based on a judgement that the benefit of survival from chemotherapy overweighs the disbenefit of adverse effects and medical risks [11]. However, the risk classification which underlies this judgement has been considered as not certain nor specific enough, so that it leaves a room for the development of a more accurate and individualised predictor of the risk of recurrence.

A multigene assay of resected breast cancer tumour tissue was implemented in order to realise more informed and individualised decision for adjuvant chemotherapy indication, which resulted in the development of the 21-gene reverse transcriptase-polymerase chain reaction (RT-PCR) assay with a patented algorithm (Oncotype DX® Breast Cancer Assay). It gives an individual case of LN−, ER+, ESBC Recurrence Score (RS) that represents individualised risk of recurrence. The accuracy of RS as criteria in assessing the risk of recurrence was validated by a prospective study of historical clinical trial data from National Surgical Adjuvant Breast Cancer Project (NSABP) B-14 study with the gene assay of preserved tumour tissue [12]. Furthermore, the accuracy of RS in predicting the magnitude of chemotherapy benefit was validated by a similar study including data from NSABP B-20 study with the gene assay [13]. In other words, patients classified as high risk of recurrence by RS criteria are likely to be highly responsive to chemotherapy, which implies that the assay is clinically efficient in identifying those who could benefit from adjuvant chemotherapy.

This development is deemed as a pathway geared towards tailor-made medicine in breast cancer care, which anticipates a similar innovative assay like 70-gene signature (MammaPrint®) [14]. Yet another significant characteristic of the 21-gene RT-PCR assay is its high price, ¥450,000 (US$3,913; US$1 = ¥115), while the reimbursement for a conventional gene diagnosis test of malignant tumour is set at ¥20,000 (US$174) in the social health insurance system of Japan. Needless to say, a valuable innovation of technology deserves patent protection and accompanying financial rewards as its own right. However, from the viewpoint of economics, it is imperative to appraise the "value for money" of such highly priced new technology [15]. The proportion of LN−, ER+ cases among breast cancer is large, 28.7% [16], and the incidence of breast cancer is estimated as 41,494 in 2005 and increasing continuously [17]. Therefore, once the assay becomes a standard procedure within social insurance benefit package, more than 12,000 assays are expected to be implemented in a year. This leads to a concern about its implication for health financing. From the viewpoint of health manager, it is also imperative to appraise the "budget impact" [18], which basically correlates to the product of the price and the quantity of health services provided.

To date, there are two studies that look at economic aspects of the 21-gene RT-PCR assay based on validation studies in the U.S. health system. Hornberger et al. carried out an economic evaluation of the assay, and reported it as cost-saving based on a reclassification of patients' risk using RS criteria, instead of NCCN criteria [19]. Lyman et al. also reported that RS-guided treatment could be cost-saving compared to the treatment with tamoxifen combined with chemotherapy for all patients, and cost-effective compared to the treatment with tamoxifen alone for all patients [20]. There is no report from any other countries nor yet a comparison with St Gallen-guided treatment.

This study aims to evaluate cost-effectiveness and budget impact of the 21-gene RT-PCR assay in Japan's health care system. The results should be useful in considering the diffusion of the assay in Japan, and could inform health care policy in the era of tailor-made medicine in developed countries.

Methods

We conduct a cost-effectiveness analysis with decision trees and Markov modelling based on the validation studies of the 21-gene RT-PCR assay [12, 13, 21], and a costing under Japan's social health insurance system including a sensitivity analysis from societal perspective. We also estimate the budget impact of the assay on Japan's social health insurance system based on our economic model.

Scenarios and comparisons

Both Japanese clinical practice [22] and consensus guidelines [23, 24] are in accordance with NCCN guideline as well as St Gallen recommendation in a mixed way. And changing criteria from NCCN/St Gallen to RS in risk reclassifications with estimated distant recurrence free survival in 10 years ($DRFS_{10}$) were reported in one of the validation studies as shown in Table 1 [21]. (Since $DRFS_{10}$ of patients with intermediate risk according to St Gallen criteria was not yet published, we assume the mid-value of $DRFS_{10}$ between high risk and low risk classified by St Gallen criteria.) Three scenarios are set up in this study: a hypothetical cohort of LN−, ER+, ESBC at the age of 55 undergoes NCCN-guided treatment, St Gallen-guided treatment, and RS-guided treatment. The age of 55 is chosen according to the average age of equivalent patient population in a nationwide cancer registry [16]. The former two scenarios intend to depict the status quo of Japanese practice to some extent. The last scenario intends to illustrate the situation in which the 21-gene RT-PCR assay is applied routinely.

Table 1 Risk reclassification by the 21-gene RT-PCR[a] assay with expected $DRFS_{10}^{b}$

			Recurrence Score criteria		
			High risk	Intermediate risk	Low risk
NCCN[c] criteria	High risk	Probability	29%	22%	49%
		$DRFS_{10}$	0.70	0.86	0.92
		Range tested in sensitivity analyses	Change by ±50%	Change by ±50%	Change by ±50%
		Probability	6%	22%	72%
	Low risk	$DRFS_{10}$	0.57	0.82	1.00
		Range tested in sensitivity analyses	Change by ±50%	Change by ±50%	Change by ±50%
St Gallen criteria	High risk	Probability	36%	22%	42%
		$DRFS_{10}$	0.67	0.82	0.92
		Range tested in sensitivity analyses	Change by ±50%	Change by ±50%	Change by ±50%
		Probability	16%	23%	61%
	Intermediate risk	$DRFS_{10}$	0.62[d]	0.82[d]	0.96[d]
		Range tested in sensitivity analyses	Change by ±50%	Change by ±50%	Change by ±50%
		Probability	6%	22%	72%
	Low risk	$DRFS_{10}$	0.57	0.82	1.00
		Range tested in sensitivity analyses	Change by ±50%	Change by ±50%	Change by ±50%

Source: Reference [21]

[a] Reverse transcriptase-polymerase chain reaction

[b] Distant recurrence free survival in 10 years

[c] National Comprehensive Cancer Network

[d] Assumed as the mid-value of $DRFS_{10}$ between high risk and low risk classified by St Gallen criteria

Regarding the use of adjuvant chemotherapy, 100% of patients classified as high risk by NCCN/St Gallen criteria and 50% of patients classified as intermediate risk by St Gallen criteria are assumed to undergo chemotherapy, while 100% of patients classified as high or intermediate risk by RS criteria are assumed to undergo chemotherapy.

Then, the two pairs of scenarios are compared: NCCN-guided treatment vs. RS-guided treatment, and St Gallen-guided treatment vs. RS-guided treatment. These comparisons intend to depict the diffusion of the assay in Japanese practice. The use of chemotherapy decreases from 92 to 49% under the former comparison, and from 75 to 49% under the latter comparison by the adoption of RS criteria.

Decision tree and Markov model

We construct decision trees with Markov model of clinical courses followed by LN−, ER+, ESBC patients, which is shown in Fig. 1.

The decision tree 1 shows the comparison between NCCN-guided treatment vs. RS-guided treatment; and the decision tree 2 shows the comparison between St Gallen-guided treatment vs. RS-guided treatment. Decision nodes of these trees are as to a decision whether to apply the 21-gene RT-PCR assay or not. Following chance nodes discern the cohort to different adjuvant therapies depending on the risk classification and human epidermal growth factor receptor type2 (HER2) status. Since the use of trastuzumab for HER2 positive (HER2+) cases as adjuvant therapy is about to be included in the social health insurance benefit according to the results of international clinical trials [25, 26], we set up three types of adjuvant therapies: hormonal therapy (HT), HT plus chemotherapy (CT), and HT plus CT plus trastuzumab. Branches with CT lead to subtree B via a chance node, which discern the cohort to different toxicities.

The Markov model shows the clinical course once the adjuvant therapy is completed. Five stages are modelled here: (1) LN−, ER+, ESBC after criteria-guided adjuvant therapy; (2) Distant recurrence with response to treatment; (3) Distant recurrence with no response to treatment; (4) Progression of disease after distant recurrence; and (5) Death. Transitions between the stages are indicated with arrows. Patients follow various courses after recurrence, so conditions other than these five stages and transitions not described with arrows here are possible. However, we model the course in this way based on available reports of prognosis model of metastatic breast cancer, which is calibrated with the results of several randomised trials [19, 27]. Patients with recurrence undergo drug treatment with HT, CT, and/or trastuzumab depending on their status.

The span of each stage is set up at 1 year. Markov process is repeated up to 10 years, since the transitional probabilities of recurrence are calculated from $DRFS_{10}$ and

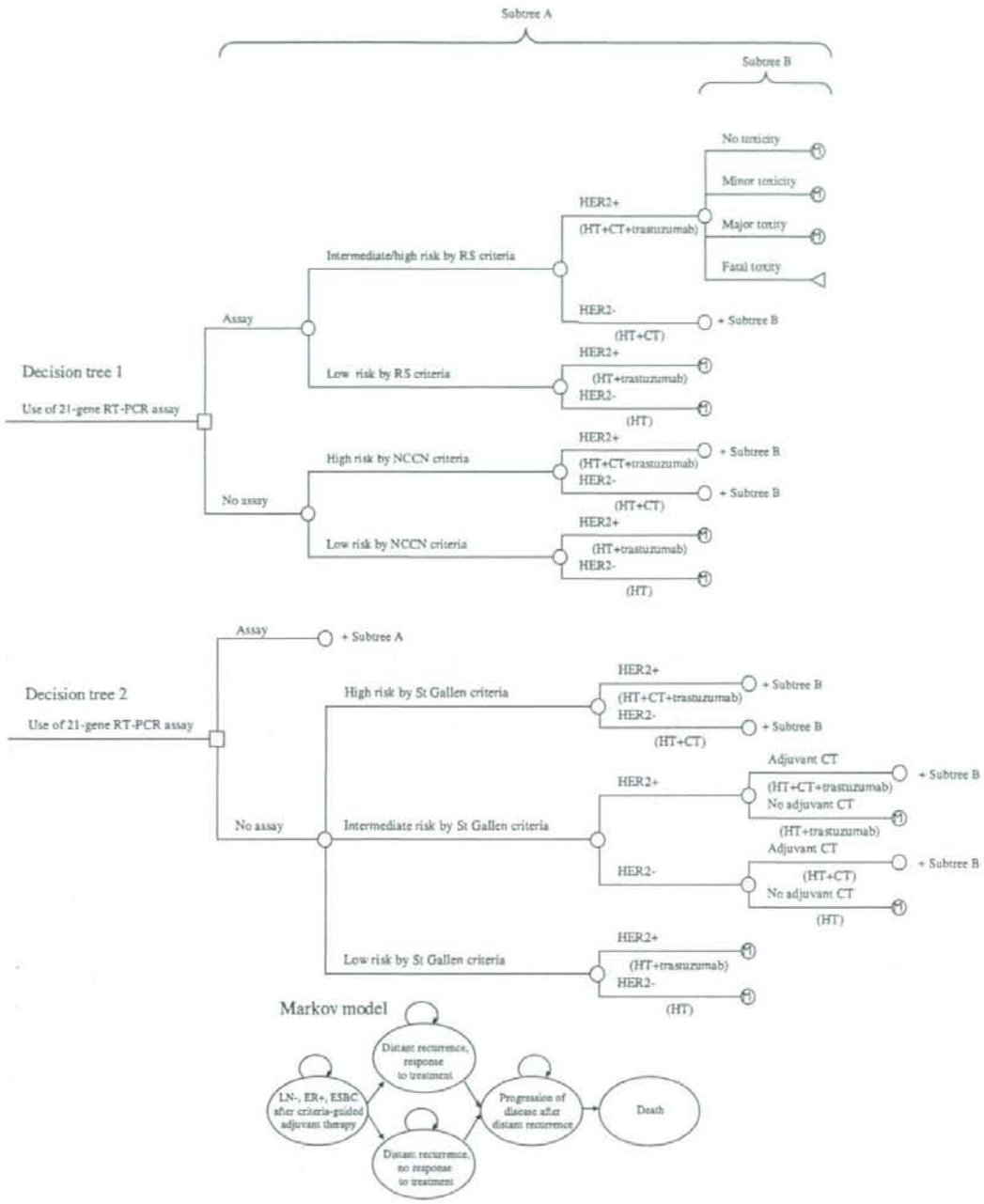


Fig. 1 Decision tree and Markov model. Abbreviations: Reverse transcriptase-polymerase reaction (RT-PCR), recurrence score (RS), human epidermal growth factor receptor type2 (HER2), hormonal therapy (HT), chemotherapy (CT), National Comprehensive Cancer Network (NCCN), lymph-node-negative, estrogen-receptor-positive, early-stage breast cancer (LN−, ER+, ESBC)

most of recurrences are expected to occur within this time horizon. After the 10-year, survived patients without recurrence are assumed to have a life expectancy for Japanese female at age 65 [28], and those with recurrence are to have a life expectancy of 2 years.

Outcome estimation

Outcomes by the scenario in terms of years of life saved (YOLSs) and quality adjusted life years (QALYs) are estimated by assigning probabilities and utility weights to the decision trees and Markov model from the literature.

Probabilities of risk classification, attached to the first chance nodes of each branch, are adopted from one of the validation studies of the 21-gene RT-PCR assay [21] shown in Table 1. Table 2 shows the other probabilities and utility weights used. A probability of HER2+, 9.3%, attached to the second chance nodes, is adopted from a nationwide breast cancer registry [16]. Probabilities of adjuvant chemotherapy toxicity, attached to the chance node in the subtree B, are assumed to be 60% for minor toxicity, 5% for major toxicity and 0.5% for fatal toxicity from a report of efficacy and cost-effectiveness of adjuvant chemotherapy in breast cancer [29].

Regarding the Markov model, transitional probabilities of recurrence with adjuvant HT are calculated from $DRFS_{10}$ in Table 1. The effectiveness of adding adjuvant CT and trastuzumab are incorporated as risk reduction of recurrence. Relative risk reductions resulted from CT among patients classified as high risk and intermediate risk by RS criteria are fixed at 74 and 39%, respectively, which are adopted from one of the validation studies of the 21-gene RT-PCR assay [13]. A relative risk reduction resulted from trastuzumab among HER2+ patients are assumed to be 36% for up to 2 years according to the results of clinical trial [26]. As mentioned earlier, transitional probabilities between stages after recurrence are adopted from prognosis model of metastatic breast cancer [19, 27]. It is assumed that the response to treatment and the prognosis after recurrence differ depending on HER2 status. Probabilities of the response to treatment for recurrence are fixed at 38.0% among HER2− patients and 54.0% among HER2+ patients [27]. Probabilities of the progression of disease after recurrence are also fixed at: 59.7% if HER2− and having responded to treatment, 53.7% if HER2+ and having responded to treatment, 98.3% if HER2− and not having responded to treatment and 88.5% if HER2+ and not having responded to treatment [19]. Probabilities of death after the progression of disease are fixed at 40.0% among HER2− patients and 37.2% among HER2+ patients [19].

In order to estimate the outcome in terms of QALYs, utility weights are chosen for various health statuses during the clinical course which patients follow. A weight for health status after adjuvant therapy without any toxicity or distant recurrence is chosen to be 0.98 [30]. Weights for toxicities are 0.90 for minor toxicity, and 0.80 for major toxicity [29], of which duration is assumed as 6 months. Health status during chemotherapy against the distant recurrence or the progression of disease weighs 0.50 [31], of which duration is assumed as 6 months. Health statuses after the chemotherapy weigh 0.84 if responded, 0.70 if stable and 0.49 if progressive [27].

Outcome is discounted at a rate of 3% [32].

Costing

From societal perspective, costing should cover the opportunity cost borne by various economic entities in the society. In the context of this study, costs borne by social insurers and patients are considered, since these two entities are major payers to health care providers under Japan's social health insurance system. The amount of direct payments by these entities, mostly according to the national medical care fee schedule, are estimated as costs, while costs to sector other than health and productivity losses are left uncounted in this study. This choice of scope in costing allows the following budget impact estimation.

Cost items are identified along the decision trees and Markov model: the 21-gene RT-PCR assay, adjuvant therapies, treatments for toxicity, monitorings, treatments for distant recurrence, and end-of-life treatments as shown in Table 3. As already mentioned, the cost of the assay is ¥450,000 (US$3,913), according to the price offered by Japanese supplier of Oncotype DX® Breast Cancer Assay. Costs of treatments except the end-of-life treatments are estimated by combining a model of breast cancer care and the national medical care fee schedule. The care model is developed based on both a nationwide survey of Japanese expert practice [22] and consensus guidelines [23, 24].

Adjuvant hormonal therapy includes outpatient care with tamoxifen, aromatase inhibitors, and LH–RH analogues depending on patient's status, and is assumed to continue up to 5 years, which costs ¥534,610 (US$4,649) per year. Adjuvant chemotherapy includes various regimens. Anthracycline-based combination chemotherapy is used for about half of the cases, and oral fluorinated pyrimidine and CMF (cyclophosphamide, methotrexate and 5-fluorouracil) therapy are frequently used among other regimens. These cost ¥343,001 (US$2,983). Adjuvant trastuzumab costs ¥3,105,120 (US$27,001) per year, of which administration is assumed to continue for 1 year.

There are three levels of toxicity in the decision tree. However, only the cost of major toxicity is estimated as ¥173,352 (US$1,507), which includes unplanned 1 month

Table 2 Probabilities and utility weights

	Base case value	Range tested in sensitivity analyses	Source
Probabilities			
Patient status			
HER2[a]+	9.3%	Change by ±50%	[16]
Adjuvant chemotherapy toxicity			
Minor	60.0%	Change by ±50%	[29]
Major	5.0%	Change by ±50%	[29]
Fatal	0.5%	Change by ±50%	[29]
Relative risk reduction of distant recurrence			
Chemotherapy			
Intermediate risk classified by RS[b] criteria	39.0%	Change 0–76%	[13]
High risk classified by RS criteria	74.0%	Change 47–87%	[13]
Trastuzumab	36.0%	Change 24–46%	
(Duration)	(2 years)	Change to 5 years	[26]
Response to treatment for distant recurrence			
HER2−	38.0%	Change by ±50%	[27]
HER2+	54.0%	Change by ±50%	[27]
Progression of disease after distant recurrence			
HER2−, response to treatment	59.7%	Change by ±50%	[19, 27]
HER2−, no response to treatment	98.3%	Change by ±50%	[19, 27]
HER2+, response to treatment	53.7%	Change by ±50%	[19, 27]
HER2+, no response to treatment	88.5%	Change by ±50%	[19, 27]
Death after progression of disease			
HER2−	40.0%	Change by ±50%	[19, 27]
HER2+	37.2%	Change by ±50%	[19, 27]
Utility weights			
After adjuvant therapy without distant recurrence	0.98	Change by ±20%	[30]
Toxicity			
Minor	0.90	Change by ±20%	[29]
Major	0.80	Change by ±20%	[29]
Distant recurrence			
Chemotherapy, 6 months only	0.50	Change by ±20%	[31]
Response to treatment	0.84	Change by ±20%	[27]
Stable	0.70	Change by ±20%	[27]
Progression of disease	0.49	Change by ±20%	[27]

[a] Human epidermal growth factor receptor type2

[b] Recurrence Score

hospitalisation in two-fifths of the cases and rescue treatment at outpatient clinic in three-fifths of the cases [33, 34]. The cost of minor toxicity, from which 60% of patients suffer, is included in the cost of adjuvant chemotherapy, since prophylactic use of antiemetic, for example, is applied routinely these days. And the clinical course of fatal toxicity is diverse and not fit to costing by modelling here, so its cost is estimated later coupled with the cost of end-of-life treatment.

Patients who complete adjuvant therapy are assumed to visit a clinic twice a year for the purpose of monitoring, which costs ¥25,340 (US$220) per year.

There are various options of treatments for the distant recurrence depending on regimens used in adjuvant therapy. Yet, we assume crossover hormonal treatments followed by capecitabine within the first year as typical first line and second line therapies for our hypothetical cohort, which cost ¥558,458 (US$4,856) per year. We further assume that this cost is applicable to second year and afterwards. For HER2+ patients, trastuzumab is additionally administered, of which cost is the same as one during the adjuvant therapy.

The end-of-life treatments are diverse in contexts and lack consensus guidelines or survey data. Its practice

Table 3 Costs

	Base case value	Range tested in sensitivity analyses
21-gene RT-PCR[a] assay (Oncotype DX™ Breast Cancer Assay)	¥ 450,000	Change by ±50%
Adjuvant therapy		
Hormonal therapy, per year	¥ 534,610	Change by ±50%
Chemotherapy	¥ 343,001	Change by ±50%
Trastuzumab, per year	¥ 3,105,120	Change by ±50%
Treatment for toxicity		
Major	¥ 173,352	Change by ±50%
Monitoring		
After adjuvant therapy without recurrence, per year	¥ 25,340	Change by ±50%
Treatment for distant recurrence		
Hormonal therapy and chemotherapy, per year	¥ 558,458	Change by ±50%
Trastuzumab, per year	¥ 3,105,120	Change by ±50%
End-of-life, per year	¥ 1,315,143	Change by ±50%

[a] Reverse transcriptase-polymerase chain reaction

reflects other factor than medical judgements, for example, patients' and their family's preference. Therefore, we do not try to build care model of these cases but exercise an insurance claim review on 80 recent fatal cases in breast cancer at Tokyo Metropolitan Cancer and Infectious Disease Center Komagome Hospital. This results in ¥1,315,143 (US$11,436) per year, which is also used as the cost of treating fatal toxicity.

Costs are also discounted at a rate of 3% [32].

Comparison of scenarios

Incremental cost-effectiveness ratios (ICER) are calculated for the purpose of comparing the scenarios:

$$\mathrm{ICER} = \frac{\mathrm{Cost}_{\mathrm{RS-guided\_treatment}} - \mathrm{Cost}_{\mathrm{NCCN/St\_Gallen-guided\_treatment}}}{\mathrm{Effect}_{\mathrm{RS-guided\_treatment}} - \mathrm{Effect}_{\mathrm{NCCN/St\_Gallen-guided\_treatment}}}$$

Sensitivity analysis

In order to appraise the stability of ICERs against assumptions and uncertainty of adopted values of probabilities, utility weights, and costs in our economic model, one way sensitivity analyses are performed. The age of cohort is changed to 45 and 65 years old. DFRS_{10}s shown in Table 1 are changed by ±50%, which embrace the relaxation of mid-value assumption of DRFS_{10} of patients with intermediate risk according to St Gallen criteria into both end values. The use of adjuvant chemotherapy in NCCN-guided treatment is changed from 50% of high risk cases only to 100% of high risk cases and 50% of low risk cases; and from 0 to 100% of intermediate risk cases in St Gallen-guided treatment. Propensity to alter treatment among patients classified as intermediate risk by RS criteria reclassification is changed from 100 to 50%. As shown in Table 2, probabilities other than relative risk reductions are changed by ±50%, while the relative risk reductions are changed according to the reported 95% confidence intervals of each value. The effectiveness of adjuvant trastuzumab is extended to 5 years. Utility weights are all changed by ±20%. And as shown in Table 3, costs are all changed by ±50%. Discount rate is also changed from 0 to 5%.

Budget impact estimation

Budget impact is defined as a forecast of rates of use (or changes in rates of use) with their consequent short- and medium-term effects on budgets and other resources to help health service managers [35]. The budget in this study is defined as funds held by social insurers. We estimate the budget impact with our economic model assuming that all new LN−, ER+, ESBC in Japan undergo RS-guided treatment instead of NCCN/St Gallen-guided treatment from 2008 to 2012. The incidence of breast cancer is adopted from a forecast [17], and a share of LN−, ER+, ESBC is fixed at 28.7% [16]. A share of the budget in costs is assumed to be 70% according to the co-payment ratio in Japan's social health insurance system.

Results

Cost-effectiveness

Table 4 shows the result of the cost-effective analysis. The cost of RS-guided treatment, ¥4,135,279 (US$35,959),

Table 4 Result of cost-effectiveness analysis

	Cost (¥)	Incremental cost (¥)	Effect (YOLS)	Incremental effect (YOLS)	Effect (QALY)	Incremental effect (QALY)	Incremental cost-effectiveness ratio	
							(¥/YOLS)	(¥/QALY)
NCCN[a]-guided treatment	3,845,923	–	19.812	–	19.309	–	–	–
vs. RS[b]-guided treatment	4,135,279[c]	289,355	19.895[c]	0.083	19.405[c]	0.097	3,465,713	2,997,495
St Gallen-guided treatment	3,841,580	–	19.679	–	19.173	–	–	–
vs. RS-guided treatment	4,134,791[c]	293,211	19.900[c]	0.221	19.410[c]	0.237	1,328,975	1,239,055

[a] National Comprehensive Cancer Network

[b] Recurrence Score

[c] The cost and effects of RS-guided treatment scenario are slightly different from each other in two comparisons because of the difference in the risk reclassification from counterpart scenarios

exceeds that of NCCN-guided treatment, ¥3,845,923 (US$33,443), which results in a positive incremental cost of ¥289,355 (US$2,516). The effect in YOLSs of RS-guided treatment, 19.895 years, exceeds that of NCCN-guided treatment, 19.812 years, which results in a positive incremental effect of 0.083 year. The effect in QALYs of RS-guided treatment, 19.405 years, exceeds that of NCCN-guided treatment, 19.309 years, which results in a positive incremental effect of 0.097 year.

Similarly, the cost of RS-guided treatment, ¥4,134,791 (US$35,955), exceeds that of St Gallen-guided treatment, ¥3,841,580 (US$33,405), which results in a positive incremental cost of ¥293,211 (US$2,550). The effect in YOLSs of RS-guided treatment, 19.900 years, exceeds that of St Gallen-guided treatment, 19.679 years which results in a positive incremental effect of 0.221 year. The effect in QALYs of RS-guided treatment, 19.410 years, exceeds that of St Gallen-guided treatment, 19.173 years, which results in a positive incremental effect of 0.237 year. The cost and effects of RS-guided treatment scenario in this comparison are slightly different from those in the former comparison because of a difference in the risk reclassification from counterpart scenarios.

In both comparisons, the routine use of the 21-gene RT-PCR assay gains more but costs more at the same time. Incremental cost-effectiveness ratios (ICERs) of the former comparison are 3,465,713 ¥/YOLS (30,137 US$/YOLS) and 2,997,495 ¥/QALY (26,065 US$/QALY), and those of the latter comparison are 1,328,975 ¥/YOLS (11,556 US$/YOLS) and 1,239,055 ¥/QALY (10,774 US$/QALY).

Stability of ICER

Figure 2 shows the results of one way sensitivity analyses. Items are listed in the order of the magnitude of ICER change in terms of yen per QALY, while those change ICER less than 200,000 ¥/QALY (1,739 US$/QALY) are not reported.

Between NCCN-guided treatment vs. RS-guided treatment, ICER is most sensitive to the change of the cost of the 21-gene RT-PCR assay, which ranges from ¥672,402 (US$5,847) to ¥5,322,588 (US$46,283). It is also sensitive to the change of the utility weight for a health status after adjuvant therapy without distant recurrence, which ranges from ¥2,861,163 (US$24,880) to ¥5,725,775 (US$49,789). The changes of ICER by the change of all items fall in a range from ¥672,402 (US$5,847) to ¥5,725,775 (US$49,789). Among the values used in the outcome estimation, $DRFS_{10}$ of patients who are reclassified as intermediate risk by RS criteria from low risk by NCCN criteria, has the largest impact on the result. Among costs of treatments, the cost of adjuvant chemotherapy is most influential to the result.

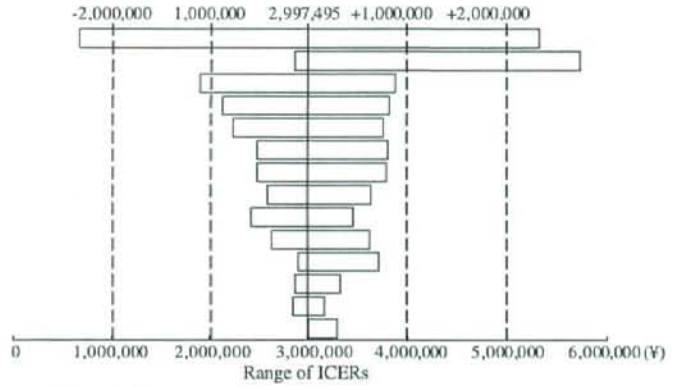
Between St Gallen-guided treatment and RS-guided treatment, ICER is most sensitive to the change of the assumption on the use of adjuvant chemotherapy among patients classified as intermediate risk by St Gallen criteria, which ranges from ¥788,230 (US$6,854) to ¥2,989,020 (US$25,991). It is also sensitive to the change of the cost of the 21-gene RT-PCR assay, which ranges from ¥290,593 (US$2,527) to ¥2,187,518 (US$19,022). The changes of ICER by the change of all items fall in a range from ¥290,593 (US$2,527) to ¥2,989,020 (US$25,991). Among values used in the outcome estimation, $DRFS_{10}$ of patients who are reclassified as high risk by RS criteria from intermediate risk by St Gallen criteria, has the largest impact on the result. Among costs of treatments, the cost of adjuvant chemotherapy is most influential to the result.

Overall, the change of ICERs by the change of assumptions and values is limited from ¥290,593 (US$2,527) to ¥5,725,775 (US$49,789).

Budget impact

Table 5 shows the result of the budget impact estimation. Annual costs per case by the scenario are calculated from our economic model. RS-guided treatment accompanies high costs in the first year, which probably reflects that the

NCCN-guided treatment vs.RS-guided treatment		Left end	Base-case	Right end
	Item	value	value	value
1.	Cost of 21-gene RT-PCR assay	¥225,000	¥450,000	¥675,000
2.	Utility weight (without distant recurrence)	1.00	0.08	0.78
3.	Discount rate	0%	3%	5%
4.	$DRFS_{10}$ (NCCN low risk to RS intermediate risk)	0.41	0.82	1.00
5.	Cost of adjuvant chemotherapy	¥514,501	¥343,001	¥171,500
6.	Risk reduction (RS intermediate risk)	76%	30%	0%
7.	Probability of fatal toxicity	0.0075	0.005	0.0025
8.	$DRFS_{10}$ (NCCN low risk to RS high risk)	0.29	0.57	0.86
9.	Utility weight (minor toxicity)	0.72	0.90	1.00
10.	Age of cohort	45	55	65
11.	$DRFS_{10}$ (NCCN high risk to RS high risk)	1.00	0.92	0.46
12.	Risk reduction (RS high risk)	87%	74%	47%
13.	Probability of minor toxicity	0.0	0.6	0.3
14.	Propensity to alter treatment (RS intermediate risk)	-	100%	50%



St Gallen-guided treatment vs. RS-guided treatment		Left end	Base-case	Right end
	Item	value	value	value
1.	Use of adjuvant chemotherapy (St Gallen intermediate risk)	0%	50%	100%
2.	Cost of 21-gene RT-PCR assay	¥225,000	¥450,000	¥675,000
3.	$DRFS_{10}$ (St Gallen intermediate risk to RS high risk)	0.31	0.62	0.93
4.	Propensity to alter treatment (RS intermediate risk)	-	100%	50%
5.	Discount rate	0%	3%	5%
6.	Risk reduction (RS intermediate risk)	76%	30%	0%
7.	$DRFS_{10}$ (St Gallen intermediate risk to RS intermediate risk)	0.41	0.82	1.00
8.	Risk reduction (RS high risk)	87%	74%	47%
9.	Utility weight (without distant recurrence)	1.00	0.08	0.78
10.	Age of cohort	45	55	65
11.	Cost of adjuvant chemotherapy	¥514,501	¥343,001	¥171,500
12.	$DRFS_{10}$ (St Gallen low risk to RS intermediate risk)	0.41	0.82	1.00
13.	Cost of end-of-life	¥1,972,715	¥1,315,143	¥657,572

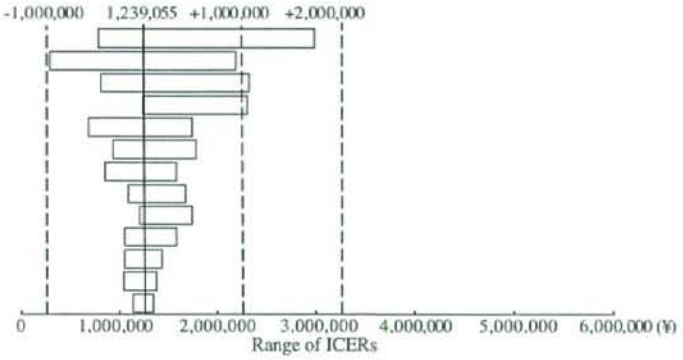


Fig. 2 Results of sensitivity analyses. Abbreviations: National Comprehensive Cancer Network (NCCN), reverse transcriptase-polymerase chain reaction (RT-PCR), recurrence score (RS), distant recurrence free survival in 10 years ($DRFS_{10}$) incremental cost-effectiveness ratio (ICER)

Table 5 Result of budget impact estimation

1. Annual cost per case

		First year	Second year	Third year	Fourth year	Fifth year
NCCN[a]-guided treatment vs. RS[b]-guided treatment	NCCN-guided treatment	¥1,677,915	¥535,596	¥541,683	¥548,444	¥579,241
	RS-guided treatment	¥1,976,790	¥536,596	¥542,448	¥548,958	¥579,614
St Gallen-guided treatment vs. RS-guided treatment	St Gallen-guided treatment	¥1,657,096	¥536,627	¥543,647	¥551,397	¥582,994
	RS-guided treatment	¥2,002,128	¥536,594	¥542,439	¥548,939	¥579,581

2. Annual incidence

	2008	2009	2010	2011	2012
Incidence of breast cancer	43,939	44,754	45,569	46,150	46,731
Incidence of LN−, ER+, ESBC	12,610	12,844	13,078	13,245	13,412

3. Budget impact estimation

		2008	2009	2010	2011	2012
NCCN-guided treatment vs. RS-guided treatment	Cost of NCCN-guided treatment	¥21,158 million	¥28,274 million	¥35,572 million	¥42,937 million	¥50,733 million
	Cost of RS-guided treatment	¥24,927 million	¥32,140 million	¥39,553 million	¥46,972 million	¥54,844 million
	Incremental cost	¥3,769 million	¥3,866 million	¥3,961 million	¥4,035 million	¥4,111 million
	Budget impact	¥2,638 million	¥2,706 million	¥2,773 million	¥2,825 million	¥2,877 million
St Gallen-guided treatment vs. RS-guided treatment	Cost of St Gallen-guided treatment	¥20,856 million	¥28,025 million	¥35,346 million	¥42,743 million	¥50,576 million
	Cost of RS-guided treatment	¥25,247 million	¥32,465 million	¥39,845 million	¥47,307 million	¥55,183 million
	Incremental cost	¥4,351 million	¥4,440 million	¥4,518 million	¥4,546 million	¥4,607 million
	Budget impact	¥3,046 million	¥3,108 million	¥3,163 million	¥3,195 million	¥3,225 million

[a] National Comprehensive Cancer Network

[b] Recurrence Score

high price of the 21-gene RT-PCR assay is not cancelled out by the reduction of adjuvant chemotherapy.

Costs treating LN−, ER+, ESBC incidence with NCCN/St Gallen/RS-guided treatment are calculated by the year taking mortality into account, and incremental costs are also calculated by the year according to comparisons. Calculated with these costs, the budget impact of the diffusion of the assay in Japan is estimated as ¥2,638 million (US$23 million) to ¥3,225 million (US$28 million).

Discussion

We evaluate the cost-effectiveness of the 21-gene RT-PCR assay in Japan's health care system with two scenarios depicting status quo and one scenario of the routine use of the assay for LN−, ER+, ESBC. Our economic model indicates that the diffusion of the assay gains more in terms of outcome but costs more at the same time. The estimated ICERs, 2,997,495 ¥/QALY (26,065 US$/QALY) and 1,239,055 ¥/QALY (10,774 US$/QALY), comparing NCCN/St Gallen-guided treatment with RS-guided treatment, respectively, are not more than a suggested social willingness-to-pay for one life year gain from an innovative medical intervention in Japan, 6,000,000 ¥/QALY (52,174 US$/QALY) [36]. Sensitivity analyses show that this result is plausibly robust, since ICERs do not exceed the threshold by various changes of assumptions made or values employed. In this sense, the assay has good value for money.

Incremental effects in terms of QALY are longer than those in terms of YOLS; and ICERs in terms of yen per QALY are smaller than those in terms of yen per YOLS in both comparisons. These imply that the assay is not only efficient in prolonging survival but also improving quality of life.

Our sensitivity analyses also reveal that the price of the assay is one of the major determinants of cost-effectiveness as expected. An intuitive comparison with the price of a conventional gene diagnosis test of malignant tumour in Japan, ¥450,000 (US$3,913) vs. ¥20,000 (US$174), seems to make a health manager feel it difficult to reimburse the cost of the assay by the social insurance, because there may be an incompatibility to an incremental manner of revising fee schedule. Our study, however, implies that the price offered by Japanese supplier of Oncotype DX® Breast Cancer Assay still makes ICER an acceptable level from the viewpoint of welfare economics.

We estimate the budget impact of the assay on the social health insurance system. The policy implication of the budget impact is not prescriptive [37]. Yet, the estimated impact, ¥2,638 million (US$23 million) to ¥3,225 million (US$28 million) per year for the coming 5 years, is substantially less than the estimated budget impact of adjuvant trastuzumab, which is about to be included into social insurance benefit, ¥16,000 million (US$139 million) to ¥32,000 million (US$278 million) [38]. The characteristics of the assay of which application is limited to only once per case probably contribute to this difference, since the cost of trastuzumab amounts through its repeated administration. This implies that the diffusion of the assay through listing as an approved diagnostic test by the social health insurance could be justifiable.

The past economic evaluation of the assay reported from the U.S. considers a change from NCCN-guided treatment to RS-guided treatment [19], while our model allows a comparison between NCCN-guided treatment and St Gallen-guided treatment as an ex ante scenario. We find a notable difference in ICERs in this comparison. The ICER of the change from St Gallen-guided treatment is more favourable than that from NCCN-guided treatment. This is interesting because the reduction of use of adjuvant chemotherapy according to the reclassification from St Gallen criteria, 26%, is smaller than that from NCCN, 43%. The difference in ICER is due to more gain in the outcome. Although caution is needed in transferring the findings from economic models to any different context [39], our model might indicate that the assay has better value for money in countries where St Gallen-guided treatment is widely used.

However, this study has its own limitations. First, our outcome estimation depends on the validation studies carried out in the U.S. Although the evidences adopted are considered as the best available knowledge, it is needless to say that there are differences in population, as well as in cancer care practice between the U.S. and Japan. With this in regard, another validation study employing Japanese historical clinical trial data with the gene assay of preserved tumour tissue is launched [40]. A further economic evaluation incorporating new evidences is necessary to confirm the findings of this study. Second, utility weights adopted here are also derived from Western countries due to an unavailability of data from Japan. Third, our model does not include potentially costly clinical stages such as local recurrence or contralateral breast cancer due to the lack of data in validation studies. Regarding these shortcomings, reports and data that refines the model are awaited. Fourth, consensus guidelines are renewed continuously by incorporating newly available evidences [11, 41], so that the relative usefulness of the assay may be diminished in the near future, or the assay may be incorporated in the guidelines in a long run.

The use of the 21-gene RT-PCR assay has just begun to have an impact on clinical recommendations made by the U.S. oncologists and patients' choice [42]. It is easy to imagine that similar change in practice will occur in Japan

soon, because patients have strong preference to innovation such as tailor-made medicine [1]. As the prognostic usefulness of the 21-gene RT-PCR assay in guiding treatment for lymph-node-positive cases is recently reported [43], the indication of the assay will expand. Further economic evaluation that responds to this contextual change may become imperative.

Once the usefulness of the assay is confirmed by the Japanese validation study, Japanese health manager inevitably needs to decide how to fit the assay to the health care system. The results of this study imply the possibility of coverage by the social insurance. If health manager gives much importance to fiscal policy or cost containment, the selective indication of the assay for higher risk patients, which results to avoid additional use of adjuvant chemotherapy, might be a potential option. Further analysis incorporating such scenarios may be useful.

In conclusion, the routine use of the 21-gene RT-PCR assay for LN−, ER+, ESBC is indicated as cost-effective with a fundable level of budget impact in Japan. The results could inform health managers in developed countries where NCCN-guided treatment as well as St Gallen-guided treatment are practiced.

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Economic evaluation of chemoprevention of breast cancer with tamoxifen and raloxifene among high-risk women in Japan

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Raloxifene was approved for chemoprevention against breast cancer among high-risk women in addition to tamoxifen by the US Food and Drug Administration. This study aims to evaluate cost-effectiveness of these agents under Japan's health system. A cost-effectiveness analysis with Markov model consisting of eight health states such as healthy, invasive breast cancer, and endometrial cancer is carried out. The model incorporated the findings of National Surgical Adjuvant Breast and Bowel Project P-1 and P-2 trial, and key costs obtained from health insurance claim reviews. Favourable results, that is cost saving or cost-effective, are found by both tamoxifen and raloxifene for the introduction of chemoprevention among extremely high-risk women such as having a history of atypical hyperplasia, a history of lobular carcinoma *in situ* or a 5-year predicted breast cancer risk of $\geqslant$5.01% starting at younger age, whereas unfavourable results, that is 'cost more and gain less' or cost-ineffective, are found for women with a 5-year predicted breast cancer risk of $\leqslant$5.00%. Therapeutic policy switch from tamoxifen to raloxifene among postmenopausal women are implied cost-effective. Findings suggest that introduction of chemoprevention targeting extremely high-risk women in Japan can be justifiable as an efficient use of finite health-care resources, possibly contributing to cost containment.
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Several clinical trials have demonstrated the effectiveness of prophylactic administration of selective oestrogen receptor modulators (SERMs) such as tamoxifen (Fisher *et al*, 2005; Cuzick *et al*, 2007; Powles *et al*, 2007; Veronesi *et al*, 2007b) and raloxifene (Cauley *et al*, 2001; Martino *et al*, 2004; Vogel *et al*, 2006) in reducing incidence of breast cancer among women at high risk of developing the disease. Tamoxifen was approved for prophylaxis by the US Food and Drug Administration in 1998, and raloxifene was also approved for postmenopausal women in 2007.

Tamoxifen reduces the risk of breast cancer whereas increasing the risk of adverse events such as endometrial cancer and pulmonary embolism. Raloxifene is a second-generation SERM usually used for osteoporosis treatment, and it reduces the risk of invasive breast cancer with a lower risk of known adverse events associated with SERMs, compared to tamoxifen. This is because raloxifene does not induce the unwanted stimulation of endometrium (Delmas *et al*, 1997). Therefore, raloxifene is considered to have a better clinical property as prophylactic agent, although it is inferior to tamoxifen in preventing noninvasive breast cancer. More women at high risk of developing breast cancer are expected to take raloxifene as their breast cancer prevention drug in the United States (Bevers, 2007).

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However, both of these agents have been neither approved nor made available for its use as breast cancer prevention in Japan, although experts have shown their expectations (Iwata and Saeki, 2006). It is said that there are five hurdles to overcome in addressing intervention in the diffusion process of new drug: quality, safety, efficacy, cost-effectiveness, and affordability (Trueman *et al*, 2001). This paper aims to present evidence to the fourth hurdle, cost-effectiveness of both agents, under Japan's health system. Although cost-effectiveness of prophylactic use of tamoxifen has been reported from the USA (Noe *et al*, 1999; Grann *et al*, 2000; Smith and Hillner, 2000; Hershman *et al*, 2002; Melnikow *et al*, 2006) and Australia (Eckermann *et al*, 2003), that of raloxifene has not been published to date except as a part of economic evaluation of osteoporosis management (Armstrong *et al*, 2001; Kanis *et al*, 2005). This paper also simulates a therapeutic policy switch from tamoxifen to raloxifene among postmenopausal women to illustrate the relative value of raloxifene. Consequently, it should have implications to the developed countries where chemoprevention with tamoxifen is already in practise.

METHODS

We conduct a cost-effectiveness analysis with Markov modelling based on the findings of the National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 trial (Fisher *et al*, 2005), the NSABP P-2 trial (Vogel *et al*, 2006), and the literature on costing under

Japan's health system including sensitivity analyses from societal perspective. Although longer follow-up results for tamoxifen are reported from the first International Breast Cancer Intervention Study (IBIS-I; Cuzick *et al*, 2007) and the Royal Marsden trial (Powles *et al*, 2007), NSABP P-1 trial with a shorter follow-up period is chosen as clinical evidence for our modelling to make clear comparisons with NSABP P-2 trial of raloxifene. The long-term outcomes for tamoxifen (Veronesi *et al*, 2007a) are considered in our sensitivity analyses. We use TreeAge Pro 2008 (TreeAge Software Inc.) for our economic modelling.

High-risk women

We model high-risk women according to the risk classifications featured in the report of clinical trials: three levels ($\geqslant$1.66, 3.01–5.00%, $\geqslant$5.01%) of a 5-year predicted breast cancer risk, with a history of lobular carcinoma *in situ* (LCIS), and with a history of atypical hyperplasia (AH). A 5-year predicted breast cancer risk of an individual woman used in the trials is based on Gail *et al* model 2 (Gail and Costantino, 2001), which is validated for white women (Rockhill *et al*, 2001) and African American women (Gail *et al*, 2007), to date. We assume the same model is good for Japanese women.

We also model the ages of starting prophylaxis: 35, 50, 60 years old for tamoxifen, and 50, 60 years old for raloxifene taking the menopause into account.

Markov model

We construct a Markov model of courses followed by high-risk women, which is shown in Figure 1. Eight health states are modelled according to clinical events monitored and found significant in P-1 trial and P-2 trial: (1) healthy; (2) invasive breast cancer; (3) noninvasive breast cancer, (4) endometrial cancer; (5) pulmonary embolism; (6) cataract; (7) hip fracture; and (8) dead. Healthy women at high risk of the disease, women with invasive and noninvasive breast cancer are the target health states for chemoprevention. An increase in risk of endometrial cancer, pulmonary embolism, and cataract are known as adverse effects of SERMs, whereas a decrease in risk of hip fracture is known as a beneficial effect. Transitions between health states are indicated with arrows.

The time span of each stage is set at 1 year, since trials report annual incidence rates. Markov process is repeated until death or age 100, whichever comes first, since all events are expected to occur within this time horizon. Women who survive after the age of 100 years are assumed to die regardless of breast cancer development.

Chemoprevention

Prophylaxis with SERMs is continued for 5 years, or discontinued in case of adverse events, which is similar to the regimen employed in clinical trials.

Comparisons

We compare outcomes and costs in terms of incremental cost-effectiveness ratios (ICERs) between *status quo* in Japan, without prophylaxis, and hypothetical practise, with prophylaxis, by the agent (tamoxifen and raloxifene), the risk classification, and the age of starting prophylaxis.

$$\mathrm{ICER} = \frac{\mathrm{Cost}_{\text{with prophylaxis}} - \mathrm{Cost}_{\text{without prophylaxis}}}{\mathrm{Effect}_{\text{with prophylaxis}} - \mathrm{Effect}_{\text{without prophylaxis}}}$$

We also compare prophylaxis with tamoxifen and prophylaxis with raloxifene to estimate the relative value of raloxifene to tamoxifen, although this does not depict any marginal change in Japan.

Outcome estimation

Outcomes in terms of life years gained (LYGs) and quality adjusted life years (QALYs) are estimated by assigning transitional probabilities and utility weights to Markov model from the literature.

Transitional probabilities from healthy state to disease states in Markov model are shown in Table 1 according to the findings from the clinical trials. Risk reduction effect of SERMs is assumed to continue during the 5-year course of prophylaxis.

Table 2 summarises other assumptions such as transitional probabilities from disease states to dead state and utility weights used in Markov model. The share of clinical stages of invasive breast cancer at diagnosis are adopted from a nationwide survey on breast cancer screening (Japan Cancer Society, 2007), of which prognosis is calculated from corresponding follow-up cases at Tokyo Metropolitan Cancer and Infectious Disease Centre Komagome Hospital. The prognosis of endometrial cancer is also adopted from a nationwide cancer registry (Japanese Society of Obstetrics and Gynecology, 2000). The prognosis of pulmonary embolism and hip fracture are taken from Sakuma *et al* (2004); Kitamura *et al* (1998), respectively. Japanese female population

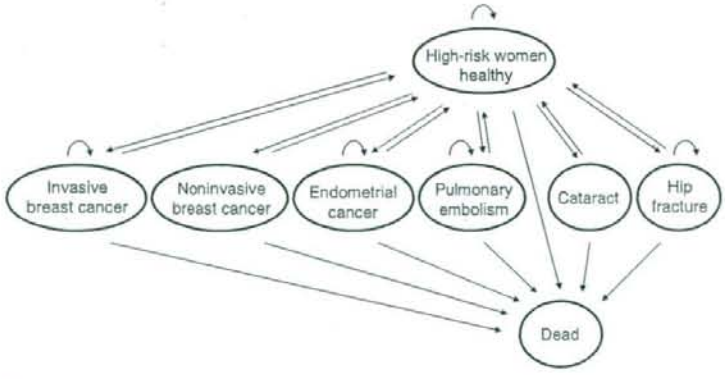

Figure 1 Markov model.

Table 1 Transitional probabilities from healthy state to disease states in Markov model

	Placebo		Tamoxifen			Raloxifene		
	Base-case value	Source	Base-case value	Range tested in sensitivity analysis[a]	Source	Base-case value	Range tested in sensitivity analysis[a]	Source
Invasive breast cancer								
Five-year predicted breast cancer risk ⩾1.66%								
Age of starting prophylaxis								
35	0.00632	Fisher *et al* (2005)	0.00404	0.00235–0.00641	Fisher *et al* (2005)			
50	0.00587	Fisher *et al* (2005)	0.00333	0.00168–0.00573	Fisher *et al* (2005)	0.00310	0.00184–0.00490	Fisher *et al* (2005), Vogel *et al* (2006)
60	0.00668	Fisher *et al* (2005)	0.00330	0.00165–0.00567	Fisher *et al* (2005)	0.00366	0.00213–0.00585	Fisher *et al* (2005), Vogel *et al* (2006)
Five-year predicted breast cancer risk 3.01–5.00%	0.00451	Fisher *et al* (2005)	0.00270	0.00108–0.00534	Fisher *et al* (2005)	0.00203	0.00101–0.00349	Fisher *et al* (2005), Vogel *et al* (2006)
Five-year predicted breast cancer risk ⩾5.01%	0.01198	Fisher *et al* (2005)	0.00515	0.00245–0.00893	Fisher *et al* (2005)	0.00561	0.00323–0.00894	Fisher *et al* (2005), Vogel *et al* (2006)
History of lobular carcinoma in situ	0.01170	Fisher *et al* (2005)	0.00627	0.00161–0.01476	Fisher *et al* (2005)	0.00614	0.00239–0.01226	Fisher *et al* (2005), Vogel *et al* (2006)
History of atypical hyperplasia	0.01042	Fisher *et al* (2005)	0.00255	0.00029–0.00686	Fisher *et al* (2005)	0.00286	0.00133–0.00523	Fisher *et al* (2005), Vogel *et al* (2006)
Noninvasive breast cancer	0.00012	Fisher *et al* (2005)	0.00004	0.00000–0.00652	Fisher *et al* (2005)	0.00006	0.00003–0.00009	Fisher *et al* (2005, Vogel *et al* (2006)
Endometrial cancer								
Age of starting prophylaxis								
35	0.00082	Fisher *et al* (2005)	0.00116	0.00010–0.00410	Fisher *et al* (2005)			
50 and 60	0.00058	Fisher *et al* (2005)	0.00308	0.00061–0.00992	Fisher *et al* (2005)	0.00194	0.00065–0.00403	Fisher *et al* (2005), Vogel *et al* (2006)
Pulmonary embolism								
Age of starting prophylaxis								
35	0.00013	Fisher *et al* (2005)	0.00025	0.00000–0.00420	Fisher *et al* (2005)			
50 and 60	0.00044	Fisher *et al* (2005)	0.00096	0.00020–0.00275	Fisher *et al* (2005)	0.00061	0.00028–0.00114	Fisher *et al* (2005), Vogel *et al* (2006)
Cataract	0.02285	Fisher *et al* (2005)	0.02775	0.02384–0.03206	Fisher *et al* (2005)	0.02192	0.01735–0.02734	Fisher *et al* (2005), Vogel *et al* (2006)
Hip fracture	0.00086	Fisher *et al* (2005)	0.00059	0.00022–0.00122	Fisher *et al* (2005)	0.00052	0.00016–0.00115	Fisher *et al* (2005), Vogel *et al* (2006)

[a]1.5 times of 95% confidence interval.

mortality rates from Vital Statistics (Ministry of Health, Labour and Welfare, 2005a) are applied for other transitions to dead state.

It is more preferable to adopt utility weights from a consistent study that assesses our six disease states in Japan, but there is no Japanese utility weight in the literature to date, which may be applied to any health states in our model. To illustrate the typical patient states, we adopt the weights assessed in developed countries considering them as the best available knowledge, and choosing them under the consensus of staff doctors at Tokyo Metropolitan Cancer and Infectious Disease Centre Komagome Hospital (de Koning *et al*, 1991; Hillner *et al*, 1993; Smith and Hillner, 1993; Grann *et al*, 1998; Earle *et al*, 2000; Armstrong *et al*, 2001; Chau *et al*, 2003; Cykert *et al*, 2004; Naeim and Keeler, 2005; Ruof *et al*, 2005).

Outcome is discounted at a rate of 3%.

Costing

From societal perspective, costing should cover the opportunity cost borne by various economic entities in the society. In the context of this study, costs borne by women or third party payers including the government and social insurers are considered, although there is no particular assumption about who bears the cost of chemoprevention. According to the national medical care fee schedule, the amount of direct payments to health-care providers is estimated as cost, whereas costs to sectors other than health and productivity losses are left uncounted.

Health states are identified as cost items in Markov model. Table 3 summarises the cost of each health states. Being in healthy state, women with chemoprevention take 20 mg per day, ¥82.6 (£0.41; £1 = ¥200), of tamoxifen, or 60 mg per day, ¥148.5 (£0.74), of raloxifene, prescribed regularly for 5 years, and annual mammography checkup. Women without chemoprevention also undergo annual mammography checkup. Although the state is labelled as 'healthy', it includes all other diseases that are not modelled in Markov model. Annual treatment costs by the age stratum are approximated by annual health-care expenditure per woman adopted from National Health-Care Expenditure (Ministry of Health, Labour and Welfare, 2005b). As it is well known that the cost of health care in the last year of life tends to be large, these are shown separately after an adjustment based on Fukawa (1998).

Table 3 also summarises the treatment cost of invasive breast cancer by the age stratum. In the case of cancer care, the cost in the first year after diagnosis tends to be large as well as in the last year of life, so here again, the costs are shown separately. These figures are obtained from insurance claim reviews at Tokyo Metropolitan Cancer and Infectious Disease Centre Komagome Hospital. As to the cost of the first year, recent breast cancer cases of stage I and

Table 2 Assumptions used in Markov model

	Assumption	Range tested in sensitivity analysis	Source
Transitional probabilities from disease states to dead state			
Invasive breast cancer	0–9 years after diagnosis: prognosis of Japanese breast cancer patients by the stage	Change by ± 50%	Calculated from follow-up patients at Komagome Hospital
	Stage I: 0.0074, 0.0155, 0.0113, 0.0218, 0.0254, 0.0248, 0.0289, 0.0165, 0.01632		
	Stage II: 0.0054, 0.0474, 0.0570, 0.0334, 0.0398, 0.0321, 0.0275, 0.0295, 0.04672		
	(Proportions of stage at diagnosis are assumed stage I as 72% and stage II as 28%)	Change by ± 50%	Japan Cancer Society (2007)
	Thereafter: Japanese female population mortality rates	Change by ± 50%	Ministry of Health, Labour and Welfare (2005a)
Noninvasive breast cancer	Japanese female population mortality rates	Change by ± 50%	Ministry of Health, Labour and Welfare (2005a)
Endometrial cancer	0–4 years after diagnosis: prognosis of Japanese endometrial cancer patients 0.0660, 0.0546, 0.0328, 0.02813	Change by ± 50%	Japanese Society of Obstetrics and Gynecology (2000)
	Thereafter: Japanese female population mortality rates	Change by ± 50%	Ministry of Health, Labour and Welfare (2005a)
Pulmonary embolism	0 year after diagnosis: 0.08	Change by ± 50%	Sakuma *et al* (2004)
	Thereafter: Japanese female population mortality rates	Change by ± 50%	Ministry of Health, Labour and Welfare (2005a)
Cataracts	Japanese female population mortality rates	Change by ± 50%	Ministry of Health, Labour and Welfare (2005a)
Hip fracture	0–1 years after diagnosis: 0.11 and 0.19, respectively	Change by ± 50%	Kitamura *et al* (1998)
	Thereafter: Japanese female population mortality rates	Change by ± 50%	Ministry of Health, Labour and Welfare (2005a)
Utility weights			
Healthy	1.00	Change by ± 20%	
Healthy under chemoprevention for 5 years	0.99	Change by ± 20%	Smith and Hillner (1993), Hillner *et al* (1993), Naeim and Keeler (2005)
Invasive breast caner	0 year after diagnosis: 0.87, thereafter: 0.89	Change by ± 20%	de Koning *et al* (1991), Grann *et al* (1998)
Noninvasive breast cancer	0.98	Change by ± 20%	Earle *et al* (2000)
Endometrial cancer	0 year after diagnosis: 0.83, thereafter: 0.88	Change by ± 20%	Armstrong *et al* (2001), Cykert *et al* (2004)
Pulmonary embolism	0.70	Change by ± 20%	Chau *et al* (2003)
Cataract surgery	0.96	Change by ± 20%	Ruof *et al* (2005)
Hip fracture	0–1 years after diagnosis: 0.61 and 0.92, respectively	Change by ± 20%	Armstrong *et al* (2001)

stage II that have undergone initial treatment with a follow-up of 1 year are retrospectively selected so that each age strata has 40 cases. As to the yearly cost of the second year and thereafter, 40 cases for each age strata are randomly selected from follow-up cases initially diagnosed as stage I and stage II. As to the cost of the last year of life, recent 80 fatal cases are retrospectively selected, as the number of these is relatively limited. Insurance claims of these total of 400 cases for 1 year are reviewed to calculate average annual costs by the age strata. Then an adjustment is made to include the cost of prescription to be filled at external pharmacies, such as in the case of adjuvant hormonal therapy, which is based on the consensus among staff doctors.

Costs of disease states are summarised in Table 3 as well. Treatment costs of noninvasive breast cancer, endometrial cancer, cataract, and hip fractures are adopted from a background study for the development of Japanese prospective payment system to health-care providers, diagnosis procedure combination (Matsuda and Ishikawa, 2003), whereas treatment cost of pulmonary embolism is adopted from Fuji *et al* (2005).

Costs are also discounted at a rate of 3%.

Sensitivity analyses

To deal with the uncertainty of probabilities, utility weights, and costs used in our economic model, one-way sensitivity analyses are performed. Transitional probabilities from healthy state to disease states shown in Table 1 are varied in 1.5 times of 95% confidence intervals (CI) reported from the clinical trials. 95% CI is often used for similar exercises of sensitivity analyses, but we set wider range for the applicability of the clinical trial data to Japanese women. The other probabilities shown in Table 2 are changed by ± 50%. Utility weights are changed by ± 20%, and we think this could cover the difference between the utility weights of Japanese women and those of the other developed nations. Costs shown in Table 3 are changed by ± 50%. Discount rate is also changed from 0 to 6%.

Acknowledging the long-term outcomes for tamoxifen in the IBIS-I trial (Cuzick *et al*, 2007) and the Royal Marsden trial (Powles *et al*, 2007), risk reduction effect of tamoxifen is prolonged from 5 to 10 and 15 years without any risk increase of adverse events after the completion of prophylaxis.

RESULTS

Outcomes

Table 4 shows the results of cost-effectiveness analysis comparing prophylaxis with no prophylaxis.

In the comparison between prophylaxis with tamoxifen *vs* no prophylaxis, most outcomes in terms of LYGs are increased by chemoprevention except for women with a 5-year predicted breast cancer risk of $\geqslant$1.66% starting at age 50, and women with a 5-year predicted breast cancer risk of 3.01–5.00% starting at age 50 and 60. Outcomes in terms of QALYs are also increased except for women with a 5-year predicted breast cancer risk of $\geqslant$1.66% starting at age 50 and 60, women with a 5-year predicted breast cancer risk of 3.01–5.00%, and women with a history of LCIS starting at age 60. The largest outcome gain in terms of QALYs, 0.105, is estimated among women with a history of AH starting at age 35.

Between prophylaxis with raloxifene *vs* no prophylaxis, all outcomes in terms of LYGs are increased by chemoprevention. Outcomes in terms of QALYs are increased except for women with a 5-year predicted breast cancer risk of $\geqslant$1.66%, and women with

Table 3 Costs (¥)

	Healthy			Breast cancer		
	Base-case value	**Range tested in sensitivity analysis**	**Source**	**Base-case value**	**Range tested in sensitivity analysis**	**Source**
Chemoprevention						
Tamoxifen	30 149	Change by ± 50%	Drug price list, etc			
Raloxifene	54 203	Change by ± 50%				
Prescription+annual mammography	44 980	Change by ± 50%				
Annual mammography	15 520	Change by ± 50%				
Ages 35–49						
First year after diagnosis				1 978 064	Change by ± 50%	
Yearly cost				383 743	Change by ± 50%	
Ages 35–39	81 937	Change by ± 50%				
Ages 40–44	94 529	Change by ± 50%	Ministry of Health, Labour and Welfare (2005b), Fukawa (1998)			Insurance claim review
Ages 45–49	110 604	Change by ± 50%				
Terminal care cost, last year of life				5 495 224	Change by ± 50%	
Ages 35–39	352 331	Change by ± 50%				
Ages 40–44	406 474	Change by ± 50%				
Ages 45–49	475 599	Change by ± 50%			Change by ± 50%	
Ages 50–64						
First year after diagnosis				2 211 083	Change by ± 50%	
Yearly cost				542 857	Change by ± 50%	
Ages 50–54	151 625	Change by ± 50%	Ministry of Health, Labour and Welfare (2005b), Fukawa (1998)			Insurance claim review
Ages 55–59	195 085	Change by ± 50%				
Ages 60–64	258 723	Change by ± 50%				
Terminal care cost, last year of life				4 106 271	Change by ± 50%	
Ages 50–54	631 986	Change by ± 50%				
Ages 55–59	838 866	Change by ± 50%				
Ages 60–64	1 112 510	Change by ± 50%				
Ages 65–79						
First year after diagnosis				1 530 259	Change by ± 50%	
Yearly cost				441 458	Change by ± 50%	
Ages 65–69	324 347	Change by ± 50%				
Ages 70–74	460 617	Change by ± 50%	Ministry of Health, Labour and Welfare (2005b), Fukawa (1998)			Insurance claim review
Ages 75–79	549 284	Change by ± 50%				
Terminal care cost, last year of life				3 252 302	Change by ± 50%	
Ages 65–69	1 394 690	Change by ± 50%				
Ages 70–74	1 980 653	Change by ± 50%				
Ages 75–79	2 361 923	Change by ± 50%				
Ages 80+						
First year after diagnosis			Ministry of Health, Labour and Welfare (2005b), Fukawa (1998)	961 181	Change by ± 50%	Insurance claim review
Yearly cost				185 151	Change by ± 50%	
Ages 80–84	576 290	Change by ± 50%				
Ages 85–89	647 941	Change by ± 50%				
Ages 90–94	557 429	Change by ± 50%				
Ages 95–100	465 059	Change by ± 50%				
Terminal care cost, last year of life				427 042	Change by ± 50%	
Ages 80–84	2 478 049	Change by ± 50%				
Ages 85–89	2 786 147	Change by ± 50%				
Ages 90–94	2 396 943	Change by ± 50%				
Ages 95–100	1 999 754	Change by ± 50%				

Table 3 (*Continued*)

	Diseases		
	Base-case value	**Range tested in sensitivity analysis**	**Source**
Noninvasive breast cancer surgery, etc (DPC090010 3x020xxx+ reimbursements by FFS)	847 928	Change by ± 50%	Matsuda and Ishikawa (2003)
Endometrial cancer Total hysterectomy, etc (DPC 1200203x01x0xx+ reimbursements by FFS)	1 183 839	Change by ± 50%	Matsuda and Ishikawa (2003)
Pulmonary embolism Total (Diagnosis) (Treatment)	469 890 (52 350) (417 540)	Change by ± 50%	Fuji *et al* (2005)
Cataract Surgery, etc (DPC 0201103x01x 000+reimbursements by FFS)	309 120	Change by ± 50%	Matsuda and Ishikawa (2003)
Hip fracture Surgery, etc (DPC 1608003x02xx0x+ reimbursements by FFS)	1553 195	Change by ± 50%	Matsuda and Ishikawa (2003)

DPC: diagnosis procedure combination; FFS: fee for service.

a 5-year predicted breast cancer risk of 3.01–5.00%. The largest outcome gain in terms of QALYs, 0.058, is estimated among women with a history of AH starting at age 50.

Table 5 shows the results of cost-effectiveness analysis of therapeutic policy switch from tamoxifen to raloxifene.

Raloxifene is consistently superior to tamoxifen across presented risk classifications and starting ages of prophylaxis.

Costs

In the comparison between prophylaxis with tamoxifen *vs* no prophylaxis (Table 4), cost savings are estimated in higher risk classifications, among women with a history of LCIS or AH, starting at younger age. The largest saving, ¥367 901 (£1840), is estimated among women with a history of AH starting at age 35.

Between prophylaxis with raloxifene *vs* no prophylaxis, prophylaxes are found more costly. A cost saving of ¥10 387 (£52) is estimated among women with a history of AH starting at age 50.

When considering the therapeutic policy switch (Table 5), the use of raloxifene is consistently more costly than tamoxifen, as anticipated by the difference in price of agents.

Cost-effectiveness

There is a suggested criterion for cost-effectiveness in Japan (Ohkusa, 2003) to be ¥6000 000 (£30 000) for one QALY gain, and both Tables 4 and 5 report judgements with this criterion.

In the comparison between prophylaxis with tamoxifen *vs* no prophylaxis, favourable results, that is 'cost less and gain more' or cost-effective, are obtained in higher risk classifications starting at younger age. Those are: women with a history of AH regardless of starting age, women with a history of LCIS starting at age 35 and 50, and women with a 5-year predicted breast cancer risk of ⩾5.01% starting at age 35 and 50.

Similar results are found between prophylaxis with raloxifene *vs* no prophylaxis. Favourable results are: women with a history of AH regardless of starting age, women with a history of LCIS starting at age 50, and women with a 5-year predicted breast cancer risk of ⩾5.01% starting at age 50.

As shown in Table 5, ICERs for the therapeutic policy switch of prophylactic agent from tamoxifen to raloxifene varies from ¥1 839 670 per QALY (£9198 per QALY) to ¥6771 100 per QALY (£33 856 per QALY). The larger ICER is yet still close to the suggested criterion of ¥6000 000 per QALY (£30 000 per QALY).

Stability of cost-effectiveness

One-way sensitivity analyses produce similar results across the agents, the risk classifications and the ages of starting prophylaxis. Therefore, we draw a cost-effectiveness plane to show the comparison between prophylaxis with raloxifene *vs* no prophylaxis among three risk classifications as an example: women with a 5-year predicted breast cancer risk of ⩾5.01%, women with a history of LCIS, and women with a history of AH.

Figure 2 plots three base-case values and 306 results (102 changes of variables × three different risk classifications). Line OA indicates the threshold of favourable ICER compared to the suggested criterion of ¥6000 000 (£30 000) for one QALY gain. Most results are plotted close to base-case value, which suggest the stability of our model. Results for women with a history of AH remain constantly favourable being cost saving or cost-effective by the change of variables except for one plot shown as in area B. However, several results for women with a 5-year predicted breast cancer risk of ⩾5.01% and for women with a history of LCIS cross the threshold line, the vertical axis or the horizontal axis from the base-case values. Three plots in area B and seven plots in area C indicate that results turn unfavourably, that is cost-ineffective or 'gain less', whereas plots in area D show that results become cost saving.

Our model is most sensitive to the utility weight for healthy state under chemoprevention, of which plots are drawn in area B. Its change to 0.79 turns incremental effectiveness into

Table 4 Results of cost-effectiveness analysis (1)

	CoCost (¥)			Effectiveness (LYGs)			Effectiveness (QALYs)			Incremental cost-effectiveness ratio	
No prophylaxis vs prophylaxis with tamoxifen	**No prophylaxis**	**Tamoxifen**	**Incremental**	**No prophylaxis**	**Tamoxifen**	**Incremental**	**No prophylaxis**	**Tamoxifen**	**Incremental**	**(¥/LYG)**	**(¥/QALY)**
Five-year predicted breast cancer risk ⩾1.66%											
Starting at age 35	13 958 679	13 983 626	24 947	25.916	25.953	0.037	25.757	25.759	0.002	678 210	14 247 447
Starting at age 50	17 630 814	17 751 353	120 538	22.168	22.167	−0.001	22.040	22.000	−0.040	Cost more, gain less	Cost more, gain less
Starting at age 60	20 160 906	20 324 294	163 388	18.806	18.807	0.001	18.688	18.654	−0.034	120 849 008	Cost more, gain less
Five-year predicted breast cancer risk 3.01–5.00%											
Starting at age 35	13 627 472	13 685 368	57 896	26.005	26.035	0.030	25.879	25.872	−0.007	1 946 092	Cost more, gain less
Starting at age 50	17 579 407	17 732 900	153 493	22.195	22.185	−0.010	22.088	22.037	−0.051	Cost more, gain less	Cost more, gain less
Starting at age 60	20 251 937	20 444 141	192 203	18.808	18.797	−0.011	18.718	18.666	−0.052	Cost more, gain less	Cost more, gain less
Five-year predicted breast cancer risk ⩾5.01%											
Starting at age 35	14 956 349	14 667 969	−288 380	25.651	25.755	0.105	25.396	25.480	0.084	Cost less, gain more	Cost less, gain more
Starting at age 50	17 867 146	17 800 766	−66 379	22.049	22.096	0.047	21.832	21.854	0.022	Cost less, gain more	Cost less, gain more
Starting at age 60	19 958 433	20 058 020	99 857	18.797	18.825	0.028	18.614	18.618	0.004	3 548 049	26 648 821
History of lobular carcinoma in situ											
Starting at age 35	14 908 314	14 717 649	−190 665	25.663	25.747	0.083	25.414	25.472	0.058	Cost less, gain more	Cost less, gain more
Starting at age 50	17 856 158	17 850 722	−5 386	22.054	22.085	0.031	21.841	21.843	0.002	Cost less, gain more	Cost less, gain more
Starting at age 60	19 968 466	20 093 211	124 745	18.798	18.815	0.017	18.618	18.606	−0.011	7 282 700	Cost more, gain less
History of atypical hyperplasia											
Starting at age 35	14 687 003	14 319 102	−367 901	25.722	25.844	0.122	25.493	25.598	0.105	Cost less, gain more	Cost less, gain more
Starting at age 50	17 806 095	17 692 020	−114 075	22.079	22.139	0.060	21.884	21.922	0.038	Cost less, gain more	Cost less, gain more
Starting at age 60	20 015 243	20 096 731	81 488	18.800	18.837	0.037	18.635	18.651	0.016	2 226 684	5 234 647[a]
No prophylaxis vs prophylaxis with raloxifene	**No prophylaxis**	**Raloxifene**	**Incremental**	**No prophylaxis**	**Raloxifene**	**Incremental**	**No prophylaxis**	**Raloxifene**	**Incremental**	**(¥/LYG)**	**(¥/QALY)**
Five-year predicted breast cancer risk ⩾1.66%											
Starting at age 50	17 630 814	17 833 020	202 206	22.168	22.190	0.022	22.040	22.027	−0.013	9 256 382	Cost more, gain less
Starting at age 60	20 160 906	20 427 386	266 480	18.806	18.822	0.016	18.688	18.670	−0.018	16 806 286	Cost more, gain less
Five-year predicted breast cancer risk 3.01–5.00%											
Starting at age 50	17 579 407	17 794 890	215 482	22.195	22.214	0.019	22.088	22.071	−0.017	11 599 422	Cost more, gain less
Starting at age 60	20 251 937	20 529 452	277 515	18.808	18.820	0.012	18.718	18.694	−0.024	23 845 594	Cost more, gain less
Five-year predicted breast cancer risk ⩾5.01%											
Starting at age 50	17 867 146	17 911 198	44 053	22.049	22.111	0.062	21.832	21.871	0.039	705 126	1 123 880[a]
Starting at age 60	19 958 433	20 161 888	203 455	18.797	18.839	0.042	18.614	18.633	0.019	4 848 677	10 664 954
History of lobular carcinoma in situ											
Starting at age 50	17 856 158	17 935 697	79 540	22.054	22.107	0.053	21.841	21.869	0.027	1 496 425	2 904 386[a]
Starting at age 60	19 968 466	20 186 549	218 083	18.798	18.833	0.036	18.618	18.628	0.010	6 133 167	21 462 765
History of atypical hyperplasia											
Starting at age 50	17 806 095	17 795 708	−10 387	22.079	22.156	0.077	21.884	21.942	0.058	Cost less, gain more	Cost less, gain more
Starting at age 60	20 015 243	20 198 328	183 085	18.800	18.852	0.052	18.635	18.668	0.033	3 527 453	5 570 154[a]

[a]Cost-effective when compared to a suggested criterion in Japan (Ohkusa, 2003) of ¥6000 000 for one QALY gain.

negative. Critical values to change the judgement are 0.98, which makes the ICERs of women with a 5-year predicted breast cancer risk of ⩾5.01% and woman with a history of LCIS cost-ineffective, and the value of 0.96 makes women with a history of AH 'gain less'. The model is also sensitive to the discount rate, of which plot is drawn in area C. Its raise of 5.9 and 4.3% makes the ICERs of women with a 5-year predicted breast cancer risk of ⩾5.01% and women with a history of

Table 5 Results of cost-effectiveness analysis (2)

Prophylaxis with tamoxifen vs prophylaxis with raloxifene	Cost (¥)			Effectiveness (LYGs)			Effectiveness (QALYs)			Incremental cost-effectiveness ratio	
	Tamoxifen	Raloxifene	Incremental	Tamoxifen	Raloxifene	Incremental	Tamoxifen	Raloxifene	Incremental	(¥/LYG)	(¥/QALY)
Five-year predicted breast cancer risk ⩾1.66%											
Starting at age 50	17751353	17833020	81667	22.167	22.190	0.023	22.000	22.027	0.027	3501723	3035955[a]
Starting at age 60	20324294	20427386	103093	18.807	18.822	0.015	18.654	18.670	0.016	7107875	6364920
Five-year predicted breast cancer risk 3.01–5.00%											
Starting at age 50	17732900	17794890	61990	22.185	22.214	0.029	22.037	22.071	0.034	2163079	1839670[a]
Starting at age 60	20444141	20529452	85312	18.797	18.820	0.023	18.666	18.694	0.028	3741906	3063477[a]
Five-year predicted breast cancer risk ⩾5.01%											
Starting at age 50	17800766	17911198	110432	22.096	22.111	0.015	21.854	21.871	0.017	7150490	6542190
Starting at age 60	20058020	20161888	103869	18.825	18.839	0.014	18.618	18.633	0.015	7476332	6771100
History of lobular carcinoma in situ											
Starting at age 50	17850772	17935697	84925	22.085	22.107	0.022	21.843	21.869	0.025	3846426	3359650[a]
Starting at age 60	20093211	20186549	93338	18.815	18.833	0.018	18.606	18.628	0.022	5064724	4311015[a]
History of atypical hyperplasia											
Starting at age 50	17692020	17795708	103688	22.139	22.156	0.018	21.922	21.942	0.019	5922294	5320037[a]
Starting at age 60	20096731	20198328	101598	18.837	18.852	0.015	18.651	18.668	0.017	6637332	5872017[a]

[a]Cost-effective when compared to a suggested criterion in Japan (Ohkusa, 2003) of ¥6000000 for one QALY gain.

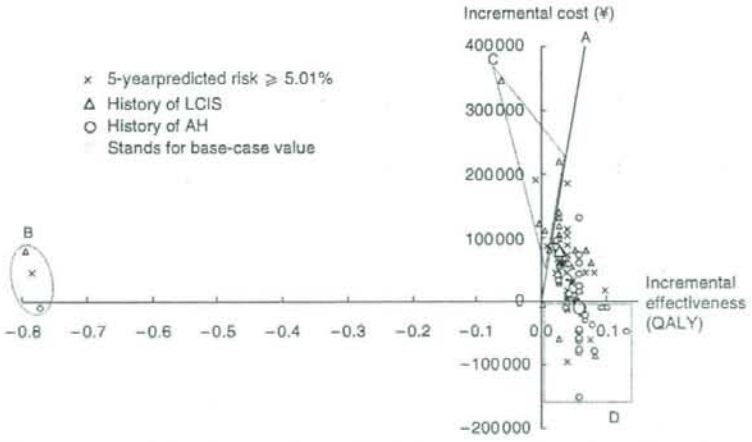

Figure 2 Illustration of key results of sensitivity analyses: prophylaxis with raloxifene vs no prophylaxis starting at age 50.

LCIS cost-ineffective, respectively. The cost of chemoprevention is also influential to the results, of which results are shown in areas C and D. A price increase of more than 30% for raloxifene makes the ICER of women with a history of LCIS cost-ineffective, whereas a price decrease of more than 16 or 29% make the results for women with a 5-year predicted breast cancer risk of ⩾5.01% and women with a history of LCIS cost saving, respectively. Changes of the probabilities of transition to invasive breast cancer, endometrial cancer, and hip fracture are also plotted in areas C and D. Raising the probability of invasive breast cancer beyond 0.00710 and 0.00683 makes the ICERs of women with a 5-year predicted breast cancer risk of ⩾5.01% and women with a history of LCIS cost-ineffective, whereas lowering to less than 0.00456 or 0.00436 make the results for women with a 5-year predicted breast cancer risk of ⩾5.01% and women a history of LCIS cost saving, respectively. Raising the probability of endometrial cancer beyond 0.00369 and 0.00271 makes the ICERs of women with a 5-year predicted breast cancer risk of ⩾5.01% and women with a history of LCIS cost-ineffective, respectively. Raising probability of hip fracture beyond 0.00098 makes the results for women with a history of LCIS cost saving. The other plots in area C reflect a raise of utility weight for invasive breast cancer after the second year.

Prolonging risk reduction effect of tamoxifen from 5 to 10 and 15 years without any risk increase of adverse events after the completion of prophylaxis brings more favourable results. For example, the effect of 10 years results in 'cost less and gain more' for every risk classification starting at age 35, whereas the effect of 15 years makes no change in the results of 'cost more and gain less' among women with a 5-year predicted breast cancer risk of ⩾1.66% starting at age 50 and 60.