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.

Acknowledgements This study is funded by Japan's Ministry of Health, Labour and Welfare research grant, a study on the construction of algorithm of multimodality therapy with biomarkers for primary breast cancer by a formulation of decision making process, led by Masakazu Toi (H18-3JIGAN-IPPAN-007, H19-3JIGAN-IPPAN-007). Authors appreciate Dr Hiroji Iwata at Aichi Cancer Center for providing his survey data.

References

1. Kondo M, Toi M (2006) Cost-effective treatment options in first-line therapy for advanced breast cancer in Japan. Expert Rev Anticancer Ther 6(2):197–204
2. Miya T (2007) Current status and problems of tailor-made medicine in anticancer therapy. Gan To Kagaku Ryoho 34(4): 515–519
3. Goldhirsch A, Wood WC, Gelber RD et al (2003) Meeting highlights: updated international expert consensus on the primary therapy of early breast cancer. J Clin Oncol 21(17):3357–3365
4. Senn HJ, Thürlimann B, Goldhirsch A et al (2003) Comments on the St. Gallen consensus 2003 on the primary therapy of early breast cancer. Breast 12(6):569–582
5. Goldhirsch A, Glick JH, Gelber RD et al (2005) Meeting highlights: international expert consensus on the primary therapy of early breast cancer 2005. Ann Oncol 16(10):1569–1583
6. Goldhirsch A, Coates AS, Gelber RD et al (2006) First – select the target: better choice of adjuvant treatments for breast cancer patients. Ann Oncol 17(12):1772–1776
7. Early Breast Cancer Trialists' Collaborative Group (2001) Tamoxifen for early breast cancer. Cochrane Database Syst Rev 2001(1):CD000486
8. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (2005) Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 365(9472):1687–1717
9. Carlson RW, McCormick B (2005) Update: NCCN breast cancer clinical practice guidelines. J Natl Compr Canc Netw 3(Suppl 1): S7–S11
10. Carlson RW, Brown E, Burstein HJ et al (2006) NCCN task force report: adjuvant therapy for breast cancer. J Natl Compr Canc Netw 4(Suppl 1):S1–S26
11. Carlson RW, Hudis CA, Pritchard KI et al (2006) Adjuvant endocrine therapy in hormone receptor-positive postmenopausal breast cancer: evolution of NCCN, ASCO, and St Gallen recommendations. J Natl Compr Canc Netw 4(10):971–979
12. Paik S, Shak S, Tang G et al (2004) A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med 351(27):2817–2826
13. Paik S, Tang G, Shak S et al (2006) Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol 24(23):3726–3734
14. Lacal JC (2007) How molecular biology can improve clinical management: the MammaPrint experience. Clin Transl Oncol 9(4):203
15. Drummond MF, Sculpher MJ, Torrance GW et al (2005) Methods for the economic evaluation of health care, 3rd edn. Oxford University Press, Oxford
16. The Japanese Breast Cancer Society (2007) Zenkoku nyugan kanja touroku chousa houkoku – kakuteiban—dai 35 gou 2004 nenji shourei (National breast cancer patient registry survey report – final report—No. 35 2004 cases). The Japanese Breast Cancer Society, Tokyo
17. Ohno Y, Nakamura T, Murata K et al (2004) Nihon no ganrikan no shoraisuikei – Bayes gata Poisson cohort model niyoru kaiseki ni motozuku 2020 nen madeno yosoku – (Future estimate of cancer incidence in Japan – Bayesian Poisson cohort model estimate until 2020). In: Oshima A, Ishiguro A, Tajima K (eds) Gan toukei hakusho – rikan, shibo, yogo – 2004 (Cancer statistics white paper – incidence, mortality, prognosis – 2004). Shinohara Shuppan Shinsha, Tokyo
18. van Oostenbruggen MF, Jansen RB, Mur K, Kooijman H (2005) Penny and pound wise: pharmacoeconomics from a governmental perspective. Pharmacoeconomics 23(3):219–226
19. Hornberger J, Cosler LE, Lyman GH (2005) Economic analysis of targeting chemotherapy using a 21-gene RT-PCR assay in lymph-node-negative, estrogen-receptor-positive, early-stage breast cancer. Am J Manag Care 11(5):313–324. Erratum in: Am J Manag Care 11(8):476
20. Lyman GH, Cosler LE, Kuderer NM et al (2007) Impact of a 21-gene RT-PCR assay on treatment decisions in early-stage breast cancer: an economic analysis based on prognostic and predictive validation studies. Cancer 109(6):1011–1018
21. Paik S, Shak S, Tang G et al (2004) Risk classification of breast cancer patients by the recurrence score assay: comparison to guidelines based on patient age, tumor size, and tumor grade. In: Abstracts of 27th annual San Antonio breast cancer symposium, Texas, 8–11 December 2004
22. Iwata H, Saeki T (2006) Current practices in breast cancer treatment in Japan – a questionnaire survey. Jpn J Breast Cancer 21(3):311–322
23. Japan Society of Clinical Oncology (2005) Kouganzai tekisei-shiyou no gaidorain: nyuugan (Guideline of appropriate use of anti cancer drugs: breast cancer). Int J Clin Oncol 10(Suppl.): 15–55
24. Japanese Breast Cancer Society (2006) Kagakuteki konkyo ni motozuku nyuugan sinryo gaidorain: 1 yakubutsu ryouhou 2006 nenban (Evidence-based breast cancer care guideline: 1 drug treatments 2006 version). Kanehara Shuppan, Tokyo

25. Piccart-Gebhart MJ, Procter M, Leyland-Jones B et al (2005) Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 353(16):1659–1672
26. Smith I, Procter M, Gelber RD et al (2007) 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. Lancet 369(9555): 29–36
27. Elkin EB, Weinstein MC, Winer EP et al (2004) HER-2 testing and trastuzumab therapy for metastatic breast cancer: a cost-effectiveness analysis. J Clin Oncol 22(5):854–863
28. Ministry of Health, Labour, Welfare (2007) The 20th life tables. Health and Welfare Statistics Association, Tokyo
29. Hillner BE, Smith TJ (1991) Efficacy and cost effectiveness of adjuvant chemotherapy in women with node-negative breast cancer. A decision-analysis model. N Engl J Med 324(3):160–168
30. Earle CC, Chapman RH, Baker CS et al (2000) Systematic overview of cost-utility assessments in oncology. J Clin Oncol 18(18):3302–3331
31. Cole BF, Gelber RD, Gelber S et al (2001) Polychemotherapy for early breast cancer: an overview of the randomised clinical trials with quality-adjusted survival analysis. Lancet 358(9278):277–286
32. Gold MR, Siegel JE, Russell LB et al (eds) Cost-effectiveness in health and medicine. Oxford University Press, New York
33. Iwata H, Nakamura S, Toi M et al (2005) Interim analysis of a phase II trial of cyclophosphamide, epirubicin and 5-fluorouracil (CEF) followed by docetaxel as preoperative chemotherapy for early stage breast carcinoma. Breast Cancer 12(2):99–103
34. Papaldo P, Ferretti G, Di Cosimo S et al (2006) Does granulocyte colony-stimulating factor worsen anemia in early breast cancer patients treated with epirubicin and cyclophosphamide? J Clin Oncol 24(19):3048–3055
35. Culyer AJ (2005) The dictionary of health economics. Edward Elgar, Cheltenham
36. Ohkusa Y (2003) Empirical research for the critical value of expenditure per QALY. Iryou to Shakai 13(3):121–130
37. Trueman P, Drummond M, Hutton J (2001) Developing guidance for budget impact analysis. Pharmacoeconomics 19(6):609–621
38. Shiroiwa T, Fukuda T, Shimozuma K et al (2007) The model-based cost-effectiveness analysis of 1-year adjuvant trastuzumab treatment: based on 2-year follow-up HERA trial data. Breast Cancer Res Treat (in press). doi:10.1007/s10549-007-9679-4
39. Drummond M, Pang F (2001) Transferability of economic evaluation results. In: Drummond M, McGuire A (eds) Economic evaluation in health care: merging theory with practice. Oxford University Press, Oxford
40. Toi M (2007) Update on the confirmatory Japanese study utilizing Oncotype DX. In: Abstracts of the 15th annual meeting of the Japanese breast cancer society, Kanagawa, 29–30 June 2007
41. Goldhirsch A, Wood W, Gelber R et al (2007) Progress and promise: highlights of the international expert consensus on the primary therapy of early breast cancer 2007. Ann Oncol 18(7): 1133–1144
42. Lo SS, Norton J, Mumby PB et al (2007) Prospective multicenter study of the impact of the 21-gene recurrence score (RS) assay on medical oncologist (MO) and patient (pt) adjuvant breast cancer (BC) treatment selection. J Clin Oncol 25(18S):577
43. Goldstein LJ, Gray R, Childs BH et al (2007) Prognostic utility of 21-gene assay in hormone receptor (HR) positive operable breast cancer and 0–3 positive axillary nodes treated with adjuvant chemohormonal therapy (CHT): an analysis of intergroup Trial E2197. J Clin Oncol 25(18S):526

British Journal of Cancer (2009) 100, 281 – 290

www.bjcancer.com

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

M Kondo*[,1,2], S-L Hoshi[1] and M Toi[3]

[1]Department of Health Care Policy and Management, Graduate School of Comprehensive Human Sciences, University of Tsukuba, 1-1-1 Tennoudai, Tsukuba, Ibaraki 305-8577, Japan; [2]Clinical Research Division, Tokyo Metropolitan Cancer and Infectious Disease Centre, Komagome Hospital, 3-18-22 Honkomagome, Bunkyo-ku, Tokyo 113-8677, Japan; [3]Department of Surgery, Graduate School of Medicine, Kyoto University, 54 Kawaracho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan

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.

British Journal of Cancer (2009) **100,** 281 – 290. doi:10.1038/sj.bjc.6604869 www.bjcancer.com
Published online 13 January 2009

Keywords: breast cancer; chemoprevention; cost-effectiveness; prophylaxis; raloxifene; tamoxifen

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).

*Correspondence: Dr M Kondo; E-mail: mkondo@md.tsukuba.ac.jp
Received 2 September 2008; revised 25 November 2008; accepted 5 December 2008; published online 13 January 2009

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

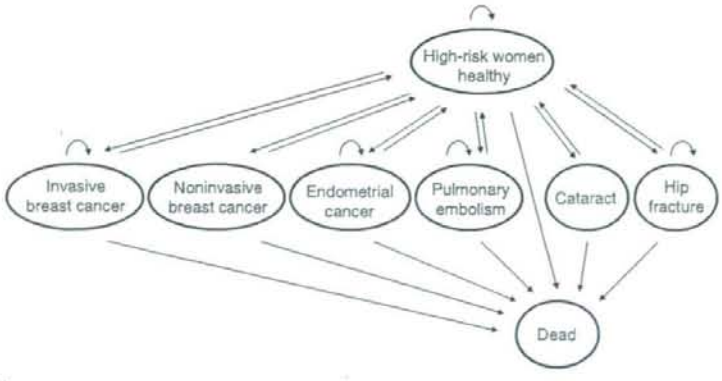

Figure 1 Markov model.

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 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	Change by ± 50%	Calculated from follow-up patients at Komagome Hospital
	(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 ⩾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 ⩾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 ⩾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	651 986	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)	1183 839	Change by ± 50%	Matsuda and Ishikawa (2003)
Pulmonary embolism			
Total	469 890		
(Diagnosis)	(52 350)	Change by ± 50%	Fuji et al (2005)
(Treatment)	(417 540)		
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 ¥1839 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	3548 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	7282 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	2226 684	5234 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	9256 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	1123 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	4848 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	1496 425	2904 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	6133 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	3527 453	5570 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	17 751 353	17 833 020	81 667	22.167	22.190	0.023	22.000	22.027	0.027	3501 723	3035 955[a]
Starting at age 60	20 324 294	20 427 386	103 093	18.807	18.822	0.015	18.654	18.670	0.016	7107 875	6364 920
Five-year predicted breast cancer risk 3.01–5.00%											
Starting at age 50	17 732 900	17 794 890	61 990	22.185	22.214	0.029	22.037	22.071	0.034	2163 079	1839 670[a]
Starting at age 60	20 444 141	20 529 452	85 312	18.797	18.820	0.023	18.666	18.694	0.028	3741 906	3063 477[a]
Five-year predicted breast cancer risk ⩾ 5.01%											
Starting at age 50	17 800 766	17 911 198	110 432	22.096	22.111	0.015	21.854	21.871	0.017	7150 490	6542 190
Starting at age 60	20 058 020	20 161 888	103 869	18.825	18.839	0.014	18.618	18.633	0.015	7476 332	6771 100
History of lobular carcinoma in situ											
Starting at age 50	17 850 772	17 935 697	84 925	22.085	22.107	0.022	21.843	21.869	0.025	3846 426	3359 650[a]
Starting at age 60	20 093 211	20 186 549	93 338	18.815	18.833	0.018	18.606	18.628	0.022	5064 724	4311 015[a]
History of atypical hyperplasia											
Starting at age 50	17 692 020	17 795 708	103 688	22.139	22.156	0.018	21.922	21.942	0.019	5922 294	5320 037[a]
Starting at age 60	20 096 731	20 198 328	101 598	18.837	18.852	0.015	18.651	18.668	0.017	6637 332	5872 017[a]

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

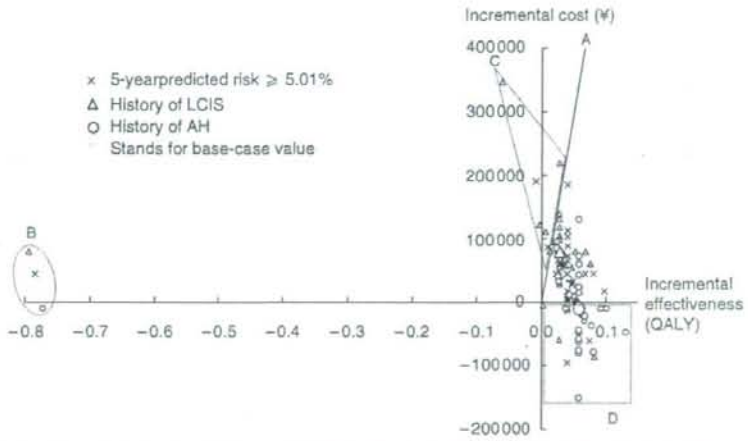

Figure 2 Illustration of key results of sensitivity analyses: prophylaxis with raloxifene vs no prophylaxis starting at age 50.

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.

DISCUSSION

We conduct a cost-effectiveness analysis of SERMs as prophylactic agents against breast cancer among high-risk women by making comparisons 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.

We find that prophylaxis with tamoxifen results in 'cost less and gain more' among extremely high-risk women such as those with a 5-year predicted breast cancer risk of $\geqslant 5.01\%$, those with a history of LCIS, and those with a history of AH starting at age 35 and 50. Prophylaxis with raloxifene is also found 'cost less and gain more' for women with a history of AH starting at age 50. The younger the age of starting prophylaxis, the more the cost saving and outcome gain. We also find that prophylaxis with tamoxifen for women with a history of AH starting at age 60 results in favourable ICER compared to the suggested criterion of ¥6000 000 (£30 000) for one QALY gain. Prophylaxis with raloxifene is also found cost-effective for women with a 5-year predicted breast cancer risk of $\geqslant 5.01\%$ starting at age 50, those with a history of LCIS starting at age 50 and those with a history of AH starting at age 60. The younger the age of starting prophylaxis, the more favourable the ICER. Within the same risk classification and starting age, raloxifene tends to gain more and cost more compared to tamoxifen. On the contrary, we also find that prophylaxes with tamoxifen or raloxifene for women with a 5-year predicted breast cancer risk of $\leqslant 5.00\%$ tend to result in 'cost more and gain less'.

These findings are similar to the previous economic evaluations of chemoprevention of breast cancer with tamoxifen including analyses of risk level differences such as Noe *et al* (1999); Grann *et al* (2000); Hershman *et al* (2002); Melnikow *et al* (2006), although these studies are carried out under the US health system.

Our findings suggest that introduction of chemoprevention with SERMs targeting extremely high-risk women in Japan can be justifiable as an efficient use of finite health-care resources, possibly contributing to cost containment. The cost saving results suggest chemoprevention not only cost-effective but also affordable. Taking the superiority of raloxifene in outcome gain and the difference in indication into account, it is recommendable to administer tamoxifen for premenopausal women and raloxifene for postmenopausal women.

Our economic model is found sensitive to the utility weight for healthy state under chemoprevention, the discount rate and the cost of chemoprevention, in addition to the probabilities of transition to invasive breast cancer, endometrial cancer, or hip fracture. This is anticipated because these variables are supposed to influence the cost-effectiveness of preventive services. We think that our economic model succeeds in explaining the context under consideration.

We also analysed the cost-effectiveness of therapeutic policy switch of agent, tamoxifen to raloxifene among postmenopausal women, although this does not depict any marginal change in Japan. All simulated ICERs by risk classifications starting at age 50 and 60 fall in a favourable level. Due caution is needed in transferring these findings from our Japanese model to other health system (Drummond and Pang, 2001), but it implies that the administration of raloxifene instead of tamoxifen for postmenopausal high-risk women could be economically acceptable in developed countries where chemoprevention with tamoxifen is already in practise.

There are a couple of points to consider when interpreting our results. Our model depends on clinical evidence established in the United States by P-1 and P-2 trial. Composition of ethnicity and life styles of participating women are different from those of Japanese women. This also relates to another point, that is the validity of the 5-year risk prediction model defining high-risk women. As already mentioned in Methods section, it is based on Gail *et al* model 2 (Gail and Costantino, 2001), which has been validated for white women (Rockhill *et al*, 2001) and African American women (Gail *et al*, 2007) only. Our approach is acceptable as to these points, as the results of P-1 and P-2 trial are the best available evidence to date for the objectives of this study, and similar risk factors to Gail *et al* model 2 are identified in a model of individualised probability of developing breast cancer for Japanese women (Ueda *et al*, 2003), and the function of ethnic difference in developing breast cancer is reported as small (Chen *et al*, 2004). Our model also depends on utility weights reported from Western countries, as none of those from Japan are available. However, our findings of consistent outcomes in terms of LYGs offer reasonable conclusions.

In summary, this study suggests that chemoprevention of breast cancer with SERMs targeting high-risk women such as a 5-year predicted breast cancer risk of $\geqslant 5.01\%$, women with a history of LCIS, and women with a history of AH, clears the hurdles of introducing new intervention by means of cost-effectiveness and affordability, with best available evidence. Although further studies and policy formulations are necessary about breast cancer chemoprevention in Japan, this study also implies that the administration of raloxifene instead of tamoxifen may be cost-effective under the context of developed countries where chemoprevention with tamoxifen has already been adopted.

ACKNOWLEDGEMENTS

This study is funded by Japan's Ministry of Health, Labour, and Welfare research grant, a study on the construction of algorithm of multimodality therapy with biomarkers for primary breast cancer by a formulation of the decision-making process, led by Masakazu Toi (H18-3JIGAN-IPPAN-007). We appreciate Mr Hitoshi Mukai and his staff at Tokyo Metropolitan Cancer and Infectious Disease Centre Komagome Hospital for conducting insurance claim reviews.

REFERENCES

Armstrong K, Chen TM, Albert D, Randall TC, Schwartz JS (2001) Cost-effectiveness of raloxifene and hormone replacement therapy in postmenopausal women: impact of breast cancer risk. *Obstet Gynecol* **98**: 996–1003

Bevers TB (2007) The STAR trial: evidence for raloxifene as a breast cancer risk reduction agent for postmenopausal women. *J Natl Compr Cancer Netw* **5**: 719–724

Cauley JA, Norton L, Lippman ME, Eckert S, Krueger KA, Purdie DW, Farrerons J, Karasik A, Mellstrom D, Ng KW, Stepan JJ, Powles TJ, Morrow M, Costa A, Silfen SL, Walls EL, Schmitt H, Muchmore DB, Jordan VC, Ste-Marie LG (2001) Continued breast cancer risk reduction in postmenopausal women treated with raloxifene: 4-year results from the MORE trial. Multiple outcomes of raloxifene evaluation. *Breast Cancer Res Treat* **65**: 125–134

Chau Q, Cantor SB, Caramel E, Hicks M, Kurtin D, Grover T, Elting LS (2003) Cost-effectiveness of the bird's nest filter for preventing pulmonary embolism among patients with malignant brain tumors and deep venous thrombosis of the lower extremities. *Support Care Cancer* **11**: 795–799

Chen Z, Wu AH, Gauderman WJ, Bernstein L, Ma H, Pike MC, Ursin G (2004) Does mammographic density reflect ethnic differences in breast cancer incidence rates? *Am J Epidemiol* **159**: 140–147

Cuzick J, Forbes JF, Sestak I, Cawthorn S, Hamed H, Holli K, Howell A, International Breast Cancer Intervention Study I Investigators (2007) Long-term results of tamoxifen prophylaxis for breast cancer – 96-month follow-up of the randomized IBIS-I trial. *J Natl Cancer Inst* **99:** 272–282

Cykert S, Phifer N, Hansen C (2004) Tamoxifen for breast cancer prevention: a framework for clinical decisions. *Obstet Gynecol* **104:** 433–442

de Koning HJ, van Ineveld BM, van Oortmarssen GJ, de Haes JC, Collette HJ, Hendriks JH, van der Maas PJ (1991) Breast cancer screening and cost-effectiveness: policy alternatives, quality of life considerations and the possible impact of uncertain factors. *Int J Cancer* **49:** 531–537

Delmas PD, Bjarnason NH, Mitlak BH, Ravoux AC, Shah AS, Huster WJ, Draper M, Christiansen C (1997) Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. *N Engl J Med* **337:** 1641–1647

Drummond M, Pang F (2001) Transferability of economic evaluation results. In *Economic Evaluation in Health Care: Merging Theory with Practice* Drummond M and McGuire A (eds). Oxford: Oxford University Press

Earle CC, Chapman RH, Baker CS, Bell CM, Stone PW, Sandberg EA, Neumann PJ (2000) Systematic overview of cost-utility assessments in oncology. *J Clin Oncol* **18:** 3302–3317

Eckermann SD, Martin AJ, Stockler MR, Simes RJ (2003) The benefits and costs of tamoxifen for breast cancer prevention. *Aust N Z J Public Health* **27:** 34–40

Fisher B, Costantino JP, Wickerham DL, Cecchini RS, Cronin WM, Robidoux A, Bevers TB, Kavanah MT, Atkins JN, Margolese RG, Runowicz CD, James JM, Ford LG, Wolmark N (2005) Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst* **97:** 1652–1662

Fuji T, Nakamura M, Yamada N, Kobayashi M, Yamauchi K, Nakano T (2005) Health economic analysis of prevention of deep vein thrombosis – an application of pharmacoeconomics. *Sogo Rinsho* **54:** 2988–2997

Fukawa T (1998) Ageing and health expenditure of the elderly. *J Jpn Soc Hosp Adm* **35:** 109–121

Gail MH, Costantino JP (2001) Validating and improving models for projecting the absolute risk of breast cancer. *J Natl Cancer Inst* **93:** 334–335

Gail MH, Costantino JP, Pee D, Bondy M, Newman L, Selvan M, Anderson GL, Malone KE, Marchbanks PA, McCaskill-Stevens W, Norman SA, Simon MS, Spirtas R, Ursin G, Bernstein L (2007) Projecting individualized absolute invasive breast cancer risk in African American women. *J Natl Cancer Inst* **99**(23): 1782–1792

Grann VR, Panageas KS, Whang W, Antman KH, Neugut AI (1998) Decision analysis of prophylactic mastectomy and oophorectomy in BRCA1-positive or BRCA2-positive patients. *J Clin Oncol* **16:** 979–985

Grann VR, Sundararajan V, Jacobson JS, Whang W, Heitjan DF, Antman KH, Neugut AI (2000) Decision analysis of tamoxifen for the prevention of invasive breast cancer. *Cancer J* **6:** 169–178

Hershman D, Sundararajan V, Jacobson JS, Heitjan DF, Neugut AI, Grann VR (2002) Outcomes of tamoxifen chemoprevention for breast cancer in very high-risk women: a cost-effectiveness analysis. *J Clin Oncol* **20:** 9–16

Hillner BE, Smith TJ, Desch CE (1993) Assessing the cost effectiveness of adjuvant therapies in early breast cancer using a decision analysis model. *Breast Cancer Res Treat* **25:** 97–105

Iwata H, Saeki T (2006) Current practices in breast cancer treatment in Japan – a questionnaire survey. *Jpn J Breast Cancer* **21:** 311–322

Japan Cancer Society (2007) *Gankenshin no jisshi jyokyo. No.39.* Tokyo: Japan Cancer Society

Japanese Society of Obstetrics and Gynecology (2000) *Zenkoku shikyutaigan chousa seiseki.* Dai 5 hou. 1989–1990 nendo shourei Tokyo: Japanese Society of Obstetrics and Gynecology

Kanis JA, Borgström F, Johnell O, Oden A, Sykes D, Jönsson B (2005) Cost-effectiveness of raloxifene in the UK: an economic evaluation based on the MORE study. *Osteoporos Int* **16:** 15–25

Kitamura S, Hasegawa Y, Suzuki S, Sasaki R, Iwata H, Wingstrand H, Thorngren KG (1998) Functional outcome after hip fracture in Japan. *Clin Orthop Relat Res* **348:** 29–36

Martino S, Cauley JA, Barrett-Connor E, Powles TJ, Mershon J, Disch D, Secrest RJ, Cummings SR, CORE Investigators (2004) Continuing outcomes relevant to Evista: breast cancer incidence in postmenopausal osteoporotic women in a randomized trial of raloxifene. *J Natl Cancer Inst* **96:** 1751–1761

Matsuda S, Ishikawa BK (2003) *Kyuuseiki nyuuiniryo shikou shindangunbunrui wo katsuyou shita chousakenkyuu.* Report of Health and Labour Sciences Research Grants (Contract No.: H13-SEISAKU-034) Tokyo: Ministry of Health, Labour and Welfare

Melnikow J, Kuenneth C, Helms LJ, Barnato A, Kuppermann M, Birch S, Nuovo J (2006) Chemoprevention: drug pricing and mortality: the case of tamoxifen. *Cancer* **107:** 950–958

Ministry of Health, Labour and Welfare (2005a) *Vital statistics of Japan.* Tokyo: Health & Welfare Statistics Association

Ministry of Health, Labour and Welfare (2005b) *Kokumin iryouhi.* Tokyo: Health & Welfare Statistics Association

Naeim A, Keeler EB (2005) Is adjuvant therapy for older patients with node (+) early breast cancer cost-effective? *Breast Cancer Res Treat* **94:** 95–103

Noe LL, Becker III RV, Gradishar WJ, Gore M, Trotter JP (1999) The cost effectiveness of tamoxifen in the prevention of breast cancer. *Am J Manag Care* **5:** S389–S406

Ohkusa Y (2003) Emprical research for the critical value of expenditure per QALY. *Iryo to Shakai* **13:** 121–130

Powles TJ, Ashley S, Tidy A, Smith IE, Dowsett M (2007) Twenty-year follow-up of the Royal Marsden randomized, double-blinded tamoxifen breast cancer prevention trial. *J Natl Cancer Inst* **99:** 283–290

Rockhill B, Spiegelman D, Byrne C, Hunter DJ, Colditz GA (2001) Validation of the Gail *et al* model of breast cancer risk prediction and implications for chemoprevention. *J Natl Cancer Inst* **93**(5): 358–366

Ruof J, Golay A, Berne C, Collin C, Lentz J, Maetzel A (2005) Orlistat in responding obese type 2 diabetic patients: meta-analysis findings and cost-effectiveness as rationales for reimbursement in Sweden and Switzerland. *Int J Obes (Lond)* **29:** 517–523

Sakuma M, Nakamura M, Nakanishi N, Miyahara Y, Tanabe N, Yamada N, Kuriyama T, Kunieda T, Sugimoto T, Nakano T, Shirato K (2004) Inferior vena cava filter is a new additional therapeutic option to reduce mortality from acute pulmonary embolism. *Circ J* **68:** 816–821

Smith TJ, Hillner BE (1993) The efficacy and cost-effectiveness of adjuvant therapy of early breast cancer in premenopausal women. *J Clin Oncol* **11:** 771–776

Smith TJ, Hillner BE (2000) Tamoxifen should be cost-effective in reducing breast cancer risk in high-risk women. *J Clin Oncol* **18:** 284–286

Trueman P, Drummond M, Hutton J (2001) Developing guidance for budget impact analysis. *Pharmacoeconomics* **19:** 609–621

Ueda K, Tsukuma H, Tanaka H, Ajiki W, Oshima A (2003) Estimation of individualized probabilities of developing breast cancer for Japanese women. *Breast Cancer* **10:** 54–62

Veronesi U, Maisonneuve P, Decensi A (2007a) Tamoxifen: an enduring star. *J Natl Cancer Inst* **99:** 258–260

Veronesi U, Maisonneuve P, Rotmensz N, Bonanni B, Boyle P, Viale G, Costa A, Sacchini V, Travaglini R, D'Aiuto G, Oliviero P, Lovison F, Gucciardo G, del Turco MR, Muraca MG, Pizzichetta MA, Conforti S, Decensi A, Italian Tamoxifen Study Group (2007b) Tamoxifen for the prevention of breast cancer: late results of the Italian Randomized Tamoxifen Prevention Trial among women with hysterectomy. *J Natl Cancer Inst* **99:** 727–737

Vogel VG, Costantino JP, Wickerham DL, Cronin WM, Cecchini RS, Atkins JN, Bevers TB, Fehrenbacher L, Pajon Jr ER, Wade III JL, Robidoux A, Margolese RG, James J, Lippman SM, Runowicz CD, Ganz PA, Reis SE, McCaskill-Stevens W, Ford LG, Jordan VC, Wolmark N, National Surgical Adjuvant Breast and Bowel Project (NSABP) (2006) Effects of tamoxifen *vs* raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. *JAMA* **295:** 2727–2741. Erratum in: JAMA 296:2926, JAMA 298:973

■ 原 著 ■

乳頭分泌液中 CEA 測定におけるイムノクロマトグラフィー（ICGA）法と酵素免疫測定（EIA）法の比較検討

多根井 智紀　増田 慎三　石飛 真人　徳田 由紀子
吉田　謙　真能 正幸　竹田 雅司　辻仲 利政

乳癌の臨床　第23巻　第2号（2008）
Jpn J Breast Cancer　Vol.23 No.2 2008

篠原出版新社

原著

2008.2.5受付

乳頭分泌液中CEA測定におけるイムノクロマトグラフィー (ICGA) 法と酵素免疫測定 (EIA) 法の比較検討

多根井 智紀[*1,6]　増田 慎三[*1]　石飛 真人[*1,4]　徳田 由紀子[*2]
吉田　謙[*2]　真能 正幸[*3]　竹田 雅司[*3,5]　辻仲 利政[*1]

Comparison of "Immunochromatograpic Assay (ICGA)" with "Enzyme Immunoassay (EIA)" For Measurement of CEA in Abnormal Nipple Discharge : Tanei T[*1,6], Masuda N[*1], Ishitobi M[*1,4], Tokuda Y[*2], Yoshida K[*2], Mano M[*3], Takeda M[*3,5] and Tsujinaka T[*1] ([*1]Department of Surgery, [*2]Department of Radiology, [*3]Department of Pathology, Osaka National Hospital, [*4]Department of Surgery Osaka Medical Center for Cancer and Cardiovascular Diseases, [*5]Department of Pathology, Yao City Hospital, [*6]Department of Surgical Oncology, Osaka University Graduate School of Medicine)

For the detecti on of early breast cancer, such as ductal carcinoma in situ (DCIS), it is important to measure CEA levels in abnormal nipple discharge. We compared Immunochromatograpic assay "Lana Mammo Card CEA®" with enzyme immunoassay "MAMMOTEC®" for the measurement of CEA levels in abnormal nipple discharge from 20 patients (13 malignant cases, 7 benign cases). When the cut off value of CEA was set at 400ng/ml for each kit, the sensitivity, specificity and accuracy were 100%, 71.4% and 90% using the "Immunochromatograpic assay (ICGA)". They were 92.3%, 71.4% and 85.0% using the "enzyme immunoassay (EIA)". The value obtained by radio immuno assay (RIA) or related with those obtained by "Immunochromatograpic assay (ICGA)" and "enzyme immunoassay (EIA)". We should recommend a carefully considered approach combined with non-invasive tools. Using the "Immunochromatograpic assay (ICGA)", the CEA level can be obtained by the easier single-step manipulation within 15 minutes. Therefore, an follow-up investigations can be planned during the initial medical examination.

Key words : Abnormal nipple discharge, Carcinoembryonic antigen (CEA), Immunochromatograpic assay (ICGA), Enzyme immunoassay (EIA)

Jpn J Breast Cancer 23 (2) : 123～128, 2008

はじめに

乳頭異常分泌は早期乳癌 (DCIS) や乳管内乳頭腫等の増殖性病変の発見動機として重要な症状であり，的確な診断と治療を行うことが求められる．乳頭異常分泌のスクリーニング法として，潜血反応，乳頭分泌細胞診があるが，いずれも診断の精度が低い為，稲治らは診断の一助として乳頭分泌液中の癌胎児性抗原 (Carcioembryonic antigen：CEA) を用いる測定法を考案した[1]．これは乳癌より乳管中に高濃度のCEAが産出されることを利用したものであり，測定法としては，酵素免疫測定法 (enzyme immunoassay；EIA) を用いたマンモチック® が以前より知られている．また，最近，イムノクロマトグラフィー法 (immuno-chromatographic assay；ICGA) を用いた簡易かつ迅速な測定キットであるラナマンモカードCEA® が販売され厚生省にて認可された．今

*1　国立病院機構大阪医療センター外科
*2　国立病院機構大阪医療センター放射線科
*3　国立病院機構大阪医療センター臨床検査科
*4　大阪府立成人病センター乳腺内分泌外科
*5　八尾市立病院病理診断科
*6　現：大阪大学大学院乳腺内分泌外科

回，われわれはICGA法(ラナマンモカードCEA®)とEIA法(マンモテック®)の2つの測定法について比較検討したので報告する．また，RIA法によるCEA定量の測定を行い，実側値との相関も検討してみた．

1. 対象と方法

2004年7月～2005年10月までの間に，乳頭異常分泌を主訴に受診した患者のうち，根治手術にて病理診断を得た20症例について検討した．全例女性で平均年齢は58歳，28歳から77歳までであり，20症例の内訳は乳癌13例（浸潤癌6例，非浸潤癌7例），良性疾患7例（乳頭腫3例，乳腺症4例）であった．全例に対して乳頭分泌液細胞診とEIA法・ICGA法による分泌液中CEAの測定を行った．また，採取した乳頭分泌液の検体は保存し，一括してSRL社にてRIA法によるCEA定量の測定を行い，この測定値を対照にして2つの測定法(EIA法とICGA法)の正確性を比較した．この研究は当院の受託研究審査委員会で承認の上，患者から同意を取得して実施した．

1) EIA法による分泌液中CEA測定（マンモテック®）の原理と方法

マンモテック®は，プラスチックフィルムに不溶化した抗CEA抗体と酵素標識抗CEA抗体を用いたmicrodot-limmunobinding assay（サンドイッチ型酵素免疫測定法）である．検体と標識抗体を添加した後，30分間乾燥させ，洗浄が必要であり，基質添加後さらに60分乾燥させる[2]．判定は目視による着色強度により半定量的に行い，測定には2時間以上を要するキットの推奨どおりの方法にて行った．

2) ICGA法による分泌液中CEA測定（ラナマンモカードCEA®）の原理と方法

ラナマンモカードCEA®は，イムノクロマトグラフィーを用いて，簡便で短時間に測定できるように考案されたキットであり，抗CEAモノクローナル抗体結合金コロイド粒子が含まれ，判定部位にも抗CEA抗体が固相化されている．分泌中のCEAがコロイド標識されたモノクローナル抗CEA抗体と反応して免疫複合体を形成し，免疫複合体は展開液により移動した後，判定部位の固相化抗CEA抗体に捉えられ，15分以上静置している間にラインを形成し目視にて確認が可能になる[3]．ラナマンモカードCEA®はこれを利用して半定量的に測定したものであり，分泌液(検体)中CEAが存在しない場合には，コロイド粒子が移動するのみにてラインは形成されない（図1）．

2. 結果

1) EIA法とICGA法との測定値および正診率

乳頭異常分泌にて根治手術を施行した20例（乳癌13例，良性疾患7例）の乳頭分泌液に対してICGA法とEIA法を測定し，2つのCEA測定値と摘出標本の病理組織診断を比較した．診断精度は，乳頭分泌CEA研究会に準じてカット・オフ値を400ng/m*l*以上を陽性としたところ，病理結果にて乳癌と診断された13例すべてにおいてICGA法にて高値を認めた(図2)．また，EIA法は乳癌13例のうち12例に高値を認めたが，浸潤癌（硬癌）1例において偽陰性（400ng/m*l*未満）であった．また，この偽陰性1例については，RIA法によるCEA定量での実測値も280ng/m*l*と低値であり，元来，乳管内成分からのCEA産生が少ない乳癌症例であったと推測される．

偽陽性については，乳腺症2例がEIA法とICGA法ともに陽性であった．診断精度は，ICGA法の診断精度は感度100%(13/13)，特異度71.4%(5/7)，正診率90%(18/20)，陽性適中率86.7%(13/15)であった．また，EIA法は感度92.3%(12/13)，特異度71.4%（5/7），正診率85.0%（17/20)，陽性適中率85.7%(12/14)であり，ICGA法とEIA法はともに同等の診断精度であった（表1)．

2) RIA法によるCEA定量値との比較

今回，われわれはEIA法，及びICGA法の測定値に対する正確性を判定する為，20例の乳頭分泌液に対して、RIA法によるCEA定量を測定して(SRL社に委託)，この定量値を対照にして両者の測定値との比較を行った．2つの測定法は図3に示すようにRIA法によるCEA定量値との間に相関

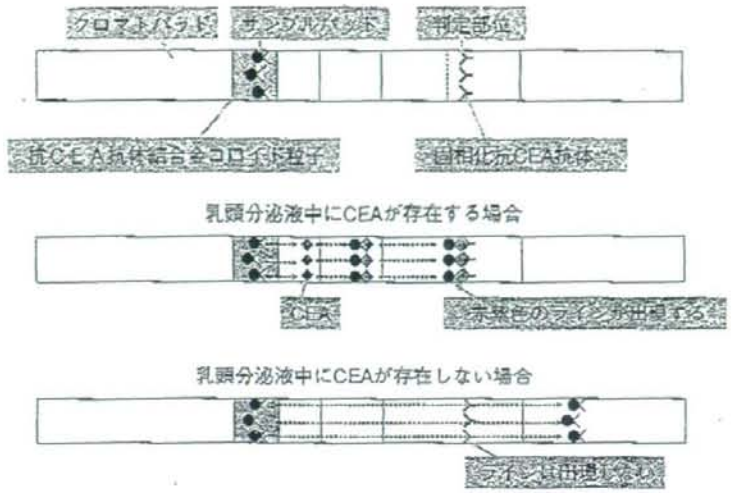

図1　イムノクロマトグラフィー法（ラナマンモカードCEA®）による乳頭分泌液中CEAの測定原理
提供：日本化薬株式会社　医薬事業本部　診断薬室　ラナマンモカード CEA イムノクロマトグラフィー法による乳頭分泌液中CEA測定試薬

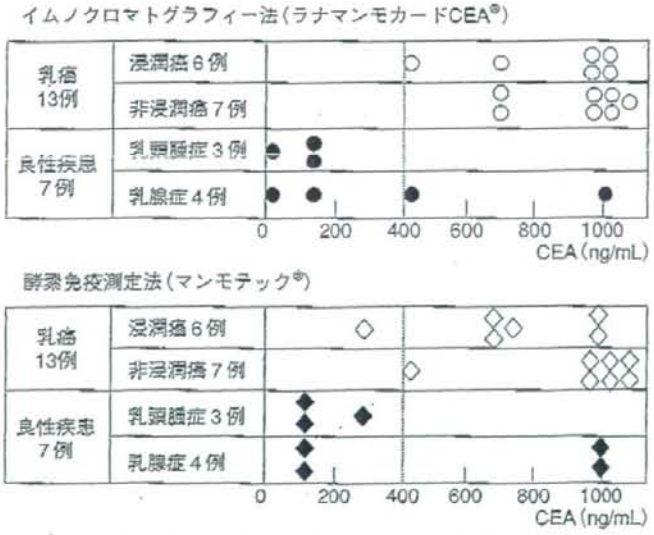

図2　当院の乳頭異常分泌（20症例）における各病理診断別のCEA測定値

傾向を認めた．ICGA法にて400-1,000ng/m*l*を示す1症例において，RIA法によるCEA定量では280ng/m*l*（400ng/m*l*未満）であることを認めたが，この1症例は病理組織結果は浸潤性乳管癌であり，RIA法によるCEA定量のほうが偽陰性であった（EIA法では0-400ng/m*l*）．

3. 考　察

乳頭異常分泌症の頻度は，全乳腺疾患の5％程度とされており[4]，基礎疾患としては乳管内乳頭腫，乳腺症，乳管拡張症などの良性疾患以外に，DCISなどの早期乳癌が含まれることがあり，これらの病態は的確な診断と治療により，100％の救命

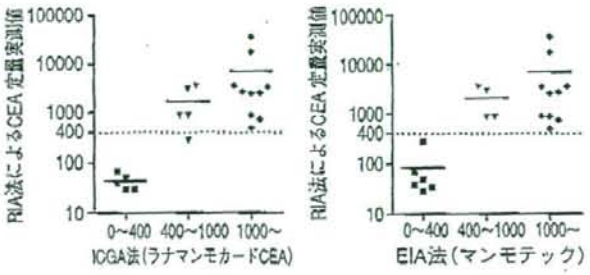

図3　RIA法によるCEA定量実測値との比較

表1　イムノクロマトグラフィー法（ラナマンモカードCEA®）と酵素免疫測定法（マンモテック®）の診断精度

	感度	特異度	正診率	陽性適中率
ラナマンモカードCEA®	100% (13/13)	71.4% (5/7)	90% (18/20)	86.7% (13/15)
マンモテック®	92.3% (12/13)	71.4% (5/7)	85% (17/20)	85.7% (12/14)

表2　イムノクロマトグラフィー法（ラナマンモカードCEA®）と酵素免疫測定法（マンモテック®）の相関

		マンモテックCEA®		
		0～400	≦400～1000	≦1000～
ラママンモカードCEA®	0～400	5		
	≦400～1000	1	2	2
	≦1000～		2	8

表3　乳頭異常分泌液中CEA測定法による乳癌診断精度

	年	CEA測定法	cut off (ng/ml)	症例数	感度	特異度
Inaji H	1987	エルモテックCEA	100	30	86%	89%
Mori T	1992	マンモテック®	400	54	76%	79%
Nishiguchi T	1992	マンモテック®	400	16	60%	75%
Yayoi E	1994	エルモテックCEA	600	60	77%	100%
Nishi T	2003	マンモテック®	400	47	79%	93%
Nishi T	2003	ラナマンモカードCEA®	400	47	68%	96%

が可能であるとされている．乳頭異常分泌に対するスクリーニング法としては，潜血反応，乳頭分泌細胞診があるが，感度において十分な成績ではなく[5]，乳管内視鏡や乳管造影は検査に時間と労力を伴う為，多くの症例に行うことは不可能であり，分泌物の細胞診は精度が低い。それらを補う為，無侵襲にて測定可能な乳頭分泌液中の腫瘍マーカーとしてCEAが注目され[6]，1987年，稲治らは乳頭分泌液中のCEA量の測定（エルモテック法）を発案し，非浸潤性乳管癌と良性疾患（乳管内乳頭腫）との鑑別に有用であることが報告した[1,7]．現在，酵素免疫測定法(EIA法)を用いたマンモテック®とイムノクロマトグラフィー法（ICGA法）を用いたラナマンモカードCEA®が，共に市販されている．表3のように，森らは，血性乳頭異常分泌52例に対してマンモテック®の測定を行い（カット・オフ値：400ng/ml），マンモテック®により感度76%，特異度79%と，良好な測定結果を報告している[5]．また，海外においてはimmunoenzymometric assay kit, AIA-PACK CEAを用いて優れた診断精度が報告されている[9]．

ICGA法は，弥生らの考案により製品化された、外来精査中の短時間で測定結果が得られる簡便な方法で、同施設の西らが乳頭異常分泌115例(うち

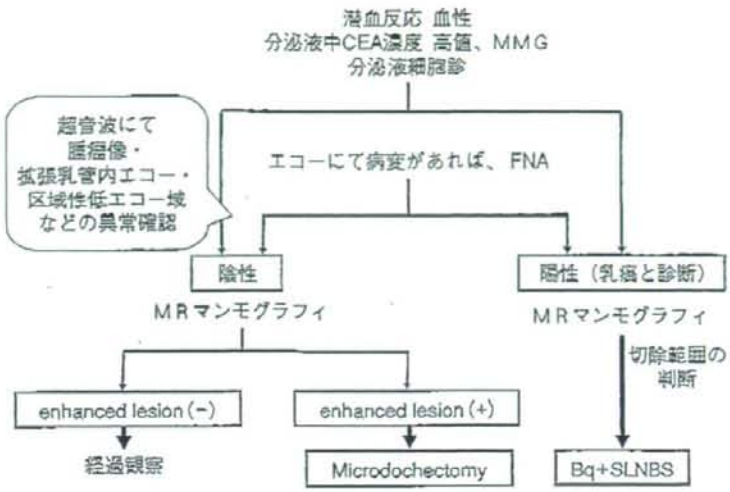

図4　当院における腫瘤非触知の乳頭異常分泌症の診断・治療方針

確定診断のついた47例）について感度68%，特異度96%，正診率85%であり，EIA法と同等の診断精度を有すると報告している[9]．しかし，同じ症例においてEIA法とICGA法との比較をした検討は今回が初めてである．ICGA法の診断能は，感度100%，特異度71.4%，正診率90%であり，EIA法については，感度92.3%，特異度71.4%，正診率85.0%であり，両者ともほぼ同等の結果が得られた．

2つの測定法は，乳頭分泌液の性状（膿性，粘性）や乳管内乳頭腫などの多寡な乳管内成分が一因となって偽陽性を生ずるとされているが，今回の偽陽性を認めた2症例は，共に乳腺症を病理診断とする同じ症例であり（図2），性状も明らかな特徴を認めなかった．また，西らは，ICGA法について，RIA法により測定されたCEA実量値とのよく相関すると報告されている[10]．

当院での乳頭異常分泌の診断・治療シェーマを示すが（図4），乳頭異常分泌がある場合，MMGや乳腺超音波検査など画像検査に加えて，分泌液の潜血反応検査，分泌液細胞診，分泌液中CEA濃度の測定を施行している．また，乳腺超音波にて腫瘤像や低エコー域などの異常を確認した場合は体表より穿刺吸引細胞診（FNA）を行う．そして，分泌液細胞診にて陽性を認めた場合や，FNAにて陽性を認めた場合は，乳癌に準じた治療をしている．現在，乳頭異常分泌症に対するマーカーとして，CEAが臨床応用されているが，その他のマーカーとしてAngiogenic growth factor (FGF-2, IGFBP-3)やKallikreins (PSA), Her2/neu protein, Urokinase-type plasminogen activator (uPA)などが挙げられ[12]，今後，さらに診断精度の高いマーカーや測定方法として期待される．

今回，ICGA法による乳頭分泌液中のCEA測定は従来のEIA法による測定と同等の良好な診断精度をもつことが明らかになった．また，EIA法（マンモテック®）は測定時間が2時間以上と長く，手技もやや煩雑であるのに対し，ICGA法（ラナマンモカードCEA®）は約15分で測定でき，手技も単純（single-step manipulation）である．したがって外来診療中に施行することが可能であり，乳頭異常分泌症例の診断，治療方針決定に有効な方法であると考えられる．

まとめ

イムノクロマトグラフィー（ICGA）法は従来の酵素免疫測定（EIA）法と同等の診断精度あった．

ICGA法はsingle step manipulationにて簡易かつ迅速に測定することが可能であり，乳頭異常分泌症例の診断，治療方針決定に有効な方法である．

文　献

1) Inaji H, Yayoi E,Maeura Y,et al：Carcinoembryonic antigen estimation in nipple discharge as an adjunctive as an adjunctive tool for the diagnosis of early breast cancer. *Cancer* 60：3008-3013, 1987

2) 稲治英生, 小山博記, 野口眞三郎, 他：乳頭分泌液中CEA. 臨床検査 39：1267-1271, 1995
3) 西　敏夫, 弥生恵司, 古妻嘉一, 他：イムノクロマトグラフィー法による乳頭分泌液中CEA測定. 日本乳癌検診学会雑誌 12：114-118, 2003
4) 弥生恵司, 稲治英生,森武貞,他：乳頭異常分泌と無腫瘤性乳癌.乳癌の臨床 3：141-146, 1988
5) 野村長久, 園尾博司, 紅林淳一, 他：乳頭異常分泌の検討. 日本乳癌検診学会雑誌 12：271-276, 2003
6) Kuhajda FP, Offutt LE, Mendelsohn G：The distribution of carcinoembryonic antigen in breast carcinoma. Diagnostic and prognostic implications. *Cancer* 52 (7)：1257-1264, 1983
7) 弥生恵司, 古川順康, 関本貢嗣, 他：乳癌の早期診断；乳頭異常分泌症例の診断.癌と化学療法 21：133-139, 1994
8) Mori T,Inaji H, koyama H,et al：Evaluation of microdot-immunobinding assay for carcinoembryonic antigen determination in nipple discharge in early breast cancer：results of a multicenter study. *Jpn J Clin Oncol* 22：371-376, 1992
9) Yashuang Zhao, Sigitas J, Verselis,et al：Nipple Fluid Carcinoembryonic Antigen and Prostate-Specific Antigen in Cancer-Bearing and Tumor-Free Breasts. *Journal of Clinical Oncology* 19 (5)：1462-1467, 2001
10) 西　敏夫, 弥生恵司, 古妻嘉一, 他：乳頭分泌液中CEA測定の新しいimmunochromatographic assay法の検討. 乳癌の臨床 16：542-543, 2001
11) Nakahara H, Namba K, Fukami A, et al：Three-dimensional MR imaging of mammographically detected suspicious microcalcifications. *Breast Cancer* 8 (2)：116-124, 2001
12) R Sascha Dua, Clare M Isacke, Gerald P H Gui：The Intraductal Approach to Breast Cancer Biomarker Discovery. *Journal of Clinical Oncology* 24 (7)：1209-1216, 2006