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 ≥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 ≤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; Martin 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).

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 (Trueeman 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, 2006) and Australia (Eckermann 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 (\(\geq 1.66, 3.01–5.00\%), \(\geq 5.01\%\)) 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.

\[
\text{ICER} = \frac{\text{Effect}_{\text{with prophylaxis}} - \text{Effect}_{\text{without prophylaxis}}}{\text{Cost}_{\text{with prophylaxis}} - \text{Cost}_{\text{without prophylaxis}}}
\]

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

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**Figure 1** Markov model.
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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 uncouunted.

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, \( 148.5 (\text{£0.74}) \) 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...
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Utility weights are changed by ± 10%, 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%, and women with

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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 | 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%) | | |
| Noninvasive breast cancer | Thereafter: 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 | Change by ± 50% | Ministry of Health, Labour and Welfare (2005a) |
| | endometrial cancer patients 0.0660, 0.0546, 0.0328, 0.02813 | | |
| Pulmonary embolism | Thereafter: Japanese female population mortality rates | Change by ± 50% | Ministry of Health, Labour and Welfare (2005a) |
| Cataracts | Thereafter: Japanese female population mortality rates | Change by ± 50% | Sakuma et al (2004) |
| Hip fracture | Thereafter: Japanese female population mortality rates | Change by ± 50% | Ministry of Health, Labour and Welfare (2005a) |
| 0–1 years after diagnosis: 0.11 and 0.19, respectively | Change by ± 50% | Ministry of Health, Labour and Welfare (2005a) |
| Healthy | 1.00 | Change by ± 20% | Smith and Hildner (1993), Hillner et al (1993), Naism and Keeler (2005) |
| Healthy under chemoprevention for 5 years | 0.99 | Change by ± 20% | Hillner et al (1993), Naism and Keeler (2005) |
| Invasive breast cancer | 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% | Rofu et al (2005) |
| Hip fracture | 0–1 years after diagnosis: 0.61 and 0.92, respectively | Change by ± 20% | Armstrong et al (2001) |
### 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 | | | | |
| Yearly cost | | | | |
| Ages 35–39 | 81,937 | Change by ±50% | Ministry of Health, Labour and Welfare (2005b), Fukawa (1998) | |
| Ages 40–44 | 94,529 | Change by ±50% | |
| Ages 45–49 | 110,604 | Change by ±50% | |
| Terminal care cost, last year of life | | | | |
| Ages 35–39 | 352,331 | Change by ±50% | Insurance claim review | |
| Ages 40–44 | 406,474 | Change by ±50% | |
| Ages 45–49 | 475,599 | Change by ±50% | |
| **Ages 50–64** | | | | |
| First year after diagnosis | | | | |
| Yearly cost | | | | |
| Ages 50–54 | 151,625 | Change by ±50% | Ministry of Health, Labour and Welfare (2005b), Fukawa (1998) | |
| Ages 55–59 | 195,085 | Change by ±50% | Insurance claim review | |
| Ages 60–64 | 258,723 | Change by ±50% | |
| Terminal care cost, last year of life | | | | |
| 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 | | | | |
| Yearly cost | | | | |
| Ages 65–69 | 324,347 | Change by ±50% | Ministry of Health, Labour and Welfare (2005b), Fukawa (1998) | |
| Ages 70–74 | 460,617 | Change by ±50% | Insurance claim review | |
| Ages 75–79 | 549,284 | Change by ±50% | |
| Terminal care cost, last year of life | | | | |
| 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 | | | | |
| Yearly cost | | | | |
| Ages 80–84 | 576,290 | Change by ±50% | Ministry of Health, Labour and Welfare (2005b), Fukawa (1998) | |
| Ages 85–89 | 647,941 | Change by ±50% | Insurance claim review | |
| Ages 90–94 | 557,429 | Change by ±50% | |
| Ages 95–100 | 465,059 | Change by ±50% | |
| Terminal care cost, last year of life | | | | |
| 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% | |
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Table 3 (Continued)

| Diseases                      | Base-case value | Range tested in sensitivity analysis | Source             |
|-------------------------------|-----------------|--------------------------------------|--------------------|
| Non-invasive breast cancer surgery, etc (DPC0900103x020xxx+ reimbursements by FFS) | 847 928         | Change by ± 50%                       | Matsuda and Ishikawa (2003) |

Endometrial cancer
Total hysterectomy, etc (DPC 1200203x01x000+ reimbursements by FFS) | 1183 839 | Change by ± 50%                       | Matsuda and Ishikawa (2003) |

Pulmonary embolism
Total (Diagnosis) | 469 890 | Change by ± 50%                       | Fuji et al (2005) |
(Treatment) | (52 350) | Change by ± 50%                       |                     |
(417 540) | Change by ± 50%                       |                     |

Cataract
Surgery, etc (DPC 0201103x01x000+reimbursements by FFS) | 309 120 | Change by ± 50%                       | Matsuda and Ishikawa (2003) |

Hip fracture
Surgery, etc (DPC 1608003x020000+ reimbursements by FFS) | 1553 195 | Change by ± 50%                       | Matsuda and Ishikawa (2003) |

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

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 35 and 50, and women with a 5-year predicted breast cancer risk of ≥5.01% starting at age 50, and women with a 5-year predicted breast cancer risk of £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
Five-year predicted breast cancer risk ≥ 1.66%  
Starting at age 35 13 958 679 13 993 626 24 947 25.916 25.953 0.037 25.757 25.759 0.002 678 210 14 247 447 Cost more, gain less  
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  
Starting at age 60 20 160 906 20 324 294 163 388 18.806 18.807 0.001 18.688 18.654 –0.034 Cost more, gain less  

Five-year predicted breast cancer risk 2.01 – 3.00%  
Starting at age 35 14 952 349 14 967 969 –288 380 25.651 25.755 0.105 25.396 25.480 0.084 Cost less, gain more  
Starting at age 50 17 867 146 17 911 198 44 053 22.049 22.096 0.047 21.832 21.854 0.022 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 Cost less, gain more  

Five-year predicted breast cancer risk ≥ 5.01%  
Starting at age 35 14 958 034 14 717 649 –190 665 25.663 25.747 0.083 25.414 25.472 0.058 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  
Starting at age 60 19 968 466 20 093 291 124 745 18.798 18.815 0.017 18.618 18.606 –0.011 Cost less, gain more  

Starting at age 35 14 687 003 14 319 020 367 901 25.722 25.844 0.122 25.493 25.598 0.105 Cost less, gain more  
Starting at age 50 17 806 095 17 795 708 10 387 22.079 22.156 0.077 21.884 22.026 0.042 Cost less, gain more  
Starting at age 60 20 015 243 20 198 328 81 488 18.800 18.852 0.052 18.635 18.668 0.033 Cost less, gain more  

No prophylaxis vs prophylaxis with raloxifene  

Five-year predicted breast cancer risk ≥ 1.66%  
Starting at age 50 17 630 814 17 833 020 202 066 22.168 22.190 0.022 22.040 22.027 –0.013 926 382 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 2.01 – 3.00%  
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  
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  

Five-year predicted breast cancer risk ≥ 5.01%  
Starting at age 35 14 956 349 14 685 368 57 986 26.005 26.035 0.030 25.879 25.872 –0.007 1 946 092 Cost more, gain less  
Starting at age 50 17 806 158 17 772 900 153 493 22.195 22.185 –0.010 22.088 22.037 –0.051 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  

History of lobular carcinoma in situ  
Starting at age 35 14 958 034 14 717 649 –190 665 25.663 25.747 0.083 25.414 25.472 0.058 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  
Starting at age 60 19 968 466 20 093 291 124 745 18.798 18.815 0.017 18.618 18.606 –0.011 Cost less, gain more  

History of atypical hyperplasia  
Starting at age 35 14 687 003 14 319 020 367 901 25.722 25.844 0.122 25.493 25.598 0.105 Cost less, gain more  
Starting at age 50 17 806 095 17 795 708 10 387 22.079 22.156 0.077 21.884 22.026 0.042 Cost less, gain more  
Starting at age 60 20 015 243 20 198 328 81 488 18.800 18.852 0.052 18.635 18.668 0.033 Cost less, gain more  

No prophylaxis vs prophylaxis with tamoxifen  

Table 4 Results of cost-effectiveness analysis (1)  

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*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 theCEERs of women with a 5-year predicted breast cancer risk of ≥ 5.01% and women 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...
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.

### Table 5 Results of cost-effectiveness analysis (2)

| Prophylaxis with | Cost (¥) | Effectiveness (LYGs) | Effectiveness (QALYs) | Incremental cost-effectiveness ratio |
|-----------------|----------|----------------------|-----------------------|-------------------------------------|
| Tamoxifen       | Incremental | Tamoxifen | Incremental | Tamoxifen | Incremental | Tamoxifen | Incremental | Tamoxifen | Incremental |
| Prophylaxis with raloxifene | | | | | | | |
| starting at age 50 | 17,975,353 | 17,833,020 | 81,667 | 22,167 | 22,190 | 0.023 | 22,000 | 22,027 | 0.027 | 350,723 | 303,955* |
| starting at age 60 | 20,324,294 | 20,427,386 | 103,093 | 18,807 | 18,822 | 0.015 | 18,654 | 18,670 | 0.016 | 710,785 | 636,920 |
| Five-year predicted breast cancer risk ≥ 5.01% | | | | | | | |
| starting at age 50 | 17,973,900 | 17,794,890 | 61,990 | 22,185 | 22,214 | 0.029 | 22,037 | 22,071 | 0.034 | 216,307 | 183,670* |
| starting at age 60 | 20,444,141 | 20,529,452 | 85,312 | 18,797 | 18,820 | 0.023 | 18,666 | 18,694 | 0.028 | 374,902 | 306,477* |
| History of lobular carcinoma in situ | | | | | | | |
| starting at age 50 | 17,800,766 | 17,911,198 | 110,432 | 22,096 | 22,111 | 0.015 | 21,854 | 21,871 | 0.017 | 715,490 | 654,190 |
| starting at age 60 | 20,058,020 | 20,161,888 | 103,869 | 18,825 | 18,839 | 0.014 | 18,618 | 18,633 | 0.015 | 746,322 | 671,100 |

*Cost-effective when compared to a suggested criterion in Japan (Ohkusa, 2003) of ¥600,000 for one QALY gain.

![Figure 2](image-url) Illustration of key results of sensitivity analyses: prophylaxis with raloxifene vs no prophylaxis starting at age 50.
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 ≥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 ¥600,000 (€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 ≥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 ≤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); Melnikov 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.

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