Clinical Trial Note

Prospective observational study estimating willingness-to-pay for breast cancer treatments through contingent valuation method in Japanese breast cancer patients (JCOG1709A)

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Abstract

In April 2016, the Japanese government introduced health technology assessment as a response to rising medical expenses due to 'medical innovation'. This study investigates how Japanese breast cancer patients who received treatment in Japan consider the financial value (willingness-to-pay; WTP) for their life and health by using the contingent valuation method (CVM) prospectively. First, 168 patients (84 primary breast cancer patients and 84 metastatic breast cancer patients) were pre-examined their WTP with dichotomous-choice method survey form. Next, 1,596 patients (798 primary breast cancer patients and 798 metastatic breast cancer patients) will be surveyed to their WTP for hypothetical scenarios in CVM. Based on our results, we will construct an evaluation axis from the patients' viewpoint for the cost-effectiveness of clinical trials to establish standard treatments for breast cancer. We believe this research can contribute to create a meaningful healthcare system for patients, clinicians, industries, and healthcare policymakers.

Key words: breast cancer treatment, willingness-to-pay, Japanese, contingent valuation method

Introduction

Japanese medical expenses are increasing owing to 'medical innovation.' Because of this trend, the Japanese government introduced health technology assessment (HTA) in April 2016 (1). HTA is the systematic evaluation process of the scientific value, economic, social and ethical issues related to medical technology with fair and robust methods while ensuring transparency. The aim of HTA is to provide information to create efficient and safe medical policies for patients to achieve an optimal value. HTA includes not only cost-effectiveness

but also the relative utility of comparable treatment (drugs) and social/ethical value. HTA decision-making is strongly influenced by the results of medical economic evaluations such as cost-effectiveness analyses (2).

Japanese cost-effectiveness analyses have comprehensively considered: (i) opportunity costs and standards of health technology currently being redeemed, (ii) past payment willingness-to-pay (WTP) surveys, (iii) national income and productivity and (iv) standards in other countries worldwide (3). Of these four items,

WTP reflects the patients' perceived financial value for the treatment. However, the results of payment willingness-to-pay (WTP) surveys may differ whether general Japanese individuals or especially breast cancer patients.

The significance of investigating WTP in breast cancer patients is that owing to the increase of breast cancer medical costs, breast cancer treatment drugs are made a target for cost-effectiveness evaluation, indicating the necessity of a patient-centered HTA decision-making evaluation axis for breast cancer ahead of other cancers. This may be the key to confirming the validity of cost-effectiveness analysis (CEA) results concerning breast cancer treatment drugs based on the general Japanese standard.

The contingent valuation method (CVM) is a specific and effective method of evaluating WTP (4–6). It is explained in detail in the Section Method. We will conduct this study to clarify the following two crucial points that are both clinically and from a health policy perspective. First, we establish an evaluation standard for the interpretation of the results of a CEA in clinical trials for standard breast cancer treatment. Second, we re-evaluate the HTA's decision-making based on the general Japanese population from the perspective of cancer patients.

Based on the above, we initiated a prospective observational study to estimate the WTP for breast cancer treatment in Japanese breast cancer patients using CVM.

Digest of the study protocol

This study investigates how Japanese breast cancer patients, who received treatment in Japan, consider the financial value for their life and health according to their WTP by using CVM prospectively.

Based on our results, we will construct an evaluation axis from the patients' perspective for the cost-effectiveness of the clinical trials to establish standard treatments for breast cancer.

Patients
Eligibility criteria (enrollment criteria).

(1) Unilateral breast cancer patients who conform to either (i) or (ii) given below.

 (i) Primary breast cancer of clinical stages 0–III, for which surgery and/or chemotherapy and/or radiotherapy has been completed as initial treatment, and patient who is currently undergoing regular follow-up observations or postoperative endocrine therapy.
 (ii) Patients who are undergoing endocrine therapy or first-line to third-line chemotherapy for metastatic or recurrent cancer for at least 2 months.

(2) Woman aged from 20 to 79 years on the day of enrollment.
(3) Patients with no history of a malignant tumor other than breast cancer.
(4) No limitations to daily lifestyle or to communicating, reading or writing Japanese.
(5) Patients with regular copayments for medical costs (any copayment ratio allowed).
(6) Patients who are not being administered a trial drug.
(7) Employment not described as 'student.'
(8) Patients who have provided written consent for study participation.

Method

Contingent valuation method
The CVM (Fig. 1) is used to evaluate the benefits and values of an asset or service, which is not specifically conferred by market values, based on the preferences of latent benefactors (consumers) who utilize these values. There are different methods of using CVM, which depend on the types of questions used to examine WTP for the hypothetical health technology being evaluated. In this study, we adopt a two-step dichotomous choice method, whereby patients respond as to whether they would accept or reject payment of displayed payment amounts. To increase the reliability of this study, we decided to set the displayed payment amounts based on a preliminary study and to use a two-stage dichotomous choice method in which the WTP display-selection process is performed twice.

Study design
This is a multicenter prospective observational study (Fig. 2). This study will be conducted by the 42 hospitals belonging to the Breast Cancer Study Group of the Japan Clinical Oncology Group (JCOG). The study procedures involve preparing hypothetical treatment scenarios for breast cancer, which are significant from the clinical and health policy perspectives, and conducting a preliminary study that would be organized by six leading hospitals in the JCOG Breast Cancer Study Group. The results of this preliminary study will be used to set the payment amounts to be displayed in the main study. Data from the main study will then be analyzed and an acceptance probability curve will be created. WTP will be calculated as 50% of the patients accepting the amount. In addition, we will collect patient questionnaire (self-recorded response on WTP for hypothetical scenarios, utility survey by EQ-5D-5L and social background survey) and healthcare professional questionnaire (disease condition survey) for conducting an exploratory investigation of factors affecting the patient WTP.

Setting hypothetical treatment scenarios for breast cancer
Primary breast cancer cohort. This study will evaluate the financial value of treatment for preventing the recurrence and breast cancer death. The two hypothetical scenarios are described in the below text.

(1) Evaluation of WTP for a new treatment that could prolong 'survival without breast cancer recurrence' by 1 year to assess the financial value of 1 year of survival. The specific hypothetical scenario is as given in the following text.

Imagine that a new method of treatment (treatment period: less than 1 year) that will allow you to live for 1 more year with no breast cancer recurrence has been developed. The total cost of treatment will be X yen. Would you like to undergo this treatment? Please answer based on the assumption that you will completely cover the costs (responsible for total expense) by yourself.

The displayed payment amount X is set by the preliminary study.

(2) Evaluation of WTP for a new treatment that would reduce the possibility of breast cancer recurrence to 40% or lower, to assess the financial value of disease-free survival with recurrence or death, and/or secondary cancer reduced to 40% or lower. This is thought to indicate clinically significant recurrence-reducing effects and is based on the European Society for Medical Oncology's clinical benefit scale (7). The specific hypothetical scenario is as given in the following text:
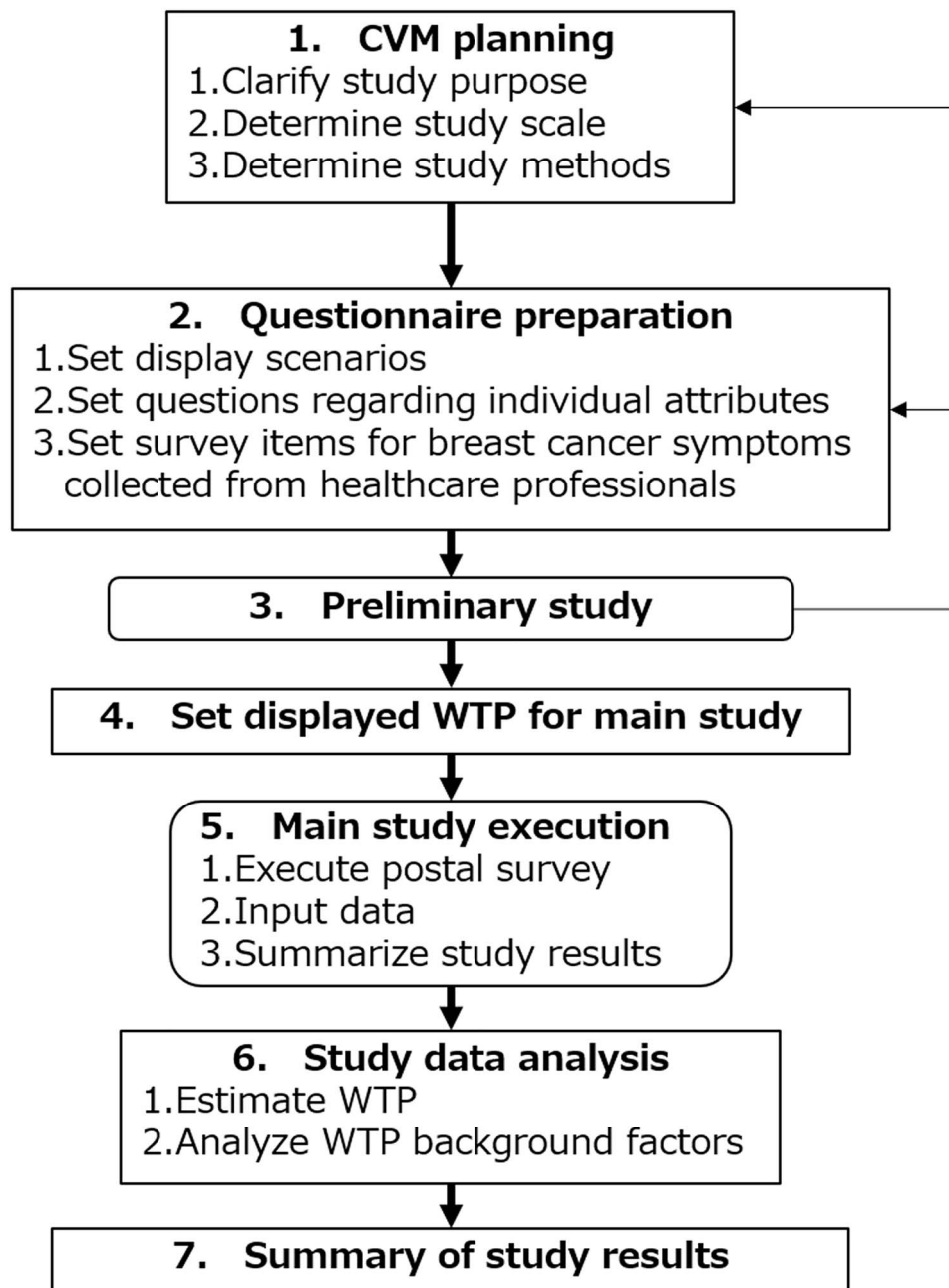
Figure 1. Contingent valuation method (CVM). WTP, willingness-to-pay.

Imagine that a new treatment (treatment duration <1 year) is developed, which reduces the chance of breast cancer recurring by 40%. The total cost of treatment will be X' yen. Would you like to undergo this treatment? Please answer based on the assumption that you will completely cover the costs (responsible for total expense) by yourself.

The displayed payment amount X' is set by the preliminary study.

Metastatic breast cancer cohort. This study will evaluate the financial value of treatment for extending survival. The two hypothetical scenarios are described in the below text.

(1) Evaluation of WTP for a new treatment that could prolong 'survival at current quality of life (QOL) level' by 1 year to assess the financial value of 1 year of survival. As it is unlikely that the utility (QOL value) would reach 1.0, indicating perfect health, in metastatic breast cancer patients, the question will be based on the assumption that they will be living with cancer. The specific hypothetical scenario is as given in the following text.

Imagine that a new treatment that would allow you to extend the period of your current lifestyle level for 1 year (treatment period less than 1 year) has been developed and treatment costs will be Y yen. Would you like to undergo this treatment?

Please answer based on the assumption that you will completely cover the costs (responsible for total expense) by yourself.

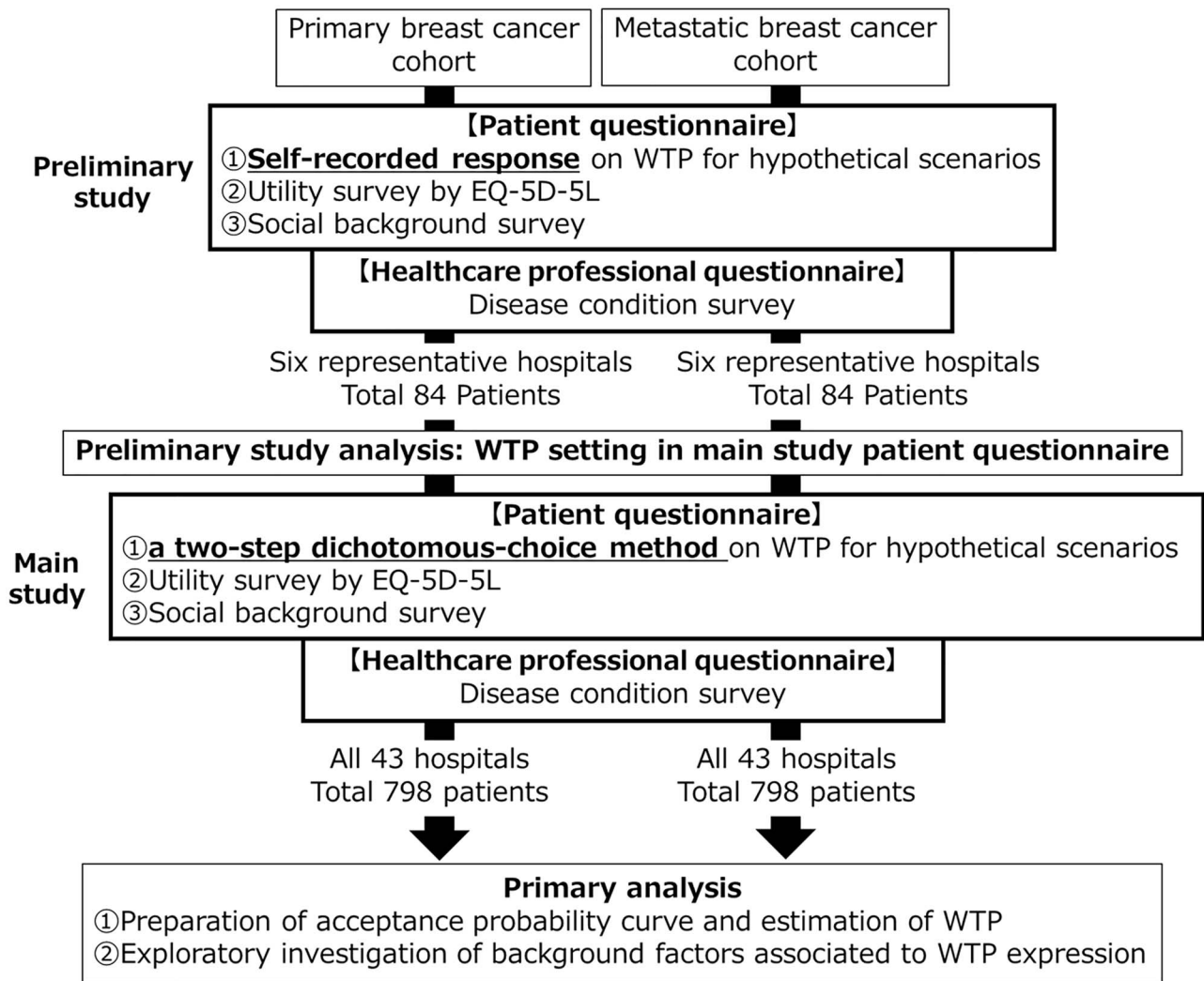The displayed payment amount Y is set by preliminary study.

Figure 2. Study design.

(2) Evaluation of WTP for 'survival for 1 year in the state of health prior to starting breast cancer treatment' to assess the financial value of 'acquiring 1 year in a state of health prior to starting breast cancer treatment'. This is equivalent to the financial value of acquiring one Quality Adjusted Life Year (QALY) for a healthy individual. The specific hypothetical scenario is as given in the following text.

Imagine that a new treatment that would allow you to live for 1 year at the same level of health as before you started breast cancer treatment (treatment period less than 1 year) has been developed and treatment costs will be Y' yen. Would you like to undergo this treatment? Please answer based on the assumption that you will completely cover the costs (responsible for total expense) by yourself.

The displayed payment amount Y' is set by preliminary study.

Social background survey

In this study, we will conduct an exploratory investigation of factors affecting the patient WTP. We will examine the social backgrounds, breast cancer treatment history and QOL (utility and visual analog scale) using EQ-5D-5L. The specific social background survey items are as follows:

(1) Family history of breast cancer
(2) Employment status
(3) Type of public health insurance and medical fee copayment ratio
(4) Residential environment
(5) Marital status
(6) Family composition
(7) Whether undergoing complementary and alternative medical treatment, and details of such treatment
(8) Educational background
(9) Main breadwinner in household
(10) Household income
(11) Loan repayment amounts
(12) Whether high-cost medical care benefit system is used
(13) Private insurance coverage
(14) Whether given explanation on prognosis

Grounds for sample size

When using the dichotomous choice method for responses based on WTP and estimating WTP according to the proportions of agreement

with the displayed payment amount, one way to determine the number of samples required for analysis is using a formula to estimate the proportion of persons in agreement in the population (8). While there are no requirements for absolute accuracy settings, if, for example, the estimated agreement proportion is to be kept within the range of ±10% (referred to as absolute accuracy) with a 95% confidence interval, 1.96 (for confidence of 95%) is inserted into the reliability coefficient and 0.1 is inserted into the absolute accuracy part of the following formula. The population attribute proportion [agreement proportion to displayed payment amount; if set at 0.5, the number of samples on the safety side (larger amount) can be obtained] and population to determine the number of samples required for analysis are also inserted.

Figure 3. Prediction chart of the acceptance probability curve and WTP.

$$\frac{\text{Population}}{\left(\text{Absolute accuracy}\Big/\text{Reliability coefficient}\right)^2 \cdot \left(\text{Population} - 1\Big/\text{Proportion of attributes in population } (1 - \text{population attributes proportion})\right) + 1}.$$

The following parameters can be inserted to determine the number of samples required for analysis: the population is set at 402 377 individuals [number of persons with disease for the last 10 years according to the report of clinical statistical studies on registered breast cancer patients in Japan (9)] and the population attribute proportion is set at 0.5.

With reliability at 90%, absolute accuracy at ±10% and a valid response proportion of 90%, the number of patients required for the preliminary study was calculated to be 78. To ensure that this number is reached, 14 cases will be surveyed at 6 representative facilities for a total of 84 patients. For primary breast cancer cohort study, we plan to survey 84 primary breast cancer patients, and for metastatic breast cancer cohort study, 84 metastatic/recurrent breast cancer patients.

The number of subjects necessary for the main study was calculated to be 768, with a 95% confidence interval, absolute accuracy of ±5% and a valid response proportion of 50%. We will therefore survey a total of 798 patients, 19 cases at each of a total of 43 facilities. The respective number of primary breast cancer and metastatic/recurrent breast cancer patients in the population is unknown. To ensure the reliability of the study, we plan to enroll 798 primary breast cancer patients and 798 metastatic/recurrent breast cancer patients.

The valid response proportion was set at 50%, because the CVM application guidelines state that 'the recovery rate for postal surveys is often just 50%, even for public surveys' (8).

Endpoint

The primary endpoint of this study is WTP for hypothetical scenarios. WTP will be shown as an acceptance probability curve. The curve (Fig. 3) will be calculated by plotting the results of our investigation of whether patients would accept the displayed payment amounts for hypothetical scenarios on the graph, with the amount shown on the *x*-axis and acceptance proportions shown on the *y*-axis. In this graph, WTP will be shown as the amount at which 50% of patients would accept payment. As this observational study will be conducted with different questionnaires for the primary breast cancer patients and the metastatic/recurrent breast cancer patients, an individual acceptance probability curve will be prepared for each patient group.

Statistical analysis

Preliminary study analysis and method of setting displayed payment amounts for the main study. The preliminary study will determine the range of WTP responses (range of monetary amounts to be displayed)
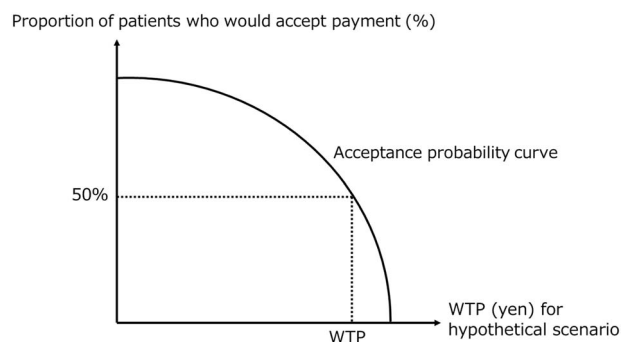
to be used in the main study. The maximum displayed amount, minimum displayed amount and median of the displayed amount will be determined based on the results of the preliminary study.

(1) Maximum displayed amount

The preliminary study will be conducted by means of self-recorded responses. Using the indicated amounts in the preliminary study, settings will be established so that the payment agreement proportion is 0%.

(2) Minimum displayed amount

This will be set as approximately 1/100th of the maximum displayed amount, in accordance with the CVM application guidelines (8).

(3) Median amounts

The amounts between the minimum and maximum displayed amounts will be divided into seven stages, and median values will be used as standards for the displayed payment amounts (8).

Main analyses and judgment criteria in the main study. For the main analysis, the acceptance probability curve will be calculated using the parametric method. The calculation will be based on the obtained responses and median WTP, which is determined by calculating the amount at which the acceptance probability curve is at 50%. The obtained amount will then be converted to WTP per one QALY based on the displayed question content. The parametric curve used will then be selected using Akaike Information Criteria. This curve is selected as the curve with the best fit, including the Weibull curve—generally used as a survival curve—and the logarithm logistic curve. The bootstrap method will then be used to obtain the 95% confidence interval for the median WTP.

As secondary WTP values, the area under the acceptance probability curve estimated using the WTP quartile point or parametric method will be calculated to determine the mean WTP. The upper limit for the integration range will be set as the upper limit for the displayed amount.

After calculating the probability curve, an explorative investigation will be conducted to investigate the demographic background factors—such as household income and academic background—as covariates as well as the factors that could affect WTP. WTP covariates will then be adjusted based on the factors determined by

the above analysis to significantly affect WTP so that the composition ratio is similar to that of the general Japanese population.

When calculating the covariate-adjusted WTP, the parametric distribution utilized in the main analysis for the acceptance probability curve will be utilized. Moreover, the coefficients for each covariate estimated in the regression model will be used to obtain the estimated WTP, incorporating representative covariate values for Japanese people in the regression formula portion. When making estimates with the above regression formula, this is equivalent to using the acceptance probability curve as the survival curve and performing an analysis with an acceleration model. Similarly, the covariate-adjusted WTP will be calculated based on the Japanese Breast Cancer Society Report of clinical statistical studies on registered breast cancer patients in Japan.

Registration of the protocol The study protocol was approved by the Protocol Review Committee of JCOG on 28 March 2019. The study commenced on 22 July 2019. The study was also registered at the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) as the study number UMIN000037445.

Funding

Conflict of interest

None declared.

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