Budget Impact Analysis of Chemoprevention of Breast Cancer with Tamoxifen and Raloxifene among High-risk Women in Japan

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Received May 13, 2009; accepted June 23, 2009; published online August 5, 2009

‘Cost saving’ was suggested in our recent economic evaluation of chemoprevention of breast cancer targeting women at high risk in Japan. However, this budget impact analysis reveals that the introduction of chemoprevention appears to be not budget saving for 20 years, whereas the level of budget impact seems affordable.

Key words: breast cancer – budget – chemoprevention – raloxifene – tamoxifen

INTRODUCTION

Tamoxifen was approved for chemoprevention against breast cancer by the US Food and Drug Administration (FDA) in 1998, and raloxifene was also approved for post-menopausal women in 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 (1).

It is said that there are five hurdles to overcome in the diffusion process of new health intervention: quality, safety, efficacy, cost-effectiveness and affordability (2). Among these hurdles, in regards to cost-effectiveness, we have recently published an economic evaluation of chemopreventive use of raloxifene as well as tamoxifen in Japan in British Journal of Cancer (3), which suggests that introduction of chemoprevention of breast cancer with tamoxifen for pre-menopausal women and raloxifene for post-menopausal women with a history of atypical hyperplasia (AH) or lobular carcinoma in situ (LCIS) can be justifiable as an efficient use of finite resources for healthcare. The economic model also shows that the use of both agents would be ‘cost saving’.

However, ‘cost saving’ in the economic evaluation framework means that the total value of cumulative costs with discount over the time horizon becomes smaller if chemoprevention is used, whereas it does not directly mean affordability such as the curtailment of public healthcare expenditure in the near future. Prevention always accompanies costs in advance and savings by effectiveness in the future, which instantly raises a question about its impact on healthcare financing over time.

This paper aims to examine the fifth hurdle, that is, affordability for chemoprevention of breast cancer under Japan’s health system by estimating its impact on public healthcare expenditure. The results should deepen our understanding about the implications of cancer chemoprevention to healthcare financing and inform health policy making in Japan as well as in other developed countries.

PATIENTS AND METHODS

We conduct a budget impact analysis of the introduction of chemoprevention for breast cancer targeting women at high risk of developing the disease, i.e. with a prior history of AH or LCIS, using tamoxifen for pre-menopausal women and raloxifene for post-menopausal women. Healthcare budget impact is defined as a forecast of rates of use (or changes in rates of use) with their consequent short- and medium-term effects on budgets and other resources to help health service managers plan such changes (4).
We take the following three steps in our analysis: (i) the estimation of annual incremental cost per head, (ii) the estimation of annual number of women who would take chemopreventive agent and (iii) the estimation of budget impact by combining the results from the first and second steps. The first step is implemented with our economic model presented in Kondo et al. (3). It includes costs borne by women and third party payers from the societal perspective according to the national medical care fee schedule, whereas costs to sectors other than health and productivity losses are uncounted. Results of insurance claims review for 1 year of 400 early-stage breast cancer cases in various stages during follow-up care at Tokyo Metropolitan Cancer and Infectious Disease Center Komagome Hospital, data from the national healthcare expenditure, etc. are built into a Markov model. The regimens for chemoprevention are tamoxifen 20 mg/day or raloxifene 60 mg/day for 5 years. Assuming the costs including drug prices constant over years, annual cost per head for 25 years is computed for cohorts of women with AH or LCIS, starting chemoprevention with tamoxifen at age 35 and 50, and with raloxifene at age 50 and 60, with which incremental costs are calculated. In the second step, we carry out a systematic and deliberate literature survey to find out the best available knowledge in order to infer the number of women who would take chemopreventive agents. In the third step, the budget impact is computed as 70% of the product of annual incremental cost per head and the number of women who would take chemopreventive agents, taking into account the standard 30% co-payment for healthcare.

RESULTS

ESTIMATION OF ANNUAL INCREMENTAL COST PER HEAD

Figure 1 shows the annual incremental costs per head of cohorts featured in our economic model for 25 years. Here, changes of annual incremental costs show a consistent pattern. Costs are positive in the first 5 years reflecting the costs of chemopreventive agents. Net cost of the prescribed agents for 1 year, which is shown as the incremental cost of the first year, amounts to more than ¥50 000 (US$500; US$1 ¥100). They turn negative after the sixth year due to the risk reduction of breast cancer developments, but they gradually increase in the later years. Costs of the raloxifene starting at age 60 cohort become positive after the 20th year, which reflect the costs of end-of-life care of older women who die of diseases other than breast cancer.

Figure 1. Annual incremental cost per head of chemoprevention.

Annual incidence rate of AH is calculated as 4211–14 724 cases per year according to the number of women who undergo mammography screening offered by health checkup programs, in addition to some assumptions as follow. The annual number of women who have mammography screening is estimated at 2 757 254 by summing up the number of those participated in the governmental program, 1 631 811 (5), and private program, 1 125 443 (6). Among these participants, a proportion of those recalled for further tests are assumed at 8.9% (5). Only one paper reports a proportion of AH detected among those recalled, 6.0% (7), but the denominator of this figure is not those screened as ‘further tests required’ but those diagnosed with calcification, which accounts for 28.6% of the recalled (8). Although AH is more often found among those diagnosed with calcification than those without it in our experience, we make two extreme assumptions that 6.0% is good for 28.6% of the ‘further tests required’ and also good for 100% of them. The number of women who undergo mammography screening at clinical consultation bypassing health checkup programs is left uncounted, since no data are available in the literature. We consider this figure small enough to be negligible.

Annual incidence rate of LCIS is calculated as 122 cases per year according to the number of breast cancer incidence, 40 675 cases per year, reported in ‘Cancer statistics in Japan ‘08’ (9) and the proportion of LCIS among diagnosed breast cancers, 0.3%, reported in a nationwide survey report of breast cancer patient registry (10).

The proportion of potential takers of chemopreventive agents is assumed as 43.0% (11). There should be a variation in uptake rates between AH and LCIS, or between tamoxifen and raloxifene, since the explanation about the balances of the risk and benefit given by oncologists to a woman varies. However, we assumed the uptake rates to be constant.
With these figures, the annual number of women who would take chemopreventive agents is estimated at 1811–6331 AH cases and 52 LCIS cases.

Additionally, we take ‘Basic Plan to Promote Cancer Control Programs’ (12) into account, in which four times increase in the number of women who undergo mammography at health checkups is stated as a policy target. The AH cases would amount to 25 444 with this scenario.

**ESTIMATION OF BUDGET IMPACT**

In order to calculate the budget impact, the estimated AH and LCIS cases who would take chemopreventive agents are apportioned among cohorts featured in our economic model according to the age and menopausal status distribution of breast cancer patients reported in the registry (10): 8% to take tamoxifen starting at age 35, 26% to take tamoxifen starting at age 50, 10% to take raloxifene starting at age 50 and 56% to take raloxifene starting at age 60.

Figure 2 shows the budget impact of chemoprevention of breast cancer over the period of 25 years. Black bars stand for the estimation assuming that 1811–6331 AH cases and 52 LCIS cases would start chemoprevention annually, whereas gray bars stand for 6331–25 244 AH cases and 52 LCIS cases. The budget impact increases during the first 6 years up to ¥240–3256 million (US$2.4—32.6 million), and then it gradually decreases. It turns negative after the 20th year, but the curtailment of public healthcare expenditure is very limited compared with the extra-expenditure in the earlier years. It is obvious that cumulative budget impact does not become ‘saving’ within 25 years.

**DISCUSSION**

We analyze the budget impact of introducing breast cancer chemoprevention in Japan. The impact becomes the largest in the sixth year, ¥240–3256 million (US$2.4—32.6 million), which is smaller than those recently estimated in breast cancer care in Japan: ¥2638–3225 million per year for the 21-gene signature diagnostic test (13), and ¥16 000–32 000 million per year for adjuvant therapy with trastuzumab (14). The latter was included into social health insurance package in 2008. These may imply affordability, although there is no established interpretation of budget impact.

Our analysis clearly reveals that a waiting period of 20 years is needed before we see any small budget saving, which contrasts with the ‘cost-saving’ results of our previous economic evaluation. It also contrasts with the estimated annual incremental costs per head, which become negative after the sixth year. This is, however, an example of a typical discrepancy of cohort level observation and population level observation.

Our analysis is simple and straightforward based on limited knowledge of epidemiology and women’s preference for chemoprevention. And, our assumption of constant costs and incidences of AH and LCIS over years may be counter-intuitive, since we often see a fall in drug prices and are facing the current rise of breast cancer incidence, which might suggest overestimation and underestimation of budget impact, respectively. However, evidences adopted are the best available ones to date, and assumptions made are the most conservative ones under the current uncertainty. If the time horizon of 25 years is prolonged, the budget savings will be much larger. However, longer time horizon is virtually meaningless considering the rapid change in breast cancer care brought about by new scientific and medical advances, such as aromatase inhibitors in this context, i.e. anastrozole (the IBISII trial) or exemestane (the MAP-3 trial) (15).

In conclusion, the introduction of chemoprevention of breast cancer with tamoxifen and raloxifene appears to be budget saving for ~20 years, whereas the level of budget impact seems affordable.

**Funding**

This study was supported 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 M.T. [H18-3JIGAN-IPPAN-007].

**Conflict of interest statement**

None declared.

**References**