate life expectancy annually based on the survival conditions in the year of interest. Therefore, survival improvement from treatment, health care, and living conditions can be evaluated over time. This method is focused on the survival of a hypothetical cohort with a disease diagnosed in a specific year under the living or survival condition in that particular year, not focused on the survival of this cohort under the condition in that year and following years. If the focus is the later, then one may follow the method proposed by Brenner and Spix [19] to obtain a good current estimate for the true survival of that cohort using the survival data not only in the diagnosis year, but also in years thereafter.

Although the method was developed for the analysis of AIDS survival, it has been applied to the analysis of survival after HIV diagnosis [20] and can be applied to the analysis of survival associated with other diseases. Life expectancy and average years of life lost after diagnosis of a particular disease can be used as a physician's tool to better communicate with patients their expected survival compared with other people in the population. This information can also be useful to policy makers and researchers in estimating costs and allocating resources.

Based on the national HIV surveillance data, we have demonstrated that survival of persons diagnosed with AIDS in the United States has significantly improved. The life expectancy of persons diagnosed with AIDS has been significantly increased after the introduction of HAART in 1996 and the improvement continued in the subsequent 12 years from 10.6 years in 1997 to 20.7 years in 2009. This improvement could be the result of more effective treatment and an increase in the number of AIDS patients getting treated. Our result is comparable with the result obtained by Fang *et al.* [4] using a different approach based on a cohort in Taiwan with six years follow up from 1997 to 2003. However, our approach has the advantage of delivering annual estimates so that the improvement of survival over time can be identified and measured by the increased life expectancy.

Although life expectancy and AYLL have significantly improved for persons diagnosed with AIDS from 1993 to 2009, life expectancy remains shorter than that for the general US population. Ongoing monitoring of life expectancy is important as therapies advance and other variables (e.g., antiretroviral resistance, toxicities, adherence, and HIV testing practices) have the potential to change. AYLL can be used in conjunction with other measures of HIV disease burden, for example, mortality and survival rates, to provide policy makers, clinicians, and patients a more comprehensive picture of burden to individuals diagnosed with AIDS.

APPENDIX

The variance of the survival probability estimator is given by:

$$V[S_x(k)] = \left(\frac{\partial S_x(k)}{\partial \varphi}\right)' \Sigma_\varphi \left(\frac{\partial S_x(k)}{\partial \varphi}\right) + \left(\frac{\partial S_x(k)}{\partial \theta}\right)' \Sigma_\theta \left(\frac{\partial S_x(k)}{\partial \theta}\right)$$

where

$$\frac{\partial S_x(k)}{\partial \varphi} = \left(\frac{\partial S_x(k)}{\partial \varphi_1}, \ldots, \frac{\partial S_x(k)}{\partial \varphi_a} \right)'$$

$$= S_x(k) \left(\sum_{i=0}^{d-1} \frac{1}{P_{x,i}} \frac{\partial P_{x,i}}{\partial \varphi_1}, \ldots, \sum_{i=0}^{d-1} \frac{1}{P_{x,i}} \frac{\partial P_{x,i}}{\partial \varphi_a} \right)'$$

$$\frac{\partial S_x(k)}{\partial \theta} = \left(\frac{\partial S_x(k)}{\partial \theta_1}, \ldots, \frac{\partial S_x(k)}{\partial \theta_b} \right)'$$

$$= S_x(k) \left(\sum_{i=d}^{k-1} \frac{1}{P_{x,i}} \frac{\partial P_{x,i}}{\partial \theta_1}, \ldots, \sum_{i=d}^{k-1} \frac{1}{P_{x,i}} \frac{\partial P_{x,i}}{\partial \theta_b} \right)'$$

The variance for the estimator of the mean survival time at diagnosis of age *x* is

$$V[M(x)] = \left(\frac{\partial M(x)}{\partial \varphi} \right)' \Sigma_\varphi \left(\frac{\partial M(x)}{\partial \varphi} \right) + \left(\frac{\partial M(x)}{\partial \theta} \right)' \Sigma_\theta \left(\frac{\partial M(x)}{\partial \theta} \right)$$

where

$$\frac{\partial M(x)}{\partial \varphi} = \sum_{k=1}^{T-x} \frac{\partial S_x(k)}{\partial \varphi}$$

$$\frac{\partial M(x)}{\partial \theta} = \sum_{k=1}^{T-x} \frac{\partial S_x(k)}{\partial \theta}$$

For the average mean survival time, we have

$$V[\bar{M}] = \left(\frac{\partial \bar{M}}{\partial \varphi} \right)' \Sigma_\varphi \left(\frac{\partial \bar{M}}{\partial \varphi} \right) + \left(\frac{\partial \bar{M}}{\partial \theta} \right)' \Sigma_\theta \left(\frac{\partial \bar{M}}{\partial \theta} \right)$$

where

$$\frac{\partial \bar{M}}{\partial \varphi} = \sum_x n(x) \cdot \frac{\partial M(x)}{\partial \varphi} \Big/ \sum_x n(x)$$

$$\frac{\partial \bar{M}}{\partial \theta} = \sum_x n(x) \cdot \frac{\partial M(x)}{\partial \theta} \Big/ \sum_x n(x)$$

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