

Module 4 Temporal Natural History Model in Cancer and Chronic Disease Screening

4.1 The rationale to elucidate the disease natural history

(A) The purpose of elucidation of disease natural history is to construct a pseudo-control group as in the RCT

(B) Applications of natural history

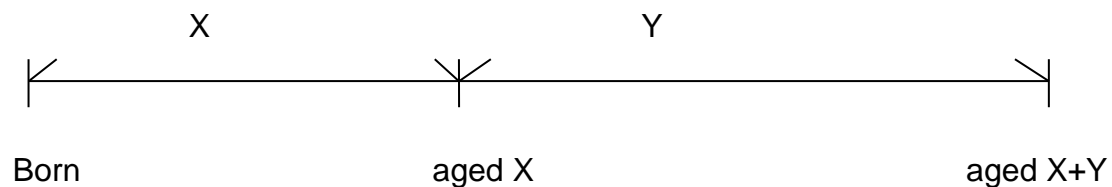
- (a) Estimation of effectiveness and sample size determination before RCT
- (b) Screening interval determination
- (c) Age at start of termination of screening
- (d) Treatment-efficacy
- (e) Cost-effectiveness analysis

(C) Opportunistic screening dominates over mass screening

- (a) Calibrating the survival benefit of screen-detected cancers (Chen et al., JASA, 2012)
- (b) Case-cohort design for the disease natural history (Chen et al., *Stat Med*, 2004)

4.2 Temporal natural history, sensitivity, and specificity

4.2.1 Temporal natural history



Three key variables

X (fixed for each subject): Age at time of entry into the PCDP

Y (fixed for each subject): Dwelling time (Sojourn time) in the PCDP

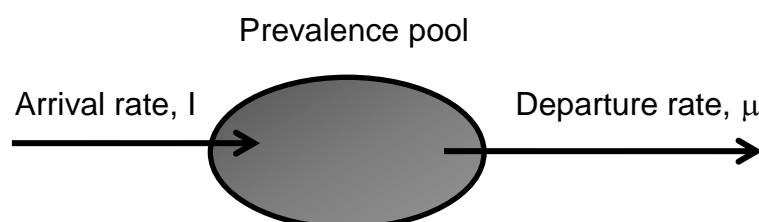
A (random variables): Age at participating screening

$X \leq A < X+Y \rightarrow$ Screen-detected case

$A \geq X+Y \rightarrow$ Clinically- detected case

4.2.2 P/I (Prevalence/Incidence) ratio (Chang et al, *Preventive Medicine* 2000)

(1) **Prevalence Pool**: It is customary to use prevalence pool to denote this concept.



Suppose a population with size N consists of m prevalent diabetes mellitus (DM) cases. In a cross-sectional survey, prevalence (P) is estimate as

$$P = \frac{m}{N}$$

In a steady population (i.e. inflow = outflow), we have the following balance equation in a small time inter (Δt)

$$I \times (N - m) \times \Delta t = \mu \times m \times \Delta t$$

$$\frac{m}{N-m} = \frac{I}{\mu}$$

If $N \gg m$, $N - m \cong N$

$$P \text{ (Prevalence)} = \frac{I \text{ (Incidence)}}{\mu}$$

$$\frac{P}{I} = \frac{1}{\mu} = \bar{D} \quad (\text{Average Duration})$$

(2) Usefulness: This indicator is used to denote the average duration of disease

If \bar{D} is estimable, μ can be estimated. We can estimate the survival function $S(t)$ by applying an exponential distribution with the parameter of μ .

$$S(t) = e^{-\mu t}$$

Ex. In an example of type 2 DM, $\bar{D}=8$ years, $\hat{\mu} = 0.125$

$$S(t) = e^{-0.125 \times t}$$

(A) The probability of surviving during five years or a type 2 DM patients is

$$S(t) = e^{-0.125 \times 5} = 0.535$$

(B) The mean time to have half of surviving population

$$t_M = \frac{0.693}{0.125} = 5.544 \text{ years}$$

4.2.3 Screening performance

(A) Basic characteristic of screening performance

		True disease, Y	
		1 (+)	0 (-)
Test X	1 (+)	a	b
	0 (+)	c	d

$$Sen(\text{Sensitivity}) = P(X = 1 | Y = 1) = \frac{a}{a + c}$$

$$Sp(\text{Specificity}) = P(X = 0 | Y = 0) = \frac{d}{b + d}$$

$$PPV(\text{Positive Predictive Value}) = P(Y = 1 | X = 1) = \frac{a}{a + b}$$

$$NPV(\text{Negative Predictive Value}) = P(Y = 0 | X = 0) = \frac{d}{c + d}$$

$$FN(\text{False negative}) = P(X = 0 | Y = 1) = \frac{c}{a + c}$$

$$FP(\text{False positive}) = P(X = 1 | Y = 0) = \frac{b}{b + d}$$

(B) Bayesian Theorem for clinical reasoning

Let Y represent true disease status (Y=1: Disease Y=0: non-disease) specified by a binomial distribution. Let X represent the result of test (X=1: positive; X=0:negative) also specified by a binomial distribution . The positive predictive value (PPV) is regarded as posterior probability

$$P(Y=1|X=1) = P(Y=1) \times P(X=1|Y=1)/(P(X=1))$$

Epidemiological viewpoint: PPV \propto Prevalence Sensitivity

Statistical viewpoint: Posterior \propto Prior \times likelihood

$P(X=1)$ is defined as marginal distribution that is irrelevant to true disease status and can be decomposed by total law of probability

$$\begin{aligned} P(X=1) &= P(Y=1) P(X=1|Y=1) + P(Y=0) P(X=1|Y=0) \\ &= P(Y=1) P(X=1|Y=1) + [1 - P(Y=1)] P(X=1|Y=0) \\ &= \text{Prevalence} \times \text{sensitivity} + (1 - \text{prevalence}) \times (1 - \text{specificity}) \end{aligned}$$

In terms of statistical viewpoint, $P(X=1)$ is also called “normalizing constant” that renders the posterior probability range between 0 and 1. Note that the likelihood is not a probability and its value may be higher than 1.

The posterior probability can be also expressed by posterior odds

$$\begin{aligned} &P(Y=1|X=1) / (P(Y=0|X=1)) \text{ \{posterior odds\}} = \\ &[P(Y=1)/P(Y=0)] \times [P(X=1|Y=1)/(P(X=1|Y=0))] \\ &\text{\{prior odds\}} \quad \text{\{sensitivity/(1-specificity=false positive)\}} \end{aligned}$$

Posterior Odds / prior odds = likelihood ratio (=sensitivity/(1-specificity))

Prevalence and HPV test

In a population with an HIV prevalence of 0.001

		HIV +	HIV –	
Test	+	95	1998	2093
Test	-	5	97902	97909

100 99900 100,000

Sen=0.95 Spe=0.98, LR=47.5, PPV=0.0454, Posterior odds =0.048;

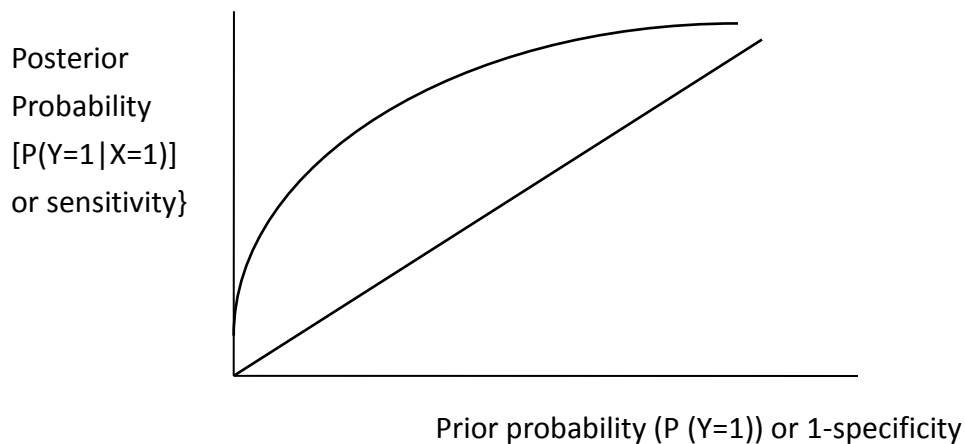
(D) Receiver operating characteristics (ROC)

The ROC curve is a very useful indicator for assessing the accuracy of clinical diagnosis. The larger the area under curve AUC), the more accurate the test is.

The curve is delineated by the following curve

Y-axis: Posterior probability or sensitivity

X: Prior probability



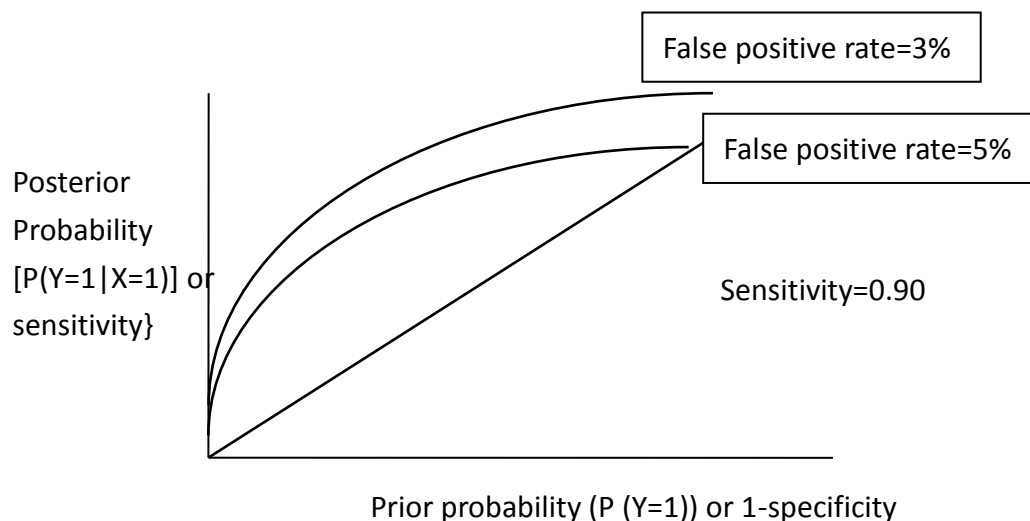
$P(Y=1|X=1)$ is highly dependent on $P(Y=1)$. $P(Y=1) \uparrow \rightarrow P(Y=1|X=1) \uparrow$.

When $P(Y=1|X=1) = P(Y=1)$, the posterior probability is equivalent to the prior probability (the angle of the linear line is 45°), the test is useless.

The ROC curve is also used to identify the optimal cutoff given the test is based on a continuous variable such as cholesterol, hypertension etc. The optimal cutoff

Clinical implication for false-Positive rate

A good test given the constant risk and cost should be characterized by high true-positive rate and low false-positive ,



False-positive rate $P(X=1|Y=1) \downarrow P(Y=1|X=1) \uparrow$

(a) When $P(Y=1)$ is very low we have to find a test with very low false positive rate in order to enhance $P(Y=1|X=1)$.

Ex: Clinical tests for detecting coronary artery disease

The prior probability of having coronary-artery disease is low and therefore non-invasive test is not very useful because its false positive rate ranges from 0.20 to 0.50. We have to consider aggressive test such as coronary arteriogram .

(b) When $P(Y=1)$ is high, the influence of false-positive rate is not so crucial.

Ex: The patients diagnosed as angina has higher probability of getting

coronary artery disease. The prior probability is around 90% or more. The posterior probability is 99% based on myocardial scan and also 98% based on exercise ECG. The difference is very minor.

(E) Sensitivity in screening

Test sensitivity

Incidence/Expected Incidence Ratio

$$Sen = 1 - \frac{I_o}{I_E}$$

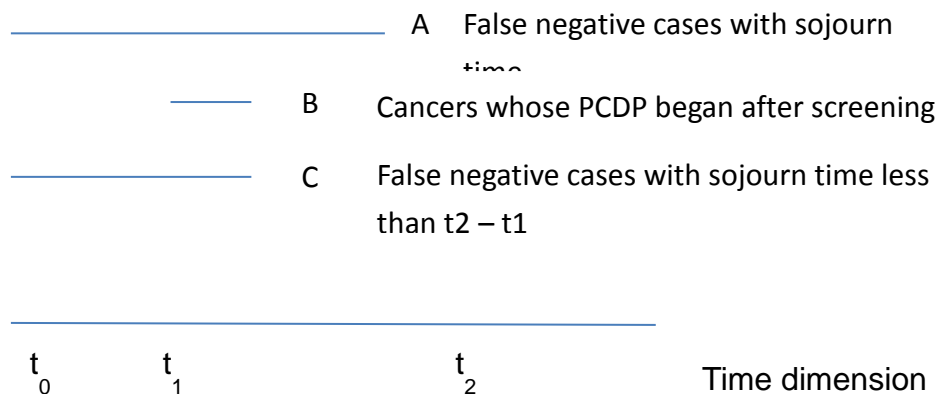
(If all of interval cases are from false negative cases)

Program sensitivity

$$\text{Sensitivity} = \frac{a}{(a+c^*)}$$

c^* is obtained as the number of cases arising clinically in a short time interval after the screen

Sojourn time of breast cancer in relation to false negative rate estimation using interval cancers in a set time period



t_0 : The beginning of PCDP (preclinical detectable phase) for A and B

t_1 : Time of screen

t_2 : Time limit for definition of missed cancers

Program sensitivity

Algebra-derived for program sensitivity

① Newly incident cases

$$I \times \int_0^T F(t) dt$$

where I is the incidence of a control group; and

$F(t)$ is the cumulative distribution function of sojourn time

② False negative cases from previous screening

$$I \times (1 - S) \times \int_0^T (1 - F(t)) dt$$

The observed interval cancer rate

$$I_t = ① + ② = I \times (1 - S) \times T + I \times S \times \int_0^T F(t) dt$$

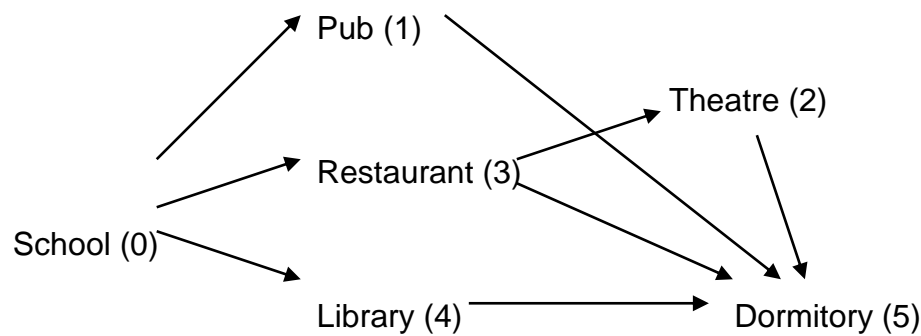
$$\hat{S} = \frac{1 - \frac{I_t}{I}}{1 - \left[\frac{1}{T} \times \left(\int_0^T F(t) dt \right) \right]}$$

4.3 Construct a Markov Chain Model: A simple illustration

Suppose one wants to use a Markov chain model to describe the life of a student after school per day. He distributes questionnaires to ask the possible places where students will go after school, also the time of staying in the place. In his investigation, pub, theatre, restaurant, library, and dormitory are frequently places to go after school. In order to construct a Markov Chain, the state space is the first thing to define.

In this case, we treat each place as a state, and accordingly have a

6-state Markov chain with state space, $\Omega=\{0: \text{school}, 1: \text{pub}, 2: \text{theatre}, 3: \text{restaurant}, 4: \text{library}, \text{and } 5: \text{dormitory}\}$.



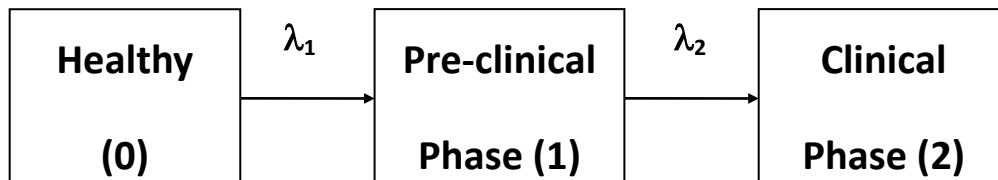
4.4 Markov Process and Disease Natural History

The multi-state model had been widely used to describe the natural history model of disease. The applications of multi-state natural history model are several-fold. First, 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. Second, the natural history model can be used to compare different screening frequencies and also to evaluate screening programs without a randomized control group (Chen et al, 1997; Chen et al, 1998; Chen et al, 2004). Third, using the stochastic model can calibrate the survival benefit of screen-detected cancers related to potential biases and measurement error.

4.4.1 A three-state Markov model for breast cancer (Chen et al, *Biometrics* 2000)

Chen et al firstly applied the three-state and five-state Markov models to the screening data for breast cancer in a Taiwanese screening program under

the scenario when interval cancer was not available in the early stage of program. In their model, they modeled 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 0 represents no disease, 1 the preclinical detectable phase (PCDP) and 2 the clinical phase (CP). The CP in this model is an absorbing state in a language of Markov process because the natural history cannot be estimated beyond diagnosis, due to the effect of therapy.



Since there are only three states (0="no disease", 1="preclinical phase" and 2="clinical phase") in Markov chain model, the transition matrix (Q) is:

$$Q = \begin{matrix} & \begin{matrix} \text{State} \\ 0 & 1 & 2 \end{matrix} \\ \begin{matrix} 0 \\ 1 \\ 2 \end{matrix} & \begin{pmatrix} -\lambda_1 & \lambda_1 & 0 \\ 0 & -\lambda_2 & \lambda_2 \\ 0 & 0 & 0 \end{pmatrix} \end{matrix} \quad (4-1)$$

λ_1 and λ_2 represent the preclinical incidence rate and the transition rate from the PCDP to the CP. The inversion of λ_2 is the mean sojourn time.

According to $P_t = A \text{diag}\{\exp(dt)\} A^{-1}$ (where A is the matrix of eigenvectors from Q) the transition probability matrix (P_t) is equal to:

$$\begin{array}{c}
\text{State} \\
0 \quad 1 \quad 2 \\
P_t = \text{State} \begin{pmatrix} P_{00} & P_{01} & P_{02} \\ 0 & P_{11} & P_{12} \\ 0 & 0 & 1 \end{pmatrix} = \begin{pmatrix} e^{-\lambda_1 t} & \frac{\lambda_1(e^{-\lambda_2 t} - e^{-\lambda_1 t})}{(\lambda_1 - \lambda_2)} & 1 - \frac{\lambda_1 e^{-\lambda_2 t} - \lambda_2 e^{-\lambda_1 t}}{(\lambda_1 - \lambda_2)} \\ 0 & e^{-\lambda_2 t} & 1 - e^{-\lambda_2 t} \\ 0 & 0 & 1 \end{pmatrix}
\end{array} \quad (4-2)$$

where the diagonal component in P_t is a vector of eigenvalues, $d=(-\lambda_1, \lambda_2, 0)$, which is identified by solving $dI-Q=0$ (I is 3×3 unit matrix).

This means, for example, that the probability of progressing from no disease to the PCDP ($0 \rightarrow 1$) during a time period of length t is $\frac{\lambda_1(e^{-\lambda_2 t} - e^{-\lambda_1 t})}{(\lambda_1 - \lambda_2)}$

Epidemiological aspect

λ_1 : annual incidence rate

λ_2 : annual transition rate (1/mean sojourn time)

P_{01} : Cumulative incidence of disease in the PCDP from normal

P_{02} : Cumulative incidence of disease in the CP from normal

P_{12} : Cumulative incidence of disease in the CP from the PCDP

Likelihood function

The likelihood function based on the prevalent screen in a screening cohort consisting N individuals is:

$$L_1(.) = \prod_{m=1}^N \left(\frac{P_{01}(v_m)}{P_{00}(v_m) + P_{01}(v_m)} \right)^{x_m} \left(\frac{P_{00}(v_m)}{P_{00}(v_m) + P_{01}(v_m)} \right)^{1-x_m} \quad (4-3)$$

where v_m represents age at first screen for m^{th} subject, $x_m=1$ when m^{th} subject is detected as positive cases, $x_m=0$ for otherwise.

Suppose there were $r-1$ rounds of subsequent screens, the likelihood function based on them was:

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

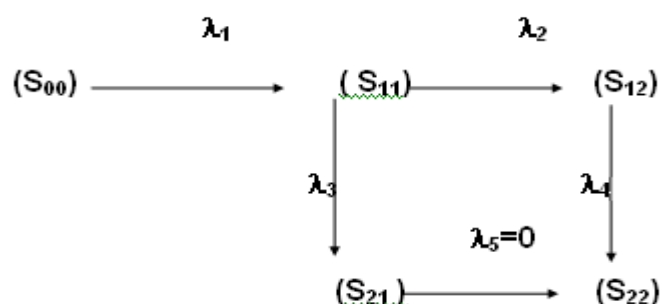
where j represent the j^{th} round of screen ($j=2, \dots, r$), $t_{ji} - t_{(j-1)i}$ represents inter-screening interval between $(j-1)^{\text{th}}$ screen and j^{th} screen for i^{th} subject, n_j represents number of attendants in the j^{th} screen, $y_{ji} = 1$ when i^{th} subject enters the PCDP during $t_{ji} - t_{(j-1)i}$, $y_{ji} = 0$ otherwise. The total likelihood function, say, $L(.)$ will be the product of $L_1(.)$ and $L_2(.)$.

Table 4-1 Numerical Results from the Swedish Two-County Trial

Age group	40-49	50-59	60-69
Parameters			
λ_1 : no disease to preclinical phase	0.00122 (0.0012-0.0013)	0.00176 (0.0017-0.0018)	0.00263 (0.0025-0.0028)
λ_2 : pre-clinical to clinical phase	0.488 (0.420-0.556)	0.320 (0.295-0.345)	0.275 (0.253-0.297)
Mean Sojourn Time ($1/\lambda_2$)	2.06 (1.79-2.38)	3.13 (2.90-3.39)	3.66 (3.48-3.86)

4.4.2 Five-state Markov model with regional lymph node spread or tumour size for breast cancer (Chen et al, *Biometrics* 2000)

A stochastic model with three transient (S_{00} , S_{11} and S_{12}) and two absorbing states (S_{21} , S_{22}) and transition rates ($\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5$) representing either node status or tumour size ($< 2\text{cm}$, $\geq 2\text{cm}$)



(S_{00}) : Normal

(S_{11}) : preclinical phase, without nodal involvement (or tumour size $< 2\text{cm}$)

(S_{12}) : preclinical phase, with nodal involvement (or tumour size $\geq 2\text{cm}$)

(S_{21}) : clinical phase, without nodal involvement (or tumour size $< 2\text{cm}$)

(S_{22}) : clinical phase, with nodal involvement or (tumour size $\geq 2\text{cm}$)

		States				
		no	pre-clinical		clinical	
		disease	N(-)	N(+)	N(-)	N(+)
		0	1	2	3	4
Q =	0	$-\lambda_1$	λ_1	0	0	0
	1	0	$-(\lambda_2 + \lambda_3)$	λ_2	λ_3	0
	2	0	0	$-\lambda_4$	0	λ_4
	3	0	0	0	$-\lambda_5$	λ_5
	4	0	0	0	0	0

N(-): without node involvement; N(+): with node involvement

In realisation of breast cancer screening, λ_5 should be constrained as 0.

Given the intensity matrix, the derivation of transition probabilities is straightforward. Referring to the previous section, the procedure used in the

three state Markov chain model to derive the transition probabilities is also applicable to the extension of the Markov chain model in this section. The transition probabilities are

$$\begin{array}{c}
 \text{States} \\
 \begin{array}{ccccc}
 & \text{no} & \text{pre-} & & \\
 & \text{disease} & \text{clinical} & \text{clinical} & \\
 & & \text{N(-)} & \text{N(+)} & \text{N(-)} & \text{N(+)} \\
 & 0 & 1 & 2 & 3 & 4 \\
 \begin{array}{c} 0 \\ 1 \\ 2 \\ 3 \\ 4 \end{array} & \left(\begin{array}{ccccc}
 p_{00} & p_{01} & p_{02} & p_{03} & p_{04} \\
 0 & p_{11} & p_{12} & p_{13} & p_{14} \\
 0 & 0 & p_{22} & p_{23} & p_{24} \\
 0 & 0 & 0 & p_{33} & p_{34} \\
 0 & 0 & 0 & 0 & 0
 \end{array} \right)
 \end{array}
 \end{array} \quad (4-5)$$

where

$$\begin{aligned}
 p_{00} &= e^{-\lambda_1 t}, \quad p_{01} = \frac{e^{-(\lambda_2 + \lambda_3)t} - e^{-\lambda_1 t}}{a}, \quad p_{02} = \frac{(b-a) \times e^{-\lambda_1 t} - b \times e^{-(\lambda_2 + \lambda_3)t} + a \times e^{-\lambda_4 t}}{ad} \\
 p_{03} &= \frac{(c-a) \times e^{-\lambda_1 t} - c \times e^{-(\lambda_2 + \lambda_3)t} + a \times e^{-\lambda_5 t}}{ae} \\
 p_{04} &= 1 + \frac{(ad + af + df - bf - cd - adf) \times e^{-\lambda_1 t}}{adf} + \frac{(bf + cd - df) \times e^{-(\lambda_2 + \lambda_3)t}}{adf} - \frac{e^{-\lambda_4 t}}{d} - \frac{e^{-\lambda_5 t}}{f} \\
 p_{11} &= e^{-(\lambda_2 + \lambda_3)t}, \quad p_{12} = \frac{b \times (e^{-\lambda_4 t} - e^{-(\lambda_2 + \lambda_3)t})}{d}, \quad p_{13} = \frac{c \times (e^{-\lambda_5 t} - e^{-(\lambda_2 + \lambda_3)t})}{f} \\
 p_{14} &= 1 + \frac{(bf + cd - df) \times e^{-(\lambda_2 + \lambda_3)t}}{df} - \frac{b \times e^{-\lambda_4 t}}{d} - \frac{c \times e^{-\lambda_5 t}}{f} \\
 p_{22} &= e^{-\lambda_4 t}, \quad p_{23} = 0, \quad p_{24} = 1 - e^{-\lambda_4 t} \\
 p_{33} &= e^{-\lambda_5 t}, \quad p_{34} = 1 - e^{-\lambda_5 t}, \\
 a &= \frac{(\lambda_1 - \lambda_2 - \lambda_3)}{\lambda_1}, \quad b = \frac{\lambda_1 - \lambda_4}{\lambda_1}, \quad c = \frac{\lambda_1 - \lambda_5}{\lambda_1} \\
 d &= \frac{(\lambda_1 - \lambda_4)(\lambda_2 - \lambda_3 - \lambda_4)}{\lambda_1 \lambda_2}, \quad f = \frac{(\lambda_1 - \lambda_5)(\lambda_2 - \lambda_3 - \lambda_5)}{\lambda_1 \lambda_3}
 \end{aligned}$$

Note that the summation of transition probabilities in each row of the transition matrix mentioned above is equal to unity, eg. $P_{00} + P_{01} + P_{02} + P_{03} + P_{04} = 1$.

Likelihood function for a case in the five-state Markov model (M-N model)

Suppose one woman has screening history as follows:

- (i) first screen at age 45 -(no disease (0), 540 months),
- (ii) 2nd and 3rd screen with two-year interval-(no disease (0), 24 months)
- (iii) diagnosed as interval cancer with node involvement between 3rd and 4th screen -(clinical cancer with node involvement (4), 14month)

The likelihood function for this individual is:

$$P_{00}(540) \times P_{00}(24) \times P_{00}(24) \times P_{04}(14)$$

1st screen second screen third screen interval cancers

The overall likelihood function is equal to the product of individual likelihood functions.

The Markov property that given the state at time t , the probability of any given state after time t is independent of the history before time t implies that probabilities of successive transitions in the same individuals can simply be multiplied in the likelihood function as if they were from different individuals. Thus, the likelihood function can be developed using the numbers of transitions between states as shown in the Table 4-2 for the Swedish Two-County trial. For illustration, the likelihood function for the age group 40-49 is given below

Table 4-2 Number of women randomized at 40-49 years old by detection mode, Two-County Trial

Age groups Detection mode and node status	40-49 Number	Transition history (Time, state ⁺)	Transition probabilities applied
1. First screen			
(1) Negative cases	18456	(540,0→0)	P ₀₀
(2) Prevalent cases			
-without nodal involvement	31	(540,0→1)	P ₀₁
-with nodal involvement	6	(540,0→2)	P ₀₂
(3) Interval cancers (between 1st and 2nd screen)			
-without nodal involvement	14	(TSL,0→3)	P ₀₃
-with nodal involvement	9	(TSL,0→4)	P ₀₄
2. Second screen			
(1) Negative cases	16396	(24,0→0)	P ₀₀
(2) Prevalent cases			
-without nodal involvement	35	(24,0→1)	P ₀₁
-with nodal involvement	10	(24,0→2)	P ₀₂
(3) Interval cancers (between 2nd and 3rd screen)			
-without nodal involvement	12	(TSL,0→3)	P ₀₃
-with nodal involvement	10	(TSL,0→4)	P ₀₄
3. Third screen			
(1) Negative cases	14437	(24,0→0)	P ₀₀
(2) Prevalent cases			
-without nodal involvement	30	(24,0→1)	P ₀₁
-with nodal involvement	6	(24,0→2)	P ₀₂
(3) Interval cancers (between 3rd and 4th screen)			
-without nodal involvement	15	(TSL,0→3)	P ₀₃
-with nodal involvement	10	(TSL,0→4)	P ₀₄

+TSL=time since last negative screen

Note that: in the model the actual times to occurrence of interval cancers are used.

The likelihood function for the first screen (Active Study Population, ASP)

The above transition probability matrix gives unconditional probabilities. We, however, need conditional probabilities at the first screen for the ASP because those found to be free of disease or to have preclinical disease at first screen are not from an entire cohort followed from birth: women with a previous (clinical) breast cancer were excluded from the trial. Thus the probability of being free of breast cancer and of having preclinical breast

cancer at the first screen should be conditional on having no clinical breast cancer between birth and first screen.

By this definition, the conditional probability of being free of disease(S_{00}) at first screen, Ψ_{00} , is given as:

$\Psi_{00} = \Pr[S_{00} \text{ at first screen conditional on the fact that there was no disease } (S_{00}) \text{ or preclinical disease only } (S_{11} \text{ or } S_{12}) \text{ between birth and the first screen}]$.

The conditional probabilities of prevalent disease without node involvement, Ψ_{11} and with node involvement, Ψ_{12} , at first screen are of the same essential form. In terms of transition probabilities, Ψ_{00} , Ψ_{11} and Ψ_{12} are

$$\begin{aligned}\psi_{00} &= \frac{P_{00}}{(P_{00} + P_{01} + P_{02})} \\ \psi_{11} &= \frac{P_{01}}{(P_{00} + P_{01} + P_{02})} \\ \psi_{12} &= \frac{P_{02}}{(P_{00} + P_{01} + P_{02})}\end{aligned}\tag{4-6}$$

Referring to the data in the form of Table 4-1, the likelihood function for first screen in the age group of 40-49, is equal to

$$L_{s_1(t_1)}(\lambda_1 \cdots \lambda_5) = (\psi_{00(t_1)})^{18456} (\psi_{11(t_1)})^{31} (\psi_{12(t_1)})^6\tag{4-7}$$

where $t_1 (=45)$ is average age at first screen.

The likelihood function for later screens

The likelihood function for later screens is based on the unconditional probabilities from the transition matrix (4-5). Since the screening interval was constant and the Markov property assumed to hold as mentioned earlier, the second and third screens may be aggregated as later screens. Accordingly, the probabilities of being disease free and of cancers without and with node involvement are P_{00} , P_{01} and P_{02} respectively. The likelihood function of later

screens in the age group of 40-49 is:

$$L_{s_2(t_2)}(\lambda_1 \cdots \lambda_5) = (P_{00(t_2)})^{30,833} (P_{01(t_2)})^{65} (P_{02(t_2)})^{16}$$

where $t_2 (=2)$ is screening interval

The likelihood function of interval cancers

Since the exact time of diagnosis is known for interval cancers, their probabilities should therefore be of becoming clinical at the time t_i rather than at some time before 0 and t_i . Since the model does not allow the probability of instantaneous transition from no disease to the CP (the transition between the transient states can be only to adjacent states), and since we wish to explicitly allow for the probability of both rapid and slow progression through the PCDP, we use our limit of accuracy, in this case one month, and further approximate the correct probability for interval cancers by the compound probability. Although it is technically possible to use the instantaneous rates in practice this leads to instability of estimation and precludes explicit modelling of both long and short preclinical times. Thus, the probabilities for interval cancers without node involvement (τ_{01}) and with node involvement (τ_{02}) are:

$$\tau_{01}(u_i) = P_{00}(u_i-1) P_{03}(1) + P_{01}(u_i-1) P_{13}(1) \text{ and}$$

$$\tau_{02}(u'_j) = P_{00}(u'_j-1) P_{04}(1) + P_{01}(u'_j-1) P_{14}(1) + P_{02}(u'_j-1) P_{24}(1)$$

where u_i and u'_j are time since last negative screen for interval cancers with and without node involvement, respectively

The likelihood function for interval cancers in the age group 40-49 is:

$$L_{s_3(u_i, u'_j)} = \prod_{i=1}^{41} \tau_{01}(u_i) \times \prod_{j=1}^{29} \tau_{02}(u'_j)$$

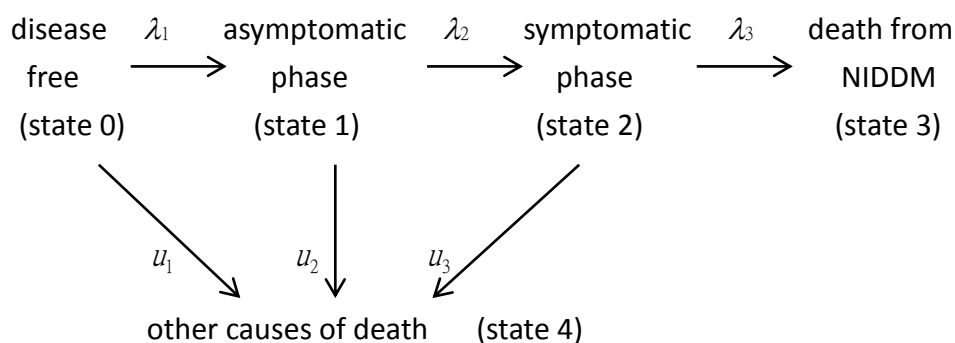
The derivation of the likelihood function for a five-state model is

particularly difficult for data without interval cases. Chen et al has proposed a reparameterization procedure in conjunction with external information on the proportion of node negative cases for a five-state Markov model to solve this issue (Chen et al, *Biometrics* 2000).

4.5 Examples

4.5.1 A Markov chain model to assess the efficacy of screening for non-insulin dependent diabetes mellitus (NIDDM)

The high prevalence and severe consequences of non-insulin dependent diabetes mellitus (NIDDM) in Taiwan calls for urgency to detect this disease in the asymptomatic phase. However, the efficacy of early detection of NIDDM is highly dependent on its natural history from the disease free, through the asymptomatic phase, symptomatic phase and death from NIDDM or other causes. In order to project the above progression, a five-state illness-and-death Markov chain model was proposed to estimate these transition parameters using data from two rounds of a blood sugar screening program for NIDDM in Puli, the middle area of Taiwan.



λ_1 : incidence of asymptomatic cases

λ_2 : transition rate from asymptomatic to symptomatic phase

λ_3 : hazard rate from symptomatic phase to death from NIDDM

u_1 : hazard rate from disease free to other causes of death

u_2 : hazard rate from asymptomatic phase to other causes of death

u_3 : hazard rate from symptomatic phase to other causes of death

Results showed that the annual incidence for asymptomatic NIDDM was 0.011 (95% CI: 0.0083–0.01379) and the average duration between the asymptomatic and symptomatic phases (called the sojourn time) is 8 years (95%CI: 5.74–11.29). The 10-year survival rate for asymptomatic NIDDM (79.35%) is better than that for symptomatic NIDDM (69.45%). Prediction of deaths from NIDDM was performed to assess how the efficacy of screening for NIDDM varied by different screening frequencies (annual, biennial, four-yearly and the control group). Results indicated there is no substantial difference in mortality reduction from NIDDM among the annual, biennial and four-yearly screening regimens. By contrast, a four-yearly screening regimen significantly reduced deaths from NIDDM by 40% (95% CI: 1%–62%). A long sojourn time and a substantial mortality reduction suggest that a four-yearly screening regime for NIDDM would be most effective and feasible in Taiwan.

Table 4-4 Results of the five-state Markov illness-and-death model

Parameters	Annual transition rate	95% CI
λ_1 (Disease free-Asymptomatic NIDDM)	0.01067	0.00826–0.01379
λ_2 (Asymptomatic NIDDM-Symptomatic NIDDM)	0.12418	0.08858–0.17409
λ_3 (Symptomatic NIDDM-Death from NIDDM)	0.02267	0.00687–0.07480
u_1 (Disease free-Other causes of death)	0.00093	0.00062–0.00140
$u_2 = u_3$ (Asymptomatic NIDDM or Symptomatic NIDDM-Other causes of death)	0.01378	0.00561–0.03384

4.5.2 Mover-Stayer Mixture Model-Phenotypic drift for breast cancer

A mover-stayer mixture model was applied to evaluate the proportion of tumour with potential of progression as follows:

A stayer is the tumour without potential of progression and the intensity transition matrix follow M_1 :

	no disease	Preclincial phase		Clinical phase	
		Grade 1 / 2	Grade 3	Grade 1 / 2	Grade3
	S_{00}	S_{11}	S_{12}	S_{21}	S_{22}
$M_1 =$	$\begin{pmatrix} -(\lambda_1 + \lambda_2) \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}$	$\begin{pmatrix} \lambda_1 \\ -\lambda_4 \\ 0 \\ 0 \\ 0 \end{pmatrix}$	$\begin{pmatrix} \lambda_2 \\ 0 \\ -\lambda_5 \\ 0 \\ 0 \end{pmatrix}$	$\begin{pmatrix} 0 \\ \lambda_4 \\ 0 \\ 0 \\ 0 \end{pmatrix}$	$\begin{pmatrix} 0 \\ 0 \\ \lambda_5 \\ 0 \\ 0 \end{pmatrix}$

A mover is the tumour with potential of progression and the intensity transition matrix follow M_2

	no disease	Preclincial phase		Clinical phase	
		Grade 1 / 2	Grade 3	Grade1 / 2	Grade3
	S_{00}	S_{11}	S_{12}	S_{21}	S_{22}
$M_2 =$	$\begin{pmatrix} -(\lambda_1 + \lambda_2) \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}$	$\begin{pmatrix} \lambda_1 \\ -(\lambda_4 + \lambda_3) \\ 0 \\ 0 \\ 0 \end{pmatrix}$	$\begin{pmatrix} \lambda_2 \\ \lambda_3 \\ -\lambda_5 \\ 0 \\ 0 \end{pmatrix}$	$\begin{pmatrix} 0 \\ \lambda_4 \\ 0 \\ 0 \\ 0 \end{pmatrix}$	$\begin{pmatrix} 0 \\ 0 \\ \lambda_5 \\ 0 \\ 0 \end{pmatrix}$

Building up the likelihood function in accordance with a mixture distribution from M_1 and M_2 enables one to estimate the proportion of tumours with potential of progression and transition rates

Table 4-5 Results from the two-county county trial

Age groups		40-49	50-59	60-69
Transition parameters & Mixing weight				
λ_1	no disease to preclinical grade 1/2	0.00096 (0.00082-0.00110)	0.00166 (0.00097-0.00235)	0.00227 (0.00192-0.00262)
λ_2	no disease to preclinical grade 3	0.000262 (0.00013-0.00039)	0.00011 (0.00000-0.05000)	0.00036 (0.00002-0.00070)
λ_3	preclinical grade1/2 to preclinical grade 3	0.0630 (0.0005-7.7369)	0.6672 (0.0029-150.70)	0.2168 (0.0173-2.8107)
λ_4	preclinical grade1/2 to clinical grade 1/ 2	0.6944 (0.5013-0.8874)	0.3071 (0.0013-7.0148)	0.2791 (0.2156-0.3426)
λ_5	preclinical grade 3 to clinical grade 3	0.6655 (0.4412-0.8898)	0.4726 (0.1452-0.8000)	0.3786 (0.2716-0.4856)
π	Proportion of tumours without potential of progression	0.1921 (0.0158-2.3350)	0.5158 (0.2630-1.0120)	0.4917 (0.2506-0.9664)

Results indicated that

(1) 81% of tumours in women aged 40-49 have the potential to deteriorate from grade1/2 to grade 3 (although they need not necessarily do so if the tumour is detected early) and only 19% will always have the same grade.

(2) For the age groups of 50-59 and 60-69, 50% have potential to deteriorate and 50% always remain the same.

This means that in terms of grade, the 40-49 group is more susceptible to phenotypic drift than over 50.

4.5.3 Estimation of natural history parameters of breast cancer based on non-randomized organized screening data - subsidiary analysis of effects of inter-screening interval, sensitivity, and attendance rate on reduction of advanced cancer (Wu et al, *BCRT* 2012)

Estimating the natural history parameters of breast cancer not only elucidates the disease progression but also make contributions to assessing the impact of inter-screening interval, sensitivity and attendance rate on reducing advanced breast cancer. We applied three-state and five-state Markov model to data on a two-yearly routine mammography screening in Finland between 1988 and 2000. The mean sojourn time was computed from estimated transition parameters. Computer simulation was implemented to examine the effect of inter-screening interval, sensitivity, and attendance rate on reducing advanced breast cancers. In three-state model, the mean sojourn time was 2.02 years and the sensitivity for detecting preclinical breast cancer was 84.83%. In five-state model, the mean sojourn time was 2.21 years for localised tumor and 0.82 year for non-localised tumor. Annual, biennial and triennial screening programs can reduce 53%, 37% and 28% of advanced cancer. The effectiveness of intensive screening with poor attendance is the same as that of infrequent screening with high attendance rate. We demonstrated how to estimate the natural history parameters using a service screening program and applied these parameters to assess the impact of inter-screening interval, sensitivity, and attendance rate on reducing advanced cancer. The proposed method makes contribution to further cost-effectiveness analysis. However, these findings had better be validated by using a further long-term follow-up data.

Table 4-6 Estimated parameters for progression rate and the sensitivity in three-state Markov model and five-state Markov model, Pirukamma, Finland

Parameters	Estimates	95% CI
Three-state model ^a		
50-59		
Normal → Preclinical cancer (λ_1)	0.0025	(0.0022, 0.0028)
Preclinical cancer → Clinical cancer (λ_2)	0.4956	(0.3816, 0.6097)
Mean sojourn time ($1/\lambda_2$)	2.02	(1.64, 2.62)
Sensitivity	84.83%	(74.88%, 94.79%)
Specificity	99.97%	(99.89%, 100%)
50-54		
Normal → Preclinical cancer (λ_1)	0.0025	(0.0022, 0.0027)
Preclinical cancer → Clinical cancer (λ_2)	0.5207	(0.4057, 0.6356)
Mean sojourn time ($1/\lambda_2$)	1.92	(1.57, 2.46)
Sensitivity	83.75%	(71.26%, 96.23%)
55-59		
Normal → Preclinical cancer (λ_1)	0.0025	(0.0021, 0.0029)
Preclinical cancer → Clinical cancer (λ_2)	0.4269	(0.3131, 0.5408)
Mean sojourn time ($1/\lambda_2$)	2.34	(1.85-3.19)
Sensitivity	89.48%	(76.56%, 100%)
Five-state model		
50-59		
Normal → Preclinical N(-) (λ_1)	0.0025	(0.0023, 0.0027)
Preclinical N(-) → Preclinical N(+) (λ_2)	0.3371	(0.2549, 0.4192)
Preclinical N(-) → Clinical N(-) (λ_3)	0.2897	(0.2186, 0.3609)
Mean sojourn time ($1/(\lambda_2 + \lambda_3)$)	2.04	
Preclinical N(+) → Clinical N(+) (λ_4)	1.2230	(0.9259, 1.5201)
Mean sojourn time ($1/(\lambda_2 + \lambda_3 + \lambda_4)$)	0.82	(0.66, 1.08)
Sensitivity of preclinical N(-) cancer	68.21%	(54.63%, 81.79%)
^b Period as a covariate for λ_1		
Normal → Preclinical N(-) (λ_1)		
Period 1988-1991	0.0026	(0.0023, 0.0028)
Period 1992-1996	0.0026	(0.0022, 0.0031)
Period 1997-2000	0.0020	(0.0015, 0.0028)
Preclinical N(-) → Preclinical N(+) (λ_2)	0.3298	(0.2488, 0.4109)
Preclinical N(-) → Clinical N(-) (λ_3)	0.2828	(0.2126, 0.3531)
Preclinical N(+) → Clinical N(+) (λ_4)	1.2052	(0.9054, 1.505)
Sensitivity of preclinical N(-) cancer	67.56%	(54.04%, 81.07%)

Goodness-of-fit for three-state model $\chi^2 = 2.69$, d.f. = 4, p-value = 0.61

Goodness-of-fit for five-state model $\chi^2 = 12.12$, d.f. = 7, p-value = 0.10

Goodness-of-fit for five-state model (piecwise method) $\chi^2 = 37.88$, d.f. = 29, p-value = 0.13

^a the estimation were independently performed for three age groups

^b baseline period: 1988-1991

Table 4-7 Relative risk of non-localised breast cancer of different screening regime by screening sensitivity

	Control group	Screening annually	Screening biennially	Screening triennially
Sensitivity of localised tumor				
68.2% ^a	1	0.47 (0.41, 0.55)	0.63 (0.55, 0.72)	0.72 (0.63, 0.82)
60%	1	0.51 (0.44, 0.59)	0.67 (0.59, 0.76)	0.75 (0.66, 0.85)
80%	1	0.42 (0.36, 0.49)	0.58 (0.50, 0.66)	0.67 (0.59, 0.77)
90%	1	0.38 (0.33, 0.45)	0.54 (0.47, 0.62)	0.64 (0.56, 0.73)

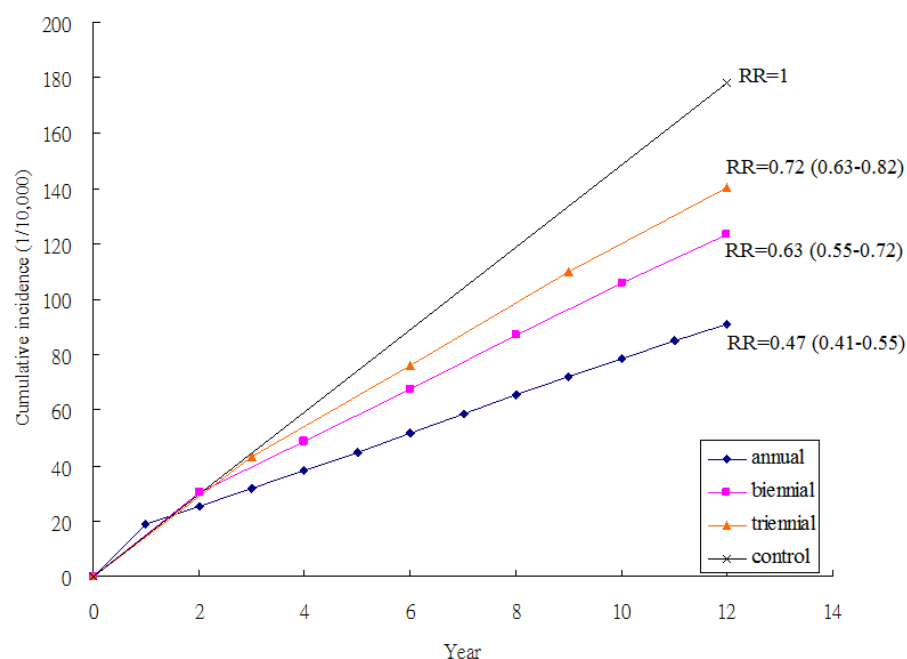
^a estimate from five-state Markov model

Table 4-8 Relative risk of non-localised breast cancer by attendance rate with 68.2^a sensitivity for localized breast cancer

Attendance rate	Control group	Screening annually	Screening biennially	Screening triennially
100%	1	0.44 (0.38, 0.51)	0.61 (0.53, 0.69)	0.70 (0.62, 0.80)
90%	1	0.49 (0.43, 0.57)	0.65 (0.57, 0.74)	0.73 (0.64, 0.83)
60%	1	0.66 (0.58, 0.75)	0.76 (0.67, 0.86)	0.82 (0.73, 0.93)
30%	1	0.83 (0.74, 0.94)	0.88 (0.78, 0.99)	0.91 (0.81, 1.03)

^a Estimate from five-state Markov model

Fig. 4-1 Cumulative incidence of non-localised tumor by different screening regimes



4.5.4 Model over-diagnosis in screening program via multistate model (Wu et al, *Biometrical J* 2012)

Wu et al further proposed a stochastic model for survival of early prostate cancer with adjustments for leadtime, length bias, and over-detection and applied it to a randomized controlled trial for PSA screening for prostate cancer.

To deal with over-diagnosis, they used two intensity matrices: (i) $\mathbf{Q}(\cdot)$ for those with potential to progress to the CP (so-called mover); and (ii) $\mathbf{Q}^S(\cdot)$ for those without potential to progress to the CP (so-called stayer). The reason for two matrices is to capture the over-detection problem: it is assumed that one group of individuals can never progress to state 2 (stayers) and that these are different from the group who do not progress to state 2 but could have done (movers).

$$\mathbf{Q}(\cdot) = \begin{array}{c} \begin{array}{c} \text{Normal} \\ \text{PCDP} \\ \text{CP} \\ \text{PCa death} \\ \text{OCD} \end{array} \begin{array}{c} \text{(State 0)} \\ \text{(State 1)} \\ \text{(State 2)} \\ \text{(State 3)} \\ \text{(State 4)} \end{array} \end{array} \begin{pmatrix} -(\lambda_0(\cdot) + u_0(\cdot)) & \lambda_0(\cdot) & 0 & 0 & u_0(\cdot) \\ 0 & -(\lambda_1(\cdot) + u_1(\cdot)) & \lambda_1(\cdot) & 0 & u_1(\cdot) \\ 0 & 0 & -(\lambda_2(\cdot) + u_2(\cdot)) & \lambda_2(\cdot) & u_2(\cdot) \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

and

$$\mathbf{Q}^S(\cdot) = \begin{array}{c} \begin{array}{c} \text{Normal} \\ \text{PCDP} \\ \text{CP} \\ \text{PCa death} \\ \text{OCD} \end{array} \begin{array}{c} \text{(State 0)} \\ \text{(State 1)} \\ \text{(State 2)} \\ \text{(State 3)} \\ \text{(State 4)} \end{array} \end{array} \begin{pmatrix} -(\lambda_0(\cdot) + u_0(\cdot)) & \lambda_0(\cdot) & 0 & 0 & u_0(\cdot) \\ 0 & -u_1(\cdot) & 0 & 0 & u_1(\cdot) \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

where PCa refers to prostate cancer; $\lambda_0(\cdot)$, $\lambda_1(\cdot)$, and $\lambda_2(\cdot)$ represent the incidence rates of pre-clinical prostate cancer (state 0→state 1), the transition rate from the PCDP to the CP (state 1→state 2), which determines the distribution of sojourn time, and the hazard rate of prostate cancer death among prostate cancers in the CP (state 2→state 3); and $u_0(\cdot)$, $u_1(\cdot)$, and $u_2(\cdot)$ are three hazard rates of death from other causes (state 4) for respectively subjects in state 0, state 1, and state 2. Again, the transition probability matrix can be derived from the backward Kolmogorov equation (Cox and Miller, 1965), and has been used for breast cancer screening (Chen et al, 1997).

4.5.5 Evaluation of the different screening frequencies (Chen et al, Cancer 1999)

To assess the effect of inter-screening interval on the efficacy of screening, one can conduct the computer simulation. As in Chen et al (1999), they use a simulation program to assess the effect of colorectal cancer screening for a high-risk group based on a split design. This design is a variant of stop-screen design. The unique characteristic of this design is that at the time the last screening is offered to the screened group, a screening is also offered to all those in the control group. The merit of this design is that it enhances the comparability of cancer cases identified in the control and intervention arms. From the practical aspect of screening, this may also partly resolve the ethical issue for the control group. This design was used in some Swedish randomized trials for breast carcinoma, such as the Stockholm trial and the Two- County trial. A hypothetical population of 25,596 subjects was randomly assigned to four groups: annual, biennial, and triennial screening regimes and a control group. Each group consists of 6399 subjects (as in the

study cohort), similar to the sample size in the current study. One hundred percent attendance and 100% sensitivity was assumed. To predict the number of cases of preclinical and clinical CRC and the corresponding deaths from CRC, transition probabilities for 1-year, 2-year, and 3-year inter-screening intervals were calculated using the estimated transition parameters from the 5-state Markov model. Taking the control group as a baseline group, relative mortalities for annual, biennial, and triennial regimes were predicted.

Table 4-7 The Relative Mortalities for Annual, Biennial, Three-Yearly Screening Regime Compared to the Control Group, TAMCAS Screening Project

	Estimated number of cases					Relative Risk (RR) of death from CRC	95% CI
	First screen	Second screen	Interval cancer	Death of CRC	OCD		
Annual	70.46	130.85	25.03	41.97	38.68	0.74	(0.50~1.10)
Biennial	70.46	110.05	43.88	43.47	39.53	0.77	(0.52~1.14)
Three-yearly	70.46	93.63	58.08	44.94	40.35	0.79	(0.53~1.17)
Control	68.64	-----	132.94	56.58	46.83	1	

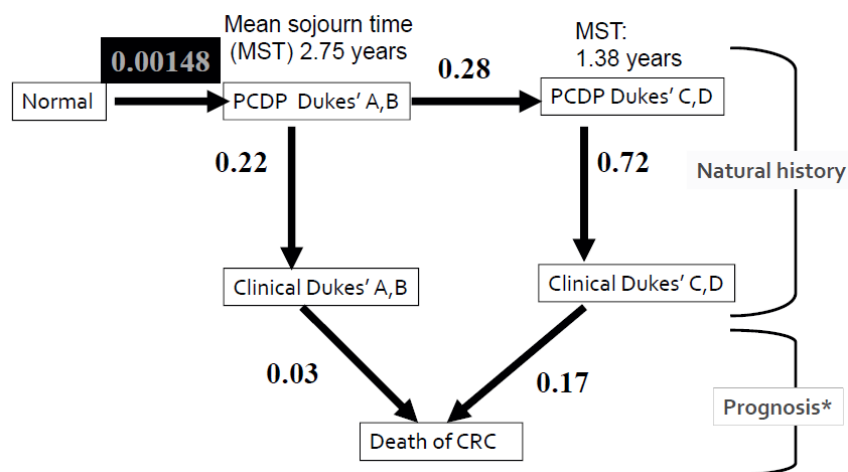
Table 4-8 Results of the simulation for predicting asymptomatic cases, symptomatic cases and deaths from NIDDM by different screening regimens

	First screen Asymptomatic NIDDM	Second screen Asymptomatic NIDDM	Symptomatic NIDDM	Deaths from NIDDM	Deaths from other causes	Relative mortality
Annual	777.37	701.77	44.19	129.99	70.76	0.54
Biennial	777.37	655.18	83.70	134.64	75.95	0.56
Four-yearly	777.37	571.75	150.38	144.00	86.18	0.60
Control group	709.29	-----	638.72	241.24	184.96	1

4.5.6 The natural history and computer-simulation approach to demonstrate the effectiveness prediction and sample size calculation for population-based colorectal cancer screening (Chiu et al., *JECP*, 2011).

(A) Estimate the natural history of colorectal cancer: transition rates from normal to preclinical and clinical stage

(1) Five-state natural history of colorectal cancer



(2) Empirical data from screening

A. RCT by Hardcastle et al. from UK

B. RCT by Kronborg et al. from Denmark

C. Data included prevalent screen-detected, subsequent screen-detected, interval cancer, non-responder

(3) Model validation

A. Internal validation

Examination for observed and expected numbers using Pearson Chi-squared test

B. External Validation

Using observed data from control group with different detected modes

(4) Meta-analysis for natural history

- (5) Computer-simulation
 - A. Markov decision tree
 - B. Transition probabilities from transition rate
 - C. Parameters about the screening scenario, ex. first round screening information from Finland (attendance rate, compliance rate of colonoscopy) or literature (sensitivity, specificity of screening tool)

- (B) Predict and compare the effectiveness of surrogate endpoint (stage distribution) of colorectal cancer by different screening strategies
 - (1) Outcome with Dukes' stage distribution were simulated from both invited and control arms

- (C) Predict and compare the effectiveness of mortality of colorectal cancer by different screening strategies
 - (1) Taking the prognosis of colorectal cancer into account
 - (2) Prognosis (survival rate) by different stage from cancer registry (before screening implementation)

- (D) Calculate the required sample size for randomized trial using either colorectal cancer mortality or surrogate endpoint for program evaluation
 - (1) Based on the Chen's method (Chen et al., *BJC*, 1999), according to the RR of surrogate and primary endpoint, required sample size and power were computed.
 - (2) Surrogate endpoint provides an opportunity for early evaluation of cancer screening and reducing required sample size for hypothetical study design.

4.5.7 Population-based Hypertension Screening (Tseng et al., 2013, *Am J Hypertension*)

We used population-based screening data to identify the multiple risk factors responsible for multi-step transitions between prehypertension and hypertension.

Temporal Natural Course of Hypertension

According to the JNC 7, blood pressure can be classified into four states: normal (systolic blood pressure [SBP] <120 mmHg and diastolic blood pressure [DBP] <80 mmHg), prehypertension (SBP 120–139 mmHg or DBP 80–89 mmHg), stage 1 hypertension (SBP 140–159 mmHg or DBP 90–99 mmHg), and stage 2 hypertension (SBP \geq 160 mmHg or DBP \geq 100 mmHg) to construct a four-state illness model in continuous time that delineates natural course of disease progression from normal to stage 2 hypertension and regression from prehypertension to normal.

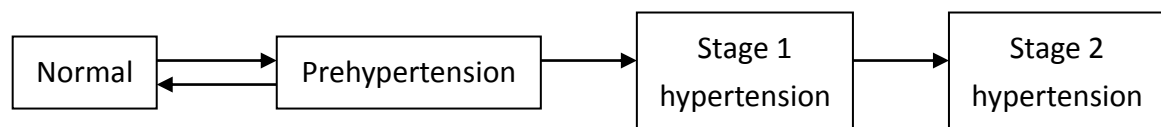


Figure The distribution of risk scores for stage 2 hypertension under different intervention scenarios

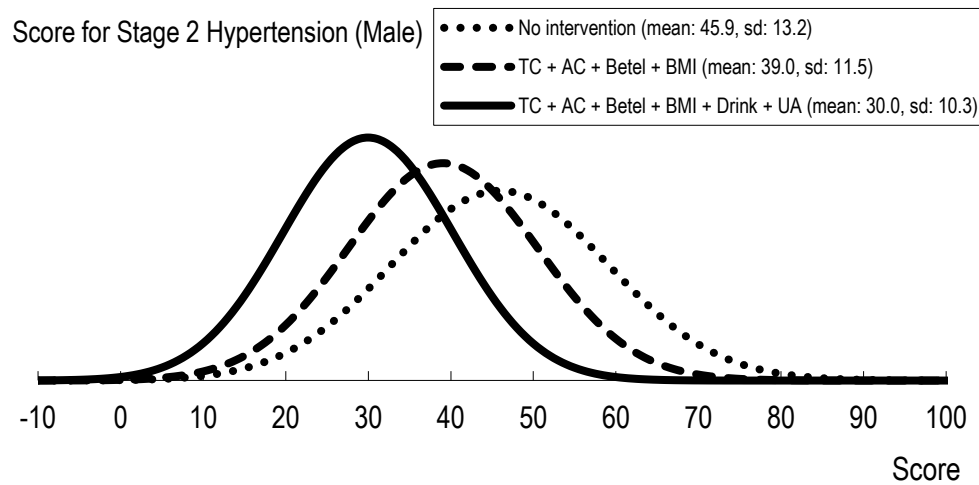
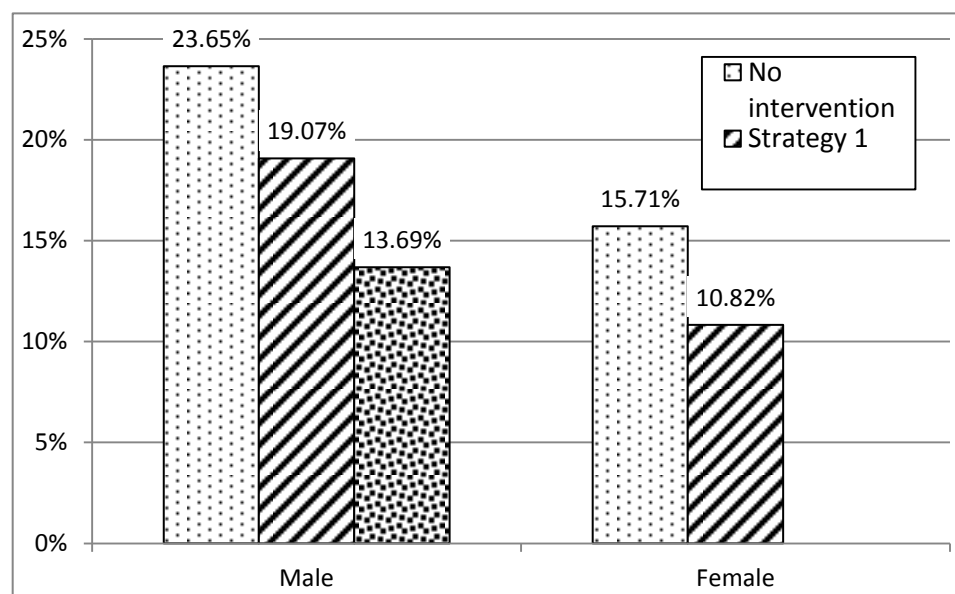


Figure Five-year predicted cumulative probabilities for stage 2 hypertension under different intervention scenarios, 1999-2002



Strategy 1 for male: “4-component intervention” with TC + AC + Betel +BMI

Strategy 2 for male: “6-component intervention” with TC + AC + Betel +BMI + Drink + UA

Strategy 1 for female: “5-component intervention” with TC + AC + BMI + Waist + UA

4.6 Case-cohort design for the disease natural history and the application of natural history for treatment efficacy (Chen et al, *Stat Med*, 2004)

4.6.1 Study design

The study design was based on a variant of case-cohort design. Firstly, in the traditional case-cohort design, the disease status is usually classified into two states, disease and non-disease. By contrast, our design was tailored for multi-state disease status. Secondly, the traditional case-cohort design follows the whole cohort to ascertain cases at different times and randomly selects a proportion of controls from the original cohort. In our design, since subjects in the cohort may progress to different disease states at different times in the light of the specific disease natural history, a series of random samples, instead of accruing all cases, for each state were selected for estimating parameters.

4.6.2 Bayesian inversion for a non-standard case-cohort design

In the three-state Markov model, for example, related to pre-cancerous lesions for oral cancer and colorectal cancer, we have three states ($j=3$), normal, leukoplakia, and invasive carcinoma for oral cancer, and normal, adenoma and invasive carcinoma for colorectal cancer, respectively. Following the above design, three sets of random samples for each state were selected for estimation. Let S_j ($j=1,2,3$) be denoted as an indicator of whether a subject in the j group was sampled.

Let π_0, π_1, π_2 be sampling fractions for normal, pre-cancerous lesion (adenoma and leukoplakia) and invasive carcinoma at time t_i .

$$\pi_0 = P(S = 1 | 0 \rightarrow 0, t_i)$$

$$\pi_1 = P(S = 1 | 0 \rightarrow 1, t_i)$$

$$\pi_2 = P(S = 1 | 0 \rightarrow 2, t_i)$$

t_i may be age at diagnosis or time since last negative examination

The probability of being the j state at time t_i given a subject was sampled ($S=1$) is:

$$\begin{aligned} & P(0 \rightarrow j, t_i | S = 1) \\ &= \frac{P(S = 1 | 0 \rightarrow j, t_i)P(0 \rightarrow j, t_i)}{P(S = 1 | 0 \rightarrow 0, t_i)P(0 \rightarrow 0, t_i) + P(S = 1 | 0 \rightarrow 1, t_i)P(0 \rightarrow 1, t_i) + P(S = 1 | 0 \rightarrow 2, t_i)P(0 \rightarrow 2, t_i)} \\ &= \frac{\pi_j P(0 \rightarrow j, t_i)}{\pi_0 P(0 \rightarrow 0, t_i) + \pi_1 P(0 \rightarrow 1, t_i) + \pi_2 P(0 \rightarrow 2, t_i)} \\ & \quad j=0, 1, 2 \end{aligned}$$

Chen et al. (Chen et al., *BJC*, 2003) applied the colorectal cancer natural history model together with the adenoma–carcinoma sequence associated with adenoma size and histological type to estimate dwelling times, the efficacy of colonoscopy, and the surveillance of polyp after polypectomy. The estimates of overall efficacy of colonoscopy in reducing CRC is 73% for the model allowing for de novo carcinoma and 88% for the model without considering de novo carcinoma theory.

Shiu et al. (Shiu, et al., *EJCP*, 2004) simultaneously quantified the effects of three risk factors, including betel chewing, smoking, and drinking habits, on

occurrence of oral leukoplakia and malignant transformation to oral cancer. Subjects who chewed betel quid were at greater risk of leukoplakia (adjusted odds ratio (OR) 17.7 (9.03–34.5)) but there was no significant effect on malignant transformation (OR 1.04 (0.61–1.76)). Smoking played a major role in the onset of leukoplakia (OR 4.26 (2.21–8.23)) but a minor role in malignant transformation (OR 1.36 (0.69–2.68)). Alcohol was positively associated with malignant transformation (OR 2.37 (1.47–3.82)) but unrelated to occurrence of leukoplakia (OR 0.76 (0.04–1.43)). This study also estimated the treatment efficacy based on a three-state Markov model.

Table 4-9 Parameter estimation and treatment efficacy based on a three-state Markov model

Parameters	Progress rate	95%CI
1. Nature history		
Normal → Leukoplakia(λ)	0.0016	0.0013~0.0020
Leukoplakia → Oral Cancer(λ_N)	0.0979	0.0759~0.120
Average Duration of Malignant transformation of leukoplakia(years)	10.2	8.3~13.7
2. Progress rate after treatment		
Leukoplakia → Oral Cancer(λ_T)	0.0267	0.0204~0.0349
3. Efficacy of treatment($1-\lambda_T/\lambda_N$)	72.7%	57.2~88.3%

4.7. The effects of covariates on multi-state transitions

4.7.1 Assessing chronic disease progression using non-homogeneous exponential regression Markov models (Heish et al, *Stat Med* 2002)

Modeling the impact of relevant covariates on multi-state transitions has a significant implication for prevention of chronic disease.

(1) Covariates acting as an initiator

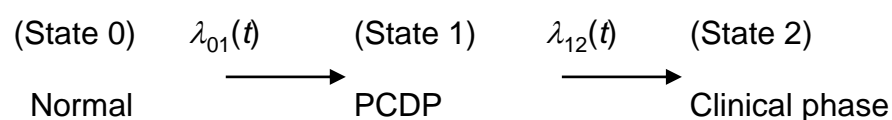
- for onset of preclinical screen-detectable breast cancer (PCDP)
- primary prevention by removing the factor should be addressed

(2) Covariates acting as a promoter

- accelerating the progression from PCDP to the CP
- different screening policies such as more frequent screening for people carrying this factor might be required.

Addressing the association between risk factors and the disease natural history may be even more important for those removable variables such as obesity or smoking. Medical consultation at regular intervals for different characteristics among women can be suggested based on this knowledge.

The transition rates from abovementioned models may vary with time. Heish et al. proposed non-homogeneous models to consider age-dependent incidence rate of preclinical disease, and to incorporate covariates of interest to the multi-state model (Hsieh et al, 2002).



The model specification was similar to previous ones, expect that the transition rates was function of time and covariates. Taking three-state Markov process as an example, the transition intensities for the process are

$$\lambda_{ij}(t) = \lim_{dt \rightarrow 0} \frac{P\{X(t+dt) = j \mid X(t) = i\}}{dt} \quad \text{for } i, j = 0, 1, 2 \quad \text{and } i \neq j$$

$$\lambda_{ii}(t) = -\sum_{i \neq j} \lambda_{ij} \quad \text{for } i = 0, 1, 2$$

They also used the exponential regression models to take account of covariate effects on intensities to model the different characteristics of random process between individuals. Let \mathbf{W} denote a vector which contains the values of all p covariates of an individual, i.e., $\mathbf{W} = [w_1, w_2, \dots, w_p]^T$, and $\lambda_{ij0}(t)$ denotes the baseline intensity at $\mathbf{W}=0$. The intensity for an individual with covariate \mathbf{W} is then modeled as

$$\lambda_{ij}(t, \mathbf{W}) = \lambda_{ij0}(t) \times \exp(\beta_{ij} \mathbf{W})$$

where β_{ij} is a regression coefficient vector with components $(\beta_{ij1}, \beta_{ij2}, \dots, \beta_{ijp})$ corresponding to w_1, \dots, w_p .

To apply a Weibull distribution with scale parameter μ_j and shape parameter k_j , the intensity formula is:

$$\lambda_{01}(t, \mathbf{X}) = \lambda_{010}(t) \times \exp(\beta_{01} \mathbf{W}), \text{ where } \lambda_{010}(t) = \mu_1 k_1 t^{k_1-1}$$

Similar to transition from the PCDP (state 1) to clinical phase (state 2),

$$\lambda_{12}(t, \mathbf{X}) = \lambda_{120}(t) \times \exp(\beta_{12} \mathbf{W}), \text{ where } \lambda_{120}(t) = \mu_2 k_2 t^{k_2-1}$$

In their study, we also developed a SAS program using PROC IML to estimate the parameters. The relative computer program was developed in 2004 by Wu et al. (2004)

Model selection: Likelihood ratio test can be used for selecting the parsimonious model among a series of nested models, not only include the addition of significant covariates or the deletion of superfluous covariates but also compare the models with covariates affecting both types of transitions (state 0 to state 1 and state 1 to state 2) with those that only include the transition from state 0 to state 1 or from state 1 to state 2.

Model diagnosis: We may compare the observed number of transitions between particular states with the expected, and a Pearson χ^2 test statistics can be used to judge whether there is a good fit for the model.

4.7.2 Individually tailored screening or breast cancer with genes, tumour phenotypes, clinical attributes, and conventional risk factors (Wu et al, *Brit J Cancer* 2013)

(1) Health policy makers are concerned that the harm (false negative and false positive cases) and cost of screening should be minimized and the benefits, mainly measured by the reduction of mortality from breast cancer, maximized. This may be relieved by using an individually tailored screening with emphasis on

- optimal age of screening
- inter-screening interval and
- the expedient use of alternative image technique.

These subsidiary issues are related to individual variation on the temporal natural history of breast cancer from free of breast cancer, through the pre-clinical detectable phase (PCDP) and finally to clinical

phase (CP). Screen-detected breast cancer represents the PCDP whereas clinically-detected one (such as interval cancer) stands for the CP.

(2) With the advent of genetic and biological markers for breast cancer, individually tailored screening for breast cancer can now be achieved by making use of information on genes, conventional risk factors, clinical attributes, and relevant tumor phenotypes such as HER-2/*neu*.

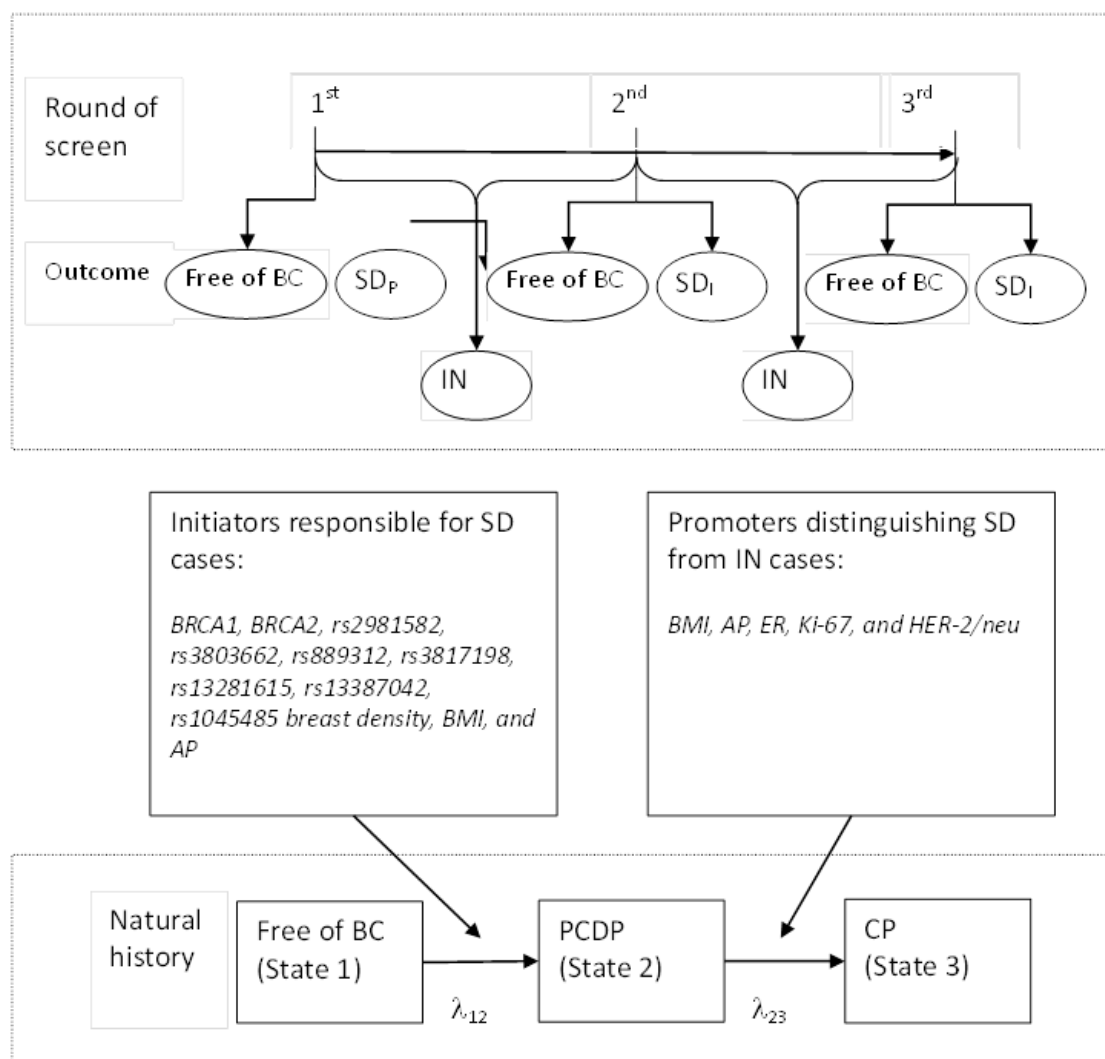

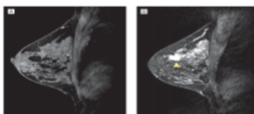



Table 4-10 The recommend age to start screening and inter-screening interval at different percentiles of risk score

priority	Percentile	Age to begin screening	Inter-screening interval (year) [†]	Alternative imaging tool (Threshold/Study) [§]
	90-100	29	0.4 (4.8 months)	M+MRI (94 th / Kuhl's Study)
	80-90	34	1	M+U (85 th / Berg's study)
	70-80	39	1.5	<div> <div>Reduce False Negative</div>  </div>
	60-70	44	2	
	50-60	50	3	<div> <div>Reduce False Positive</div>  </div>
	40-50	57	4	
	30-40	60	8	
	20-30	60	10	
	10-20	60	10	
	0-10	60	10	

M: Mammography
U: Ultrasound

