

eAppendix 1. Details of the statistical model

Four-state continuous-time Markov model

We used a four-state homogenous Markov model to describe the natural history of breast cancer (**Figure 3**). The natural history of the disease was modeled with 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 $\Omega = \{0, 1, 2, 3\}$, where 0 represents “free of breast cancer”, 1 for the PCDP, 2 for the CP, and 3 for deaths due to causes other than breast cancer.

We assigned the time of transition between states with exponential distributions due to the Markov property. States 2 and 3 are defined as the absorbing states. The transition rates in the four-state model can be expressed as an intensity matrix:

$$Q = \begin{matrix} & \begin{matrix} 0 & 1 & 2 & 3 \end{matrix} \\ \begin{matrix} 0 \\ 1 \\ 2 \\ 3 \end{matrix} & \begin{bmatrix} -(\lambda_1 + \mu_0) & \lambda_1 & 0 & \mu_0 \\ 0 & -(\lambda_2 + \mu_1) & \lambda_2 & \mu_1 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} \end{matrix} \quad (\text{A1})$$

Based on the backward Kolmogorov equations, and according to the convention for denoting stochastic processes, the transition probability matrix $\mathbf{P}(t)$, where $P_{ij}(t)$ denotes the transition probability from state i to state j , as related to \mathbf{Q}_t ¹⁶⁻²⁰, may be written as follows:

$$\frac{d}{dt} \mathbf{P}(t) = \mathbf{Q}_t \mathbf{P}(t) \quad t \geq 0 \quad (\text{A2})$$

subject to $\mathbf{P}(0) = \mathbf{I}$

The matrix of transition probabilities denoted by $\mathbf{P}(t)$ for transitions between states can be expressed as follows:

$$P(t) = \begin{pmatrix} P_{00}(t) & P_{01}(t) & P_{02}(t) & P_{03}(t) \\ 0 & P_{11}(t) & P_{12}(t) & P_{13}(t) \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix} \quad (\text{A3})$$

The elements in the transition probability matrix $\mathbf{P}(t)$ are functions of λ s, and μ s.

Incorporation of patient-specific covariates

The effect of patient-specific covariates (e.g., x) on the four-state Markov model was assessed by the exponential regression model. It is expressed as follows:

$$\lambda_i^m = \lambda_{i0} \exp(\beta_i \chi^m) \quad (\text{A4})$$

where λ_{i0} denotes the baseline transition rate i ($i=1, 2$), where χ^m is a vector of covariates for subject m and where β_i is a vector for the corresponding regression coefficients.

eTable 1. The layout of data used for the four-state Markov model

Age	Screen-detected	Interval cancer	Women free of breast cancer		Women in the PCDP	
			OCD	Women-years	OCD	Women-years
40	17	3	46	48,958	0	146.6
41	11	10	37	48,140	0	102.5
42	18	11	49	47,713	0	127.2
43	12	5	42	48,401	0	83.6
44	21	12	62	49,064	1	157.1
45	23	17	63	48,469	2	194.2
46	22	20	83	49,354	0	172.2
47	35	20	76	50,763	0	323.7
48	44	24	81	51,512	1	356.1
49	39	19	87	51,255	1	340.6
50	57	27	99	51,805	1	460.1
51	52	27	110	52,558	1	458.2
52	57	29	139	52,086	0	464.9
53	39	36	126	51,979	0	270.2
54	55	32	144	51,638	2	446.5
55	45	33	171	51,699	0	352.6
56	60	20	173	52,037	4	433.2
57	75	25	210	53,028	4	563.5
58	65	33	217	53,251	2	435.4
59	72	29	241	51,631	4	501.4
60	66	33	258	50,058	6	464.1
61	83	35	282	50,045	7	514.4
62	84	27	318	48,162	4	595.2
63	103	31	333	47,594	7	715.5
64	88	37	392	46,879	4	619.0
65	102	43	466	45,078	7	707.4
66	110	35	448	44,611	11	619.0
67	85	34	515	44,328	5	572.2
68	99	32	515	43,165	23	591.3
69	106	27	656	41,723	22	710.2
70+	179	245	2,084	67,211	63	1,282.6
Total	1,924	1,011	8,523	1,544,195	182	13,780.7

OCD, other causes of death; PCDP, pre-clinical detectable phase.

eTable 2. The frequency of risk factors by detection mode during the period of 1977-2010

Risk factors	Free of breast cancer	Breast cancer	Detection Mode		<i>P</i> value*	<i>P</i> value†
			Screen-detected	Clinically detected		
Period	49,345	1,321	789	532		
1977-1992						
BMI, kg/m ²					0.091	0.005
<25	19,535 (49.0)	335 (45.9)	175 (40.3)	160 (54.1)		
≥25	20,299 (51.0)	395 (54.1)	259 (59.7)	136 (45.9)		
Age at menarche, years					0.405	0.423
≤11	1,216 (3.89)	34 (4.86)	23 (5.58)	11 (3.82)		
12-13	12,826 (41.0)	288 (41.1)	173 (42.0)	115 (39.9)		
≥14	17,244 (55.1)	378 (54.0)	216 (52.4)	162 (56.2)		
Age at first full-term pregnancy, years					0.000	0.322
≤25	31,225 (68.1)	786 (63.2)	465 (62.1)	321 (64.9)	2	
>25	14,612 (31.9)	458 (36.8)	284 (37.9)	174 (35.2)		
Breast density					0.909	0.435
Non-dense	35,580 (83.8)	832 (84.0)	514 (84.7)	318 (82.8)		
Dense	6,868 (16.2)	159 (16.0)	93 (15.3)	66 (17.2)		
Family history					0.051	0.199
No	35,771 (96.2)	693 (94.8)	401 (93.9)	292 (96.1)		
Yes	1,414 (3.80)	38 (5.20)	26 (6.09)	12 (3.95)		
Period 1996-1998 & 2002-2010						

Risk factors	Free of breast cancer	Breast cancer	Detection Mode		<i>P</i> value *	<i>P</i> value†
			Screen- detected	Clinically detected		
Estrogen receptor						<0.001
Neg.			94 (10.9)	101 (26.8)		
Pos.			768 (89.1)	276 (73.2)		
Progesterone receptor						<0.001
Neg.			267 (31.1)	171 (45.8)		
Pos.			593 (68.9)	202 (54.2)		
HER-2						0.023
Neg.			626 (88.5)	232 (83.2)		
Pos.			81 (11.5)	47 (16.8)		
Triple-negative						<0.001
Yes			42 (6.0)	55 (20.1)		
No			660 (94.0)	219 (79.9)		
Ki-67						<0.001
Neg.			272 (67.0)	73 (44.0)		
Pos.			134 (33.0)	93 (56.0)		
Basal phenotype						<0.001
Non-basal			418 (95.4)	142 (81.6)		
Basal-like			20 (4.6)	32 (18.4)		
Molecular subtypes						0.008
Luminal A			122 (81.3)	46 (63.9)		
Luminal B			11 (7.33)	8 (11.1)		
HER2+			8 (5.33)	3 (4.17)		
Basal-like			5 (3.33)	11 (15.3)		
Triple-negative			4 (2.67)	4 (5.56)		

BMI, body mass index.

Data are presented as a number followed by a percentage in parentheses

* *P* value for initiators

† *P* value for promoters

Table 3. Estimated incidence of preclinical breast cancer ($\hat{\lambda}_1$), the transition rate from the pre-clinical to the clinical phase ($\hat{\lambda}_2$), and the mean sojourn time by body mass index, age at first full-term pregnancy, breast density, family history, and molecular subtypes

BMI, kg/m ²	Age at first full-term pregnancy, years	Breast density	Family History	Molecular subtypes	$\hat{\lambda}_1$	$\hat{\lambda}_2$	MST	$\frac{MST}{\hat{\lambda}_1}$
≥25	>25	Dense	Yes	Triple-negative	0.0036	0.57	1.77	486
≥25	>25	Dense	Yes	Basal-like	0.0036	1.16	0.86	237
≥25	>25	Dense	Yes	HER2+	0.0036	0.41	2.42	665
≥25	>25	Dense	Yes	Luminal B	0.0036	0.48	2.10	578
≥25	>25	Dense	Yes	Luminal A	0.0036	0.27	3.64	1003
≥25	>25	Dense	No	Triple-negative	0.0019	0.57	1.77	920
≥25	>25	Dense	No	Basal-like	0.0019	1.16	0.86	448
≥25	>25	Dense	No	HER2+	0.0019	0.41	2.42	1258
≥25	>25	Dense	No	Luminal B	0.0019	0.48	2.10	1093
≥25	>25	Dense	No	Luminal A	0.0019	0.27	3.64	1896
≥25	>25	Non-dense	Yes	Triple-negative	0.0026	0.39	2.58	1004
≥25	>25	Non-dense	Yes	Basal-like	0.0026	0.80	1.26	489
≥25	>25	Non-dense	Yes	HER2+	0.0026	0.28	3.53	1374
≥25	>25	Non-dense	Yes	Luminal B	0.0026	0.33	3.06	1193
≥25	>25	Non-dense	Yes	Luminal A	0.0026	0.19	5.32	2071
≥25	>25	Non-dense	No	Triple-negative	0.0014	0.39	2.58	1899
≥25	>25	Non-dense	No	Basal-like	0.0014	0.80	1.26	924
≥25	>25	Non-dense	No	HER2+	0.0014	0.28	3.53	2598
≥25	>25	Non-dense	No	Luminal B	0.0014	0.33	3.06	2257
≥25	>25	Non-dense	No	Luminal A	0.0014	0.19	5.32	3916
≥25	≤25	Dense	Yes	Triple-negative	0.0029	0.57	1.77	600
≥25	≤25	Dense	Yes	Basal-like	0.0029	1.16	0.86	292
≥25	≤25	Dense	Yes	HER2+	0.0029	0.41	2.42	821
≥25	≤25	Dense	Yes	Luminal B	0.0029	0.48	2.10	713
≥25	≤25	Dense	Yes	Luminal A	0.0029	0.27	3.64	1237
≥25	≤25	Dense	No	Triple-negative	0.0016	0.57	1.77	1135
≥25	≤25	Dense	No	Basal-like	0.0016	1.16	0.86	552
≥25	≤25	Dense	No	HER2+	0.0016	0.41	2.42	1552
≥25	≤25	Dense	No	Luminal B	0.0016	0.48	2.10	1348
≥25	≤25	Dense	No	Luminal A	0.0016	0.27	3.64	2340
≥25	≤25	Non-dense	Yes	Triple-negative	0.0021	0.39	2.58	1239
≥25	≤25	Non-dense	Yes	Basal-like	0.0021	0.80	1.26	603
≥25	≤25	Non-dense	Yes	HER2+	0.0021	0.28	3.53	1695
≥25	≤25	Non-dense	Yes	Luminal B	0.0021	0.33	3.06	1472
≥25	≤25	Non-dense	Yes	Luminal A	0.0021	0.19	5.32	2555
≥25	≤25	Non-dense	No	Triple-negative	0.0011	0.39	2.58	2344
≥25	≤25	Non-dense	No	Basal-like	0.0011	0.80	1.26	1141

BMI, kg/m ²	Age at first full-term pregnancy, years	Breast density	Family History	Molecular subtypes	$\hat{\lambda}_1$	$\hat{\lambda}_2$	MST	$\frac{\text{MST}}{\hat{\lambda}_1}$
≥25	≤25	Non-dense	No	HER2+	0.0011	0.28	3.53	3206
≥25	≤25	Non-dense	No	Luminal B	0.0011	0.33	3.06	2785
≥25	≤25	Non-dense	No	Luminal A	0.0011	0.19	5.32	4833
<25	>25	Dense	Yes	Triple-negative	0.0032	0.87	1.14	362
<25	>25	Dense	Yes	Basal-like	0.0032	1.80	0.56	176
<25	>25	Dense	Yes	HER2+	0.0032	0.64	1.56	495
<25	>25	Dense	Yes	Luminal B	0.0032	0.74	1.36	430
<25	>25	Dense	Yes	Luminal A	0.0032	0.42	2.36	746
<25	>25	Dense	No	Triple-negative	0.0017	0.87	1.14	684
<25	>25	Dense	No	Basal-like	0.0017	1.80	0.56	333
<25	>25	Dense	No	HER2+	0.0017	0.64	1.56	936
<25	>25	Dense	No	Luminal B	0.0017	0.74	1.36	813
<25	>25	Dense	No	Luminal A	0.0017	0.42	2.36	1411
<25	>25	Non-dense	Yes	Triple-negative	0.0022	0.60	1.67	747
<25	>25	Non-dense	Yes	Basal-like	0.0022	1.23	0.81	364
<25	>25	Non-dense	Yes	HER2+	0.0022	0.44	2.28	1022
<25	>25	Non-dense	Yes	Luminal B	0.0022	0.50	1.98	888
<25	>25	Non-dense	Yes	Luminal A	0.0022	0.29	3.44	1541
<25	>25	Non-dense	No	Triple-negative	0.0012	0.60	1.67	1413
<25	>25	Non-dense	No	Basal-like	0.0012	1.23	0.81	688
<25	>25	Non-dense	No	HER2+	0.0012	0.44	2.28	1934
<25	>25	Non-dense	No	Luminal B	0.0012	0.50	1.98	1679
<25	>25	Non-dense	No	Luminal A	0.0012	0.29	3.44	2915
<25	≤25	Dense	Yes	Triple-negative	0.0026	0.87	1.14	447
<25	≤25	Dense	Yes	Basal-like	0.0026	1.80	0.56	217
<25	≤25	Dense	Yes	HER2+	0.0026	0.64	1.56	611
<25	≤25	Dense	Yes	Luminal B	0.0026	0.74	1.36	531
<25	≤25	Dense	Yes	Luminal A	0.0026	0.42	2.36	921
<25	≤25	Dense	No	Triple-negative	0.0014	0.87	1.14	845
<25	≤25	Dense	No	Basal-like	0.0014	1.80	0.56	411
<25	≤25	Dense	No	HER2+	0.0014	0.64	1.56	1155
<25	≤25	Dense	No	Luminal B	0.0014	0.74	1.36	1004
<25	≤25	Dense	No	Luminal A	0.0014	0.42	2.36	1742
<25	≤25	Non-dense	Yes	Triple-negative	0.0018	0.60	1.67	922
<25	≤25	Non-dense	Yes	Basal-like	0.0018	1.23	0.81	449
<25	≤25	Non-dense	Yes	HER2+	0.0018	0.44	2.28	1262
<25	≤25	Non-dense	Yes	Luminal B	0.0018	0.50	1.98	1096
<25	≤25	Non-dense	Yes	Luminal A	0.0018	0.29	3.44	1902
<25	≤25	Non-dense	No	Triple-negative	0.0010	0.60	1.67	1744
<25	≤25	Non-dense	No	Basal-like	0.0010	1.23	0.81	849
<25	≤25	Non-dense	No	HER2+	0.0010	0.44	2.28	2386
<25	≤25	Non-dense	No	Luminal B	0.0010	0.50	1.98	2073
<25	≤25	Non-dense	No	Luminal A	0.0010	0.29	3.44	3597

BMI, body mass index; MST, mean sojourn time.