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Estimation of Sojourn Time in Chronic Disease Screening Without Data on Interval Cases

Tony H. H. Chen,[1,*] H. S. Kuo,[2] M. F. Yen,[2] M. S. Lai,[3] L. Tabar,[4] and S. W. Duffy[5]

[1]Graduate Institute of Epidemiology, College of Public Health, National Taiwan University, Room 213, Number 19, Hsu-Chow Road, Taipei, Taiwan
[2]Graduate Institute of Public Health, College of Medicine, National Yang-Ming University, Taipei, Taiwan
[3]Department of Health, Taipei, Taiwan
[4]Mammography Department, Central Hospital, 79182 Falun, Sweden
[5]MRC Biostatistics Unit, Cambridge, U.K.
* *email:* stony@episerv.cph.ntu.edu.tw

SUMMARY. Estimation of the sojourn time on the preclinical detectable period in disease screening or transition rates for the natural history of chronic disease usually rely on interval cases (diagnosed between screens). However, to ascertain such cases might be difficult in developing countries due to incomplete registration systems and difficulties in follow-up. To overcome this problem, we propose three Markov models to estimate parameters without using interval cases. A three-state Markov model, a five-state Markov model related to regional lymph node spread, and a five-state Markov model pertaining to tumor size are applied to data on breast cancer screening in female relatives of breast cancer cases in Taiwan. Results based on a three-state Markov model give mean sojourn time (MST) 1.90 (95% CI: 1.18–4.86) years for this high-risk group. Validation of these models on the basis of data on breast cancer screening in the age groups 50–59 and 60–69 years from the Swedish Two-County Trial shows the estimates from a three-state Markov model that does not use interval cases are very close to those from previous Markov models taking interval cancers into account. For the five-state Markov model, a reparameterized procedure using auxiliary information on clinically detected cancers is performed to estimate relevant parameters. A good fit of internal and external validation demonstrates the feasibility of using these models to estimate parameters that have previously required interval cancers. This method can be applied to other screening data in which there are no data on interval cases.

KEY WORDS: Breast cancer; Chronic disease; Interval cases; Markov model; Screening; Sojourn time.

1. Introduction

Estimating sojourn time for the natural history of chronic disease can throw light on how disease screening works and how screening frequencies can be determined. For example, previous research found that women aged under 50 years have a shorter sojourn time than women aged 50–74 years (Tabar et al., 1995). Accordingly, a more intensive breast cancer screening with mammography for women aged under 50 years was suggested. Regarding the relationship between sojourn time and mortality, it is believed that a short sojourn time distribution may suggest that screening would likely be ineffective whereas a long sojourn time distribution implies that screening would reduce mortality if it is able to detect the disease in its early stage. For example, the poor efficacy of breast cancer screening with mammography observed for women aged under 50 years might be due to a shorter sojourn time or poor sensitivity (Tabar et al., 1995). It is therefore valuable to estimate sojourn time in chronic disease screening in order to throw light on the natural history of chronic disease.

Methods for the estimation of sojourn time in relation to screening data are numerous. They include the simple estimate ratio of prevalence at first screen to expected annual incidence rate (Zelen and Feinleib, 1969), parametric models using a specific sojourn time distribution (Day and Walter, 1984; Paci and Duffy, 1991), nonparametric methods to split time into discrete interval (Chen and Porok, 1983), simulation models based on assigned parameters (van Oortmarssen et al., 1990), and Markov models for the natural history of disease process from disease-free state first to the preclinical-screen detectable phase (PCDP) and then to the clinical phase (Duffy et al., 1995). Some methods of quantitative evaluation (e.g., Baker and Chu, 1990) do not require estimation of sojourn time.

It should be noted that estimation of sojourn time based on the above methods requires data on prevalent screen, incident screen, and interval cancers (Day and Walter, 1984) or at least on interval cancers (Paci and Duffy, 1991). These methods suggest that estimation of sojourn time cannot be per-

formed without interval cancers. Practical aspects of screening sometimes make ascertaining interval cases difficult, particularly for some chronic diseases, e.g., diabetes mellitus (DM). This is especially so in developing countries lacking a complete registration system. Even in cancer screening projects, although interval cancers can in theory be readily identified from the cancer registry, underreporting systems and patient confidentiality may render the ascertainment of such cases impractical. We were faced with a particular example of this problem in evaluation of the Taiwan project of screening for breast cancer in women with a family history of the disease. A total of 2629 female relatives of breast cancer index cases were invited for screening by a combination of physical examination, mammography, and ultrasound examination annually between 1994 and 1996. Index cases were identified from 12 hospitals. Invited women were aged 35–80 years. Data were available on two complete rounds of screening, but interval cancers were not ascertained in a timely manner partly due to underreporting in Taiwan's cancer registration system and partly due to the concern about patient confidentiality. In an uncontrolled intervention in a high-risk group such as this, it is essential to attempt a quantitative evaluation despite the unavailability of some information, in this case the interval cancer data. The need to do so provided the motivation for the current work. In this paper, we propose a method overcoming this problem and estimate transition rates on prevalent and incident screens only.

The rest of the article is organized as follows. We begin with a three-state Markov model in Section 2. Section 3 extends a three-state Markov model to the five-state Markov models with respect to regional lymph node spread and tumor size. Model diagnostics are given in Section 4. Limitations of these models in evaluating chronic disease screening are given in Section 5.

2. A Three-State Markov Model

2.1 *Model Specification*

We model the disease process for a chronic disease as a continuous-time Markov process in which $X(t)$, the state of an individual at time t, is a random variable with a state space $\Omega = \{0, 1, 2\}$, where zero represents no disease, one represents PCDP, and two represents clinical phase. The clinical phase in this model is an absorbing state in the language of Markov processes because the natural history cannot be estimated beyond diagnosis due to the effect of therapy. We also assume this is a progressive model.

The transition rates in the three-state model can be expressed as an intensity matrix,

$$\begin{array}{c} \\ 0 \\ 1 \\ 2 \end{array} \begin{array}{c} \begin{array}{ccc} 0 & 1 & 2 \end{array} \\ \begin{pmatrix} -\lambda_1 & \lambda_1 & 0 \\ 0 & -\lambda_2 & \lambda_2 \\ 0 & 0 & 0 \end{pmatrix} \end{array}, \tag{1}$$

where λ_1 and λ_2 represent the transition rate from no disease to the PCDP (the preclinical incidence rate) and the transition rate from the PCDP to the clinical phase. The inversion of λ_2 is mean sojourn time (MST). If there is no data on interval cases, transition from the PCDP to the clinical phase are not observable. Given the transition intensity matrix in (1), transition probabilities for a three-state model can be expressed as

$$\begin{array}{c} \\ 0 \\ 1 \\ 2 \end{array} \begin{array}{c} \begin{array}{ccc} 0 & 1 & 2 \end{array} \\ \begin{pmatrix} P_{00}(t) & P_{01}(t) & P_{02}(t) \\ 0 & P_{11}(t) & P_{12}(t) \\ 0 & 0 & 1 \end{pmatrix} \end{array}, \tag{2}$$

where

$$\begin{aligned} P_{00}(t) &= e^{-\lambda_1 t}, \\ P_{01}(t) &= \frac{\lambda_1(e^{-\lambda_1 t} - e^{-\lambda_2 t})}{(\lambda_2 - \lambda_1)}, \\ P_{02}(t) &= 1 - \frac{\lambda_2 e^{-\lambda_1 t}}{\lambda_2 - \lambda_1} + \frac{\lambda_1 e^{-\lambda_2 t}}{\lambda_2 - \lambda_1}, \\ P_{11}(t) &= e^{-\lambda_2 t}, \\ P_{12}(t) &= 1 - e^{-\lambda_2 t}. \end{aligned}$$

The derivation of transition probabilities is based on the Kolmogorov equation, which has been described in full elsewhere (Cox and Miller, 1965).

2.2 *The Likelihood Function and Data*

Due to screening, detection modes for subjects invited for screening can be classified into normal, screen-detected cases (i.e., cases in the PCDP) and clinically detected cases (i.e., cases in the clinical phase) corresponding to the above three-state model. Screen-detected cases usually consist of prevalent screen (cases detected at first screen) and incident screens (cases detected at subsequent screens). Clinically detected cases include interval cases (lesions surfacing to the clinical phase with symptoms between two screens), refusers (invited to screen but refuse to attend), and, in the case of a randomized trial, control group (not invited to screen). As we focus on estimation of sojourn time without interval cases, the likelihood function only consists of prevalence screen and incident screen. For prevalence screen, if the time of onset of screen-detected cases is recorded according to when they enter into the PCDP, cases detected at first screen are usually defined as prevalent screen-detected cases because some of them have already entered into the PCDP before the first screen. Since the exact time entering into the PCDP for prevalent screen is unknown but must be ahead of the first screen, prevalent screen is usually defined as left-censored cases in which survival time from normal to the PCDP cases is denoted by age at first screen. Likewise, cases detected at incident screens are interval-censored cases because the actual time entering into the PCDP is also uncertain but must lie between two consecutive screens, i.e., within an interscreening interval.

Suppose N individuals attend the first screen. It is relatively straightforward to write down the likelihood functions according to transition probabilities in (2). The likelihood function based on the prevalent screen is

$$L_1(\cdot) = \prod_{m=1}^{N} \left(\frac{P_{01}(v_m)}{P_{00}(v_m) + P_{01}(v_m)} \right)^{x_m} \times \left(\frac{P_{00}(v_m)}{P_{00}(v_m) + P_{01}(v_m)} \right)^{1-x_m}, \tag{3}$$

where v_m represents age at first screen for mth subject, $x_m = 1$ when the mth subject is detected as a positive case, and $x_m = 0$ otherwise.

The likelihood for the prevalence screen is the probability of the outcome of that screen conditional on no previous clinical cancer (i.e., conditional on being either negative or screen-detected cases). This is because those reporting a previous breast cancer are excluded.

Suppose we have $r-1$ rounds of subsequent screens. The likelihood function based on them is

$$L_2(\cdot) = \prod_{j=2}^{r}\prod_{i=1}^{n_j}\{P_{01}(t_{ji}-t_{(j-1)i})\}^{y_{ji}}\{P_{00}(t_{ji}-t_{(j-1)i})\}^{1-y_{ji}}, \tag{4}$$

where j represent the jth round of screen ($j = 2,\ldots,r$), $t_{ji} - t_{(j-1)i}$ represents the interscreening interval between the $(j-1)$th screen and jth screen for the ith subject, n_j represents the number of attendants in the jth screen, $y_{ji} = 1$ when the ith subject enters the PCDP during $t_{ji} - t_{(j-1)i}$, and $y_{ji} = 0$ otherwise.

The likelihood for incidence screens is a product of unconditional probabilities because we are not explicitly excluding those with interval cancers from the population at this stage. We are merely unable to identify them *a priori*. The likelihood in (4) approximates a conditional likelihood based on exclusion of interval cancer cases because the number of the latter is small. The total likelihood function will be the product of $L_1(\cdot)$ and $L_2(\cdot)$.

It should be noted that, compared with a three-state model using interval cases (Duffy et al., 1995), our model may have a lower precision for estimation of parameters due to the absence of interval cases, which provide an exact time to clinical phase via the observed transition from no disease to the clinical phase ($0 \rightarrow 2$).

Estimation of parameters is performed by using the total likelihood to estimate the number of expected transitions of each type, all then use to solve the series of equations by letting observed equal expected plus the error term using a nonlinear regression. This is a quasilikelihood approach, which has been used by Gallant (1987) and Duffy et al. (1995) and is regarded as equivalent to generalized estimation equations.

Thus, for example, at the second screen, in the three-state model, the expected number of cancers diagnosed, as calculated from the likelihood, is

$$n_2 \times \frac{\lambda_1\left(e^{-\lambda_1 t} - e^{\lambda_2 t}\right)}{(\lambda_2 - \lambda_1)},$$

where n_2 is the number of attendant at the second screen. The corresponding observed number is $\Sigma_i\, y_{2i}$. Therefore, one of the equations is

$$\sum_i y_{2i} = n_2 \times \frac{\lambda_1\left(e^{-\lambda_1 t} - e^{-\lambda_2 t}\right)}{(\lambda_2 - \lambda_1)}.$$

An illustrative example comes from a project on breast cancer screening in female relatives of breast cancer index cases. As stated in Section 1, a particular example of the situation where evaluation is necessary in the absence of interval cases is the Taiwan program of screening relatives of breast cancer cases. Here we have the data on cancers detected at two successive screening rounds but not on interval cancers diagnosed between the rounds. Data on transition types and transition probabilities for a three-state model are given in Table 1.

Table 2 presents the estimates of parameters for a three-state Markov model assuming 100% sensitivity. The transition rate from the PCDP to the clinical phase is 0.53, the inverse of which gives an estimate of 1.90 (1.18–4.86) years for the mean sojourn time.

3. The Five-State Markov Model

3.1 *Model Specification*

Without loss of generality, a three-state Markov process can be extended to a generalized Markov process with state space $\Omega = \{0, 1, 2\ldots, k, k+1, \ldots, 2k\}$, where 0 represents normal, $1, 2, \ldots, k$ represent disease states in the PCDP, and $k+1, \ldots, 2k$ represent disease states in the clinical phase. For simplification, we only consider the five-state Markov model with $k = 2$. The first model is related to regional lymph node spread of breast cancer. Five states for this model are defined as follows: no disease (0), PCDP without lymph node involvement (1), PCDP with lymph node involvement (2), clinical phase without lymph node involvement (3), and clinical phase with lymph node involvement (4). Similarly, the second five-state progressive model in relation to tumor size can be formulated based on tumor size dichotomized by <2 cm and ≥2 cm.

The intensity matrix for the five-state model according to the above definition is

$$\begin{array}{c} \\ 0 \\ 1 \\ 2 \\ 3 \\ 4 \end{array}\!\!\begin{array}{c} \begin{array}{ccccc} 0 & 1 & 2 & 3 & 4 \end{array} \\ \begin{pmatrix} -\lambda_1 & \lambda_1 & 0 & 0 & 0 \\ 0 & -(\lambda_2+\lambda_3) & \lambda_2 & \lambda_3 & 0 \\ 0 & 0 & -\lambda_4 & 0 & \lambda_4 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix} \end{array}, \tag{5}$$

where λ_j ($j = 1, 2, 3, 4$) in the above matrix represents transition rates between states. States 3 and 4, similar to the clinical phase in a three-state model, are defined as absorbing states. The derivation of transition probabilities for a five-state model is similar to that for a three-state model. The intensity matrix and transition probabilities for the five-state model in relation to tumor size are identical to the above five-state model based on regional lymph node spread.

3.2 *Reparameterization*

The derivation of the likelihood function for a five-state model is identical to that for a three-state model. However, while more states are defined, more empirical data are required to estimate parameters. This is particularly difficult for data without interval cases. Accordingly, convergence of estimating parameters for a five-state model could not be achieved without the adjustment. We therefore propose a reparameterization procedure in conjunction with external information on the proportion of node negative cases for a five-state Markov model. The procedure is as follows:

(a) Suppose the transition rate from PCDP to clinical phase, say q, can be estimated from a three-state Markov model. The formula for the expected proportion of the transition from preclinical node negative to clinical node negative during time t is the probability of surfacing to clinical node negative before progressing to preclinical node positive divided by the probability of becoming either clinical node negative or clinical node positive, i.e.,

Table 1
Number of transitions, transition history, and transition probabilities by detection mode for a three-state Markov model

Detection mode	Transition history	Number	Transition probability
	1. Prevalent Screen		
Negative cases	$(0 \to 0, v_m, x_m = 0)$	2598	$P_{00}(v_m)/P_{00}(v_m) + P_{01}(v_m)$
Positive cases	$(0 \to 1, v_m, x_m = 1)$	31	$P_{01}(v_m)/P_{00}(v_m) + P_{01}(v_m)$
	1. Second Screen		
Negative cases	$(0 \to 0, t_{2i} - t_{1i}, y_{2i} = 0)$	572	$P_{00}(t_{2i} - t_{1i})$
Positive cases	$(0 \to 1, t_{2i} - t_{1i}, y_{2i} = 1)$	3	$P_{01}(t_{2i} - t_{1i})$

$$\begin{aligned}
&\text{E(preclinical } N(-) \to \text{clinical } N(-)) \\
&= \frac{\int_0^t \lambda_3 e^{-\lambda_3 s} e^{-\lambda_2 s} ds}{\int_0^t q e^{-qv} dv} \\
&= \frac{\lambda_3 \left\{1 - e^{-(\lambda_2+\lambda_3)t}\right\}}{(1 - e^{-qt})(\lambda_2 + \lambda_3)} \\
&= \frac{\lambda_3 \left\{1 - e^{-(\lambda_2+\lambda_3)t}\right\}}{B(\lambda_2 + \lambda_3)}, \qquad (6)
\end{aligned}$$

where $B = 1 - e^{-qt}$.

Suppose the proportion of clinically diagnosed tumors that are node negative, say p, can be obtained from clinical experience. Then, letting the observed equal the expected, E(preclinical $N(-) \to$ clinical $N(-)$), an auxiliary equation in relation to λ_2 and λ_3 is

$$p = \frac{\lambda_3 \left\{1 - e^{-(\lambda_2+\lambda_3)t}\right\}}{B(\lambda_2 + \lambda_3)}. \qquad (7)$$

(b) The relationship between λ_2 and λ_3 can be reparameterized by letting

$$\theta = \frac{\lambda_2}{\lambda_3}, \qquad \lambda_2 = \lambda_3 \theta. \qquad (8)$$

Substitution of (8) into (7) and taking the logarithm of both sides gives

$$\lambda_3 = \frac{-\log\{1 - p \times B \times (1 + \theta)\}}{(1 + \theta) \times t}. \qquad (9)$$

Replacing λ_2 and λ_3 in the transition probabilities to preclinical node negative and preclinical node positive in the likelihood function of a five-state model by (8) and (9) yield three equations in these parameters, i.e., λ_1, λ_4, and θ.

The bottom panel of Table 2 shows estimates of parameters for a five-state model with respect to regional lymph node spread. Since explicit estimation of λ_1 and λ_4 is unstable due to high correlation between λ_1 and λ_4, we constrain the preclinical incidence rate for the five-state model to be that of the three-state model. Thus, the preclinical incidence rate, λ_1, is constrained to a constant value of 0.0057 (see Table 2) when θ and λ_4 are estimated.

In addition to the constraint for λ_1, estimation of parameters, as pointed out earlier, requires reparameterization and auxiliary information on the proportion of clinically de-

Table 2
Results of estimation of transition rates for three-state and five-state models

Parameters	Estimates	95% CI
	1. Three-State Model	
(1) Assuming 100% sensitivity		
λ_1, no disease to preclinical	0.0057	0.0026–0.0088
λ_2, PCDP to clinical phase (MST)	0.5250 (1.90)	0.2057–0.8443
(2) Simultaneous estimation of λ_1, λ_2 and sensitivity		
λ_1, no disease to preclinical	0.0056	0.0023–0.0089
λ_2, PCDP to clinical phase (MST)	0.5017 (1.99)	0.1403–0.8630
Sensitivity	0.9476	0.5111–1.0000
	2. Five-State Model Related to Regional Lymph Node Spread	
λ_1, no disease to preclinical	0.0057	—
λ_2, preclinical $N(-)$ to preclinical $N(+)$	0.3940	0.3034–0.6393
λ_3, preclinical $N(-)$ to clinical $N(-)$	0.3380	0.2185–0.4353
λ_4, preclinical $N(+)$ to clinical $N(+)$	1.1149	0.8758–1.5523
θ, relative rate between λ_2 and λ_3	1.1657	0.4402–2.8238

Table 3
Comparison of estimated results between a three-state Markov model without interval cases and the model of Duffy et al. (1995) for age groups 50–59 and 60–69 from the Swedish Two-County Trial

	Age groups	λ_1	λ_2	MST
Three-state model without interval cases	50–59	0.00150 (0.0011–0.00207)	0.3020 (0.1883–0.4845)	3.31 (2.06–5.31)
	60–69	0.0024 (0.00182–0.00313)	0.2610 (0.1826–0.3729)	3.83 (2.68–5.5)
Duffy et al. (1995)	50–59	0.00150 (0.0014–0.0016)	0.3012 (0.2703–0.3401)	3.32 (2.94–3.70)
	60–69	0.0024 (0.0022–0.0026)	0.2610 (0.2398–0.2900)	3.83 (3.45–4.17)

tected breast cancer cases without node involvement. As the estimate of MST from the three-state Markov chain model for female relatives of breast cancer index cases is comparable to that for women aged 40–49 years in the Two-County Trial, we use the observed results in that study to estimate the proportion of clinically diagnosed node negative tumor. In the Two-County Trial, we estimated this proportion (p in equation [7]) as 0.546. This proportion is applied to equation (9) between λ_3 and θ. Results in Table 2 show that breast tumors with regional lymph node spread in the PCDP are 3.3 ($\lambda_4/\lambda_3 = 1.11/0.34$) times more likely to surface to the clinical phase than those without regional lymph node spread. A similar result is observed for tumor size (data not shown).

4. Model Diagnostics

For internal validation, we compare the observed with expected cases for a three-state Markov model. The absence of a significant difference between both ($x^2_{(2)} = 0.29, p = 0.8365$) suggests a good fit for this model.

To further validate whether these models are valid, an external validation is performed by using data for age groups 50–59 and 60–69 years from the Swedish Two-County Trial. One way is to use the model of Duffy et al. (1995) to estimate transition parameters to assess whether dispensing with the interval cancers has caused bias. Table 3 shows that estimates based on our three-state model dispensing with the requirement of interval cancers are very close to those from the model of Duffy et al. (1995), which took interval cancers into consideration. The alternative is to estimate parameters using the Two-County Trial data excluding interval cancers. The predicted interval cancers may then be calculated and compared with the observed. Results in Table 4 show that the predicted numbers of interval cancers for both age groups are close to the observed. There is no significant difference between the predicted and observed.

5. Discussion

This study demonstrates the feasibility of using Markov models to estimate transition rates for the natural history of chronic disease only based on prevalent and incident screen-detected cases without interval cases.

Nonetheless, there are three limitations in this study. First, the precision of estimates from the present models is poorer than that from the previous Markov models taking account of interval cancers. Although point estimates are very similar between both models, interval estimation for all parameters is much narrower using the Duffy et al. model (1995) (Table 3). However, this suggests that interval cases may only improve the aspect of precision rather than the point estimate.

Second, in the context of screening, as the efficacy of screening might be also affected by sensitivity, the results above use the assumption that sensitivity is 100%, which may of course be wrong. We therefore attempted an analysis that simultaneously estimated sensitivity together with the transition rates based on two rounds of screen with a regular interscreening

Table 4
The external validation of a three-state model and a five-state model related to lymph node spread using the Swedish Two-County Trial data

Age groups	Negative cases since last negative screen	Predicted interval cancers[a]	Observed interval cancers
1. A Three-State Markov Model			
Aged 50–59			
Prevalent screen	21,457	28.40	29
Second screen	18,731	24.79	22
Aged 60–69			
Prevalent screen	20,395	38.25	47
Second screen	16,372	30.70	22
2. A Five-State Markov Model			
Aged 50–59			
Prevalent screen	21,457		
Node (−)		15.29	16
Node (+)		9.95	12
Second screen	18,731		
Node (−)		13.35	9
Node (+)		8.69	12
Aged 60–69			
Prevalent screen	20,395		
Node (−)		22.71	28
Node (+)		11.43	16
Second screen	16,372		
Node (−)		18.07	13
Node (+)		9.10	9

[a] Screening interval = 2.75 years.

interval, say x, as in the above example of breast cancer screening. Taking sensitivity (S) into account, the expected screen-detected cases for prevalence screen (F_{e_A}) is

$$N_A \times S \times \frac{P_{01}(v_A)}{P_{00}(v_A) + P_{01}(v_A)},$$

where N_A represents the number of attendants given a specific age at first screen denoted by v_A. The expected number of the second screen (L_e) is

$$\left\{ n_2 \times P_{01}(x) + F_0 \times \frac{1-S}{S} \times P_{11}(x) \right\},$$

where n_2 represents the number of attendants at the second screen and F_0 ($= \Sigma F_{e_A}$) represents a total of breast cancers at the first screen. The $(1-S)/S$ in the equation is due to the fact that the true number of cancers at the first screen is the observed number divided by the sensitivity, and the number of such cancers missed at the first screen is the true number of cancers multiplied by $(1-S)$. Equating the expected with the observed, as in Section 2.2, yields estimated results as shown in Table 2. The sensitivity is estimated as 94.8% (95% CI: 51.1%–100%). There is no substantial difference between the estimate of MST assuming 100% sensitivity and that simultaneously estimating sojourn time and sensitivity. A high estimate of sensitivity may be due to a combination of physical examination, mammography, and ultrasound examination employed in this study.

Third, it could be argued that the exponential distribution from birth to entering preclinical state may be unrealistic. To test this assumption, one may use a nonhomogeneous Markov model to estimate the preclinical incidence as a function of age, but rare cases in this study preclude us from doing this. However, we have found in the past that the estimation is robust to the assumption of constant lifetime incidence (Tabar et al., 1995). Another justification for upholding this assumption is that modeling the occurrence of interval cancers usually works well with Poisson process, which, in essence, assumes a constant incidence (Day and Walter, 1984; Paci and Duffy, 1991). Nonetheless, the future research should be carried out to test this assumption based on a nonhomogeneous Markov model.

In conclusion, although variance estimates based on our models are less precise than those obtained when interval cases are available, these models are tailored to estimate sojourn time without interval cancers and can do so with accuracy.

Résumé

L'estimation du temps de séjour en période de détection préclinique dans le dépistage d'une maladie, ou des taux de transitions pour l'histoire naturelle de maladies chroniques, s'appuie habituellement sur des observations intermédiaires (c'est-à-dire diagnostiquées entre les examens de dépistage). Cependant, il peut s'avérer difficile d'obtenir de telles observations dans des pays en voie de développement à cause de systèmes de registre incomplets, ou de difficultés dans le suivi. Pour contourner ce problème, nous proposons trois modèles de Markov pour estimer les paramètres sans observation intermédiaire. Un modèle de Markov à Trois états, un modèle de Markov à cinq états, lié au développement régional des nodules lymphatiques, et un modèle de Markov à cinq états qui a trait à la taille de la tumeur, sont appliqués à des données de dépistage de cancer du sein chez des femmes parentes de cancéreuses du sein à Taiwan. Les résultats issus d'un modèle de Markov à trois états donnent un temps de séjour moyen (TSM) de 1,9 (IC 95%: $1,18 - 4,86$) années dans le groupe à risque élevé. La validation de ces modèles à partir de données de dépistage de cancer du sein pour les tranches d'âge 50–59 et 60–69 dans l'étude Suédoise des Deux Contés montre que les estimations obtenues par le modèle de Markov à trois états qui n'utilise pas les observations intermédiaires sont très proches de celles du modèle de Markov qui les prend en compte. Dans le cas des modèles de Markov à cinq états, une procédure de reparamétrage qui utilise l'information issue de cancers détectés cliniquement est réalisée pour l'estimation des paramètres pertinents. Le bon ajustement des validations interne et externe démontre qu'il est possible d'utiliser ces modèles pour estimer les paramètres qui nécessitaient auparavant la connaissance de cancers intermédiaires. Cette méthode peut être appliquée à d'autres données de dépistage dans lesquelles on ne dispose pas d'observations intermédiaires.

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