RESEARCH ARTICLE

Evaluation of Health-related Quality of Life for Hypothesized Medical States Associated with Cervical Cancer

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Abstract

Background: When evaluating health-economics for cervical cancer prevention policies in Japan, it is important to use Japanese value settings. This study aimed to obtain preference-based measures (preference measures) for hypothesized health states among healthy Japanese women, and to examine differences between the EuroQol-5D (EQ-5D) and standard gamble (SG) instruments. Materials and Methods: The investigation was performed among female students at a nursing university. We used written hypothetical scenarios describing three grades of cervical intraepithelial neoplasia (CIN) and eight stages of cervical cancer, both at diagnosis and after medical intervention. Preference measures were evaluated using both EQ-5D and SG. Results: We received responses from 136 women. The mean number of respondents per stage was 24.6 (SD: 2.7). At diagnosis, average EQ-5D scores for CIN1, CIN2, CIN3, IA1, IA2, IB1, IB2, IIA, IIB, III, and IV stages were 0.84 (0.14), 0.78 (0.12), 0.73 (0.10), 0.78 (0.12), 0.72 (0.12), 0.63 (0.13), 0.64 (0.12), 0.68 (0.08), 0.62 (0.13), 0.55 (0.21), and 0.18 (0.24), respectively. Using one-way analysis of variance with the Tukey-Kramer method for multiple comparisons (each stage vs. CIN1), we found significant differences for IB1 and more advanced stages (p<0.05). After medical intervention, corresponding EQ-5D scores were 0.84 (0.12), 0.81 (0.12), 0.84 (0.12), 0.80 (0.15), 0.78 (0.11), 0.64 (0.15), 0.63 (0.15), 0.71 (0.15), 0.50 (0.17), 0.52 (0.17), 0.21 (0.28). The multiple comparisons identified significant differences for IB1 and more advanced stages, excepting IIA (p<0.05). SG evaluations were more variable and relatively higher than EQ-5D evaluations. Conclusions: We obtained preference measures for three grades of CIN1-3 and eight stages of cervical cancer. In combination with appropriate sensitivity analyses, these preference measures will provide a basis for an economic evaluation of cervical cancer prevention in Japan. We suggest that EQ-5D is appropriate for cost-utility analysis of this topic.

Keywords: Cervical cancer - quality of life - EuroQol-5D (EQ-5D) - Standard Gable - Japanese women

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Introduction

Among women, cervical cancer is the third most common cancer in the world (Ferlay et al., 2012). In Japan, cervical cancer is diagnosed in 21,000 women each year (Matsuda et al., 2007). Further, it has been estimated that over 2,700 women die as a result of this disease each year in Japan (Vital Statistics Japan, 2012). The age-adjusted mortality rate is higher in Japan than it is in the USA and the UK (Cancer Statistics Japan Editorial Board, 2009). The incidence rate has been increasing among women in their 20's and 30's and, more generally, the women of maternal age (Matsuda et al., 2007), especially in recent years. Since the 1950's, cytology-based screening for the cervical cancer prevention has been provided in Japan, contributing to downward trends in mortality rates (Konno, 2010).

Research in molecular biology has made it clear that cervical cancer and its precancerous lesions are caused by human papillomavirus (HPV) (zur Hauzen, 1991). For cervical cancer prevention, it is important to have clinical economic evaluations, which provide information to support economically effective decisions (Canfell et al., 2012). Clinical economic evaluations of cervical cancer prevention, especially those regarding the timing of the vaccination and the types of vaccines, are especially essential (Canfell et al., 2012). Cost-effectiveness analysis is a method of economic evaluation that generally uses the incremental cost-effectiveness ratio (ICER), which is the ratio of incremental cost divided to the incremental effectiveness of a new strategy (Drummond et al., 1997; Gold et al., 1996). Cost-utility analysis is especially focused around the life-year as an effect measure, which is adjusted according to quality of life (quality of life adjusted life year; QALY) (Drummond et al., 1997; Gold et al., 1996). QALY uses preference-based measures (Drummond et al., 1997) (preference measures) to represent health-related quality of life (QOL) for various

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health states. QOL falls within the range 0 ≤ QOL ≤ 1, where 0 indicates death, 1 indicates perfect health, and life-years are weighted by preference measures (Drummond et al., 1997).

Many studies of QOL have been conducted (Lang et al., 2012). For example, studies have used QOL in comparisons of patients before and after cytology-based screening (Korfage et al., 2012), as evaluated using a disease-specific module (Singer et al., 2012). However, studies of preference measures for HPV-related diseases differ by country (Galante et al., 2011). It is important to use the original preference measures for each country.

To obtain preference measures that would be useful for cost-utility analyses of cervical cancer prevention in Japan, we focused on healthy female students at a nursing university. These students generally belong to the age group at which the incidence of cervical cancer is rising. Further, they have proper medical knowledge. We used health-related QOL evaluations to assess the health conditions of hypothetic states, employing Standard Gamble (SG) (Drummond et al., 1997), the direct standard bet method, and EuloQol-5D-3L (EQ-5D) (Drummond et al., 1997; The Japanese EuroQol Translation Team, 1998), an indirect appraisal method.

Materials and Methods

Subjects

This research was conducted cross-sectionally, using a self-reported questionnaire that was administered in October, 2013. The subjects were healthy female students at a nursing university who were at least 20 years old (enrolled in the 3rd or 4th year of the nursing education program).

Evaluation of preference measures

We prepared scenarios for 11 health states (disease grade and stage), describing the health condition both "at diagnosis (AD)" and "after medical intervention (AI)" for cervical intraepithelial neoplasia (CIN)1, CIN2, CIN3, and eight stages of cervical cancer. The gynecologic oncologist based these scenarios on the International Federation of Gynecology and Obstetrics (FIGO) standards.

The preference measure evaluations were administered as follows. (1) Two different health state scenarios were given to one subject at random. (2) The subjects read the portion regarding the AD of the one health state scenario, as first presented with two scenarios. Subsequently, they answered the self-reported questionnaire using EQ-5D and SG. (3) Then, the subjects read the portion of the AI scenario and answered the questionnaire as described above. (4) The subjects responded to another assigned scenario, similarly as in (2) and (3). Example questions from EQ-5D and SG are shown in Figure 1 and Figure 2, respectively.

EQ-5D preference measures were calculated using the Japan-specific tariff, combining the answers for five questions (The Japanese EuroQol Translation Team, 1998). For SG, answers were specified in the range of 0%-100% probability to the preference measures.

Statistical analysis

The number of respondents were totaled for each age and school year. For the preference measures obtained in each health state, the average, median, and standard deviation (SD) were calculated. In addition, scatter plots of the preference measures were created. Head-to-head comparisons of scores between the two groups (AD and AI), school years (3rd and 4th), and evaluation methods (EQ-5D and SG) were tested using Student's t test. Moreover, multiple comparisons were performed using one-way analysis of variance (ANOVA) to confirm differences in the health states between the AD and AI groups. Subsequently, the Tukey-Kramer method was used to adjust for multiple comparisons, based on the CIN1 between each of the health states.

Furthermore, we conducted regression analyses to investigate the relationships between disease-related health states and preference measures for AD and AI, using both EQ-5D and SG, and treating health state as an ordinal scale. Correlation coefficients were also calculated.

Multiple regression analyses were conducted to investigate the influences of AD and AI, school years, ages, and health states, using the preference measures specified with EQ-5D and SG as explanatory variables.

The level of statistical significance was set at 5% ($p<0.05$). Microsoft Excel 2013, Statcel3 add-in software, and SPPS 15J were used for our analyses.

Ethical consideration

As part of the ethical considerations in this study, we explained to subjects that the study was anonymous, involved only voluntary cooperation, that there was no obligation or disadvantage regarding the decision to cooperate, that they could recall or drop out at any time during our investigation, and that submitting a questionnaire would constitute cooperation.

In addition, we received approvals from the Ethics Committee of Teikyo Heisei University (No.25-027) and the Medical Ethics Committee of University of Tsukuba (data-analysis 2013 No. 808).

Results

Of the 174 targeted students at a nursing university, 136 subjects responded (78.6%; 63 in their third school year and 73 in their fourth school year). The mean number of respondents per health state was 24.6 (SD: 2.7). The respondent's average age was 21.3 years old (±1.2, excluding two subjects who did not provide their ages). There were 5, 1, 1, and 0 missing answers for AD evaluated by EQ-5D (EQ-5D AD), AI evaluated by EQ-5D (EQ-5D AI), AD evaluated by SG (SG AD), and AD evaluated by SG (SG AI), respectively.

The variances of the preference measures are shown in Figure 3. The numbers of respondents, averages, SDs, and medians are shown in Table 1. Figure 4 presents average preference measures for each health state. When comparing the preference measures between two groups (AD and AI), evaluation methods (EQ-5D and SG), and school years (3rd and 4th), we found no characteristic tendencies among the significant difference ($p<0.05$).

Table 1 includes the results of a Student's t test for the preference measures in the AD and AI groups at the same health state.

With one-way ANOVA, we confirmed differences between preference measures for each health state at EQ-5D AD and AI, at SG AD and AI (EQ-5D AD, AI, and SG AI: $p<0.001$; SG AD: $p<0.002$). Subsequently, the Tukey-Kramer method was used for multiple comparison of each health state relative to each of the preference measures of CIN1. We found a significant difference after IB1 stage with EQ-5D (except for IIA stage at AI, $p<0.05$). On the other hand, we confirmed a significant difference ($p<0.05$) only at stage IIA, III at AI, and stage IV for AD (Table 2).

To analyze the relationship between the health states and the preference measures for AD and AI with EQ-5D and SG, we performed a simple regression analysis at 11 health states, from CIN1 to cervical cancer stage IV, as an ordinal scale. The correlations (r) were 0.6, 0.7, 0.2, and 0.2 for the EQ-5D AD, EQ-5D AI, SG AD, and SG AI groups, respectively.

Table 1. Preference Measures of Cervical Intraepithelial Neoplasia (CIN) and 8 FIGO Terms of Cervical Cancer, as Measured by (a) EuloQol-5D (EQ-5D) and (b) Standard Gamble (SG)

(a) EQ-5D

Health State	At diagnosis				After medical intervention				P*
	n	Mean	(SD)	Median	n	Mean	(SD)	Median	
CIN1	24	0.84	-0.14	0.79	24	0.84	-0.12	0.79	0.96
CIN2	30	0.78	-0.12	0.79	30	0.81	-0.12	0.79	0.35
CIN3	25	0.73	-0.1	0.79	26	0.84	-0.12	0.79	<0.01
IA1	27	0.78	-0.12	0.79	26	0.8	-0.15	0.79	0.49
IA2	24	0.72	-0.12	0.76	26	0.78	-0.11	0.79	0.05
IB1	21	0.63	-0.13	0.64	21	0.64	-0.15	0.65	0.67
IB2	26	0.64	-0.12	0.64	26	0.63	-0.15	0.6	0.69
IIA	19	0.68	-0.08	0.66	20	0.71	-0.15	0.71	0.55
IIB	24	0.62	-0.13	0.66	24	0.5	-0.17	0.53	0.01
III	24	0.55	-0.21	0.61	25	0.52	-0.17	0.54	0.59
IV	23	0.18	-0.24	0.28	23	0.21	-0.28	0.28	0.7

(b) SG

Health State	At diagnosis				After medical intervention				P*
	n	Mean	(SD)	Median	n	Mean	(SD)	Median	
CIN1	24	0.83	-0.17	0.9	24	0.78	-0.27	0.9	0.45
CIN2	30	0.69	-0.28	0.7	30	0.71	-0.28	0.7	0.8
CIN3	26	0.73	-0.21	0.75	26	0.74	-0.21	0.8	0.95
IA1	27	0.68	-0.22	0.75	27	0.72	-0.23	0.8	0.51
IA2	25	0.68	-0.14	0.7	26	0.73	-0.18	0.73	0.3
IB1	21	0.72	-0.15	0.8	21	0.77	-0.13	0.8	0.21
IB2	26	0.68	-0.18	0.7	26	0.68	-0.17	0.73	0.98
IIA	20	0.63	-0.19	0.7	20	0.69	-0.2	0.7	0.3
IIB	24	0.71	-0.19	0.73	24	0.69	-0.19	0.7	0.64
III	25	0.64	-0.18	0.7	25	0.63	-0.2	0.7	0.86
IV	23	0.54	-0.24	0.5	23	0.48	-0.3	0.5	0.44

*Results Student's t test of the means of the preference measures "at diagnosis" and "after medical intervention" for the same disease-related health state of disease; FIGO: The International Federation of Gynecology and Obstetrics

Please answer the following questions.
Assume that, while you were at a medical institution, you recieved a diagnosis indicating that you were suffering from cervical cancer or its related disease
By placing a tick in one box in each group below, please indicate which statements best describe your own health state.

Mobility
- □ I have no problems in walking about.
- □ I have some problems in walking about.
- □ I am confined to bed.

Self-Care
- □ I have no problems with self-care.
- □ I have some problems washing or dressing myself.
- □ I am unable to wash or dress myself.

Usual Activities
(e.g work, study, housework, family or leisure activities)
- □ I have no problems with performing my usual activities.
- □ I have some problems with performing my usual activites.
- □ I am unable to perform my usual activities.

Pain/Discomfort
- □ I have no pain or discomfort.
- □ I have moderate pain or discomfort.
- □ I have extreme pain or discomfort.

Anxiety/Depression
- □ I am not anxious or depressed
- □ I am moderately anxious or depressed
- □ I am extremely anxious or depressed

Figure 1. EuroQol-5D Questionnaire (Example for "at diagnosis"). The original questionnaire was written in Japanese

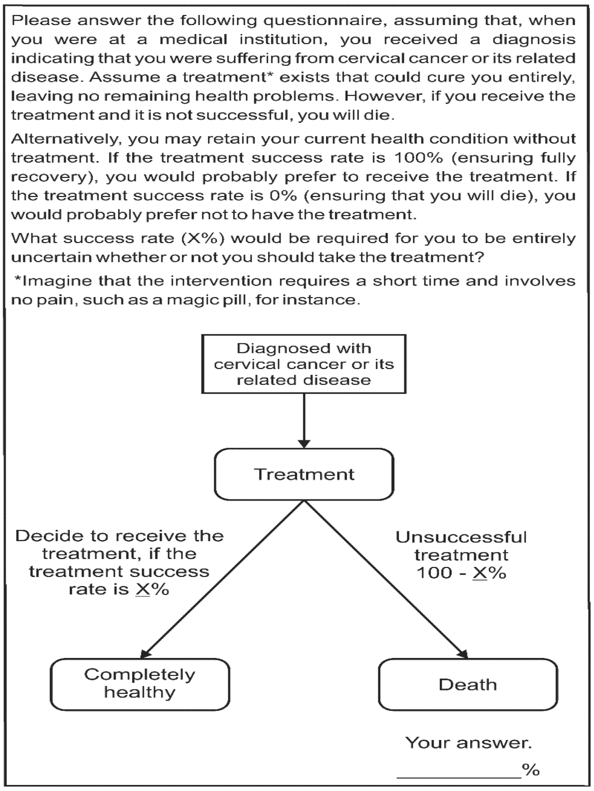

Figure 2. Standard Gamble Questionnaire (Example for "at diagnosis"). The original questionnaire was written in Japanese

Finally, to evaluate the influences of AD and AI, school year, age, and health state on preference measures, we performed a multiple regression analysis (adjusted R2: 0.557), using the preference measures measured by EQ-5D as an explanatory variable. The stages from IB2 to IV were significant variables (p<0.05). However,

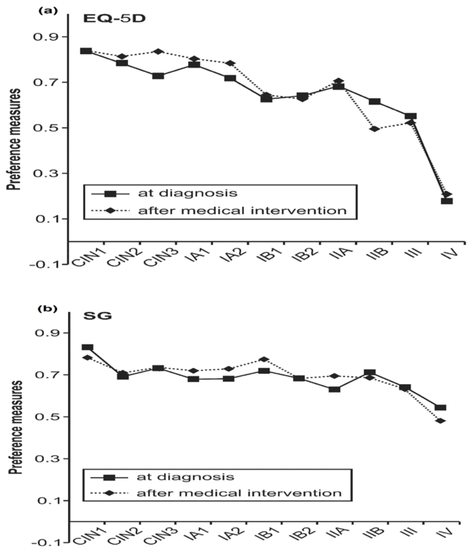

Figure 4. Means of the Preference Measures for Each Disease-Related Health State, as Measured by EQ-5D (a) and SG (b). EQ-5D: EuroQol-5D, SG: Standard Gamble

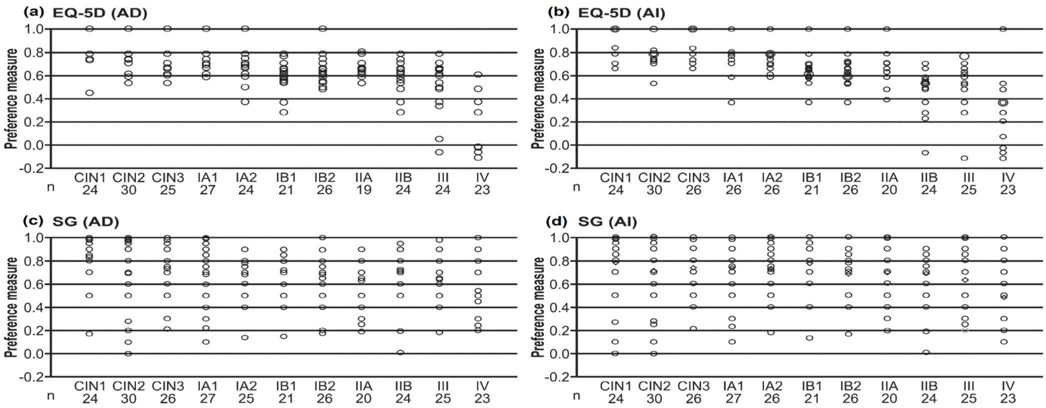

Figure 3. Scatter Plots of Preference Measures, as Assessed by EQ-5D and SG. Each plot was obtained by evaluating one of the 11 hypothesized cervical cancer-related medical states, both at diagnosis (AD) and after medical intervention (AI). Preference measures of the hypothesized health AD statuses, as measured by EQ-5D (a); AI health statuses, as measured by EQ-5D (b); AD health statuses, as measured by SG (c); AI health statuses, as measured by SG (d). The score ranges of EQ-5D and SG were -0.111 to 1.0 and 0 to 1, respectively. EQ-5D: EuroQol-5D. SG: standard gamble. AD: after diagnosis. AI: after medical intervention. CIN: cervical intraepithelial neoplasia

Table 2. One-Way ANOVA Followed by Multiple Comparisons among the (a) EQ-5D and (b) SG Preference Measures, Based on CIN1 between Each Disease-Related Health State. P values were obtained using Tukey-Kramer multiple comparison tests

(a) EQ-5D	CIN1	CIN2	CIN3	IA1	IA2	IB1	IB2	IIA	IIB	III	IV
AD	-	0.96	0.22	0.92	0.14	***	***	0.02*	***	***	***
AI	-	1	1	1	0.98	<0.01**	***	0.19	***	***	***
(b) SG	**CIN1**	**CIN2**	**CIN3**	**IA1**	**IA2**	**IB1**	**IB2**	**IIA**	**IIB**	**III**	**IV**
AD	-	0.3	0.82	0.22	0.26	0.75	0.26	0.05*	0.62	0.05*	***
AI	-	0.98	1	1	1	1	0.9	0.97	0.92	0.39	***

****p<0.001, ** p<0.01, * p<0.05; "ANOVA: analysis of variance. AD: At diagnosis. AI: After medical intervention. CIN: cervical intraepithelial neoplasia; EQ-5D: EuroQol-5D. SG: standard gamble"

AD and AI, school year, and age were not significant variables. We performed a similar multiple regression analysis (adjustment R2: 0.005), using the preference measures measured by SG as an explanatory variable. Grade CIN3, cancer stages IA2 and IB1-IV (excepting IB2) were significant variables ($p<0.05$). However, AD and AI, school year, and age were not significant variables.

Discussion

We conducted health-related QOL evaluations using EQ-5D and SG, and obtained preference measures for CIN1-3 and eight stages of cervical cancer, as hypothesized by healthy female students at a nursing university (Table 1). Regarding QOL evaluations of cervical cancer in Japan, previous studies have used mental measures (CES-D, HADS) (Ohara-Hirano et al., 2004; Suzuki et ail., 2011), as well as evaluations after radiotherapy using FACT-G, which is a cancer-specific instrument (Kobayashi et al., 2009). To our knowledge, however, no previous studies have stated the preference measures that are used for cost-utility analysis. We expect that the preference measures specified by our research will be the first report to include these measures.

The preference measures obtained by EQ-5D in this study are appropriate for an economic evaluation of cervical cancer prevention in Japan. Indeed, EQ-5D results had a smaller distribution than SG results (Table 1) in most of the health states. Further, EQ-5D had a higher correlation between preference measures and health states than did SG. Additionally, the EQ-5D preference measures tended to be significantly lower than CIN1 after stage IB1. On the other hand, few stages were significantly different from CIN1 with SG (Table 2). EQ-5D is a close-ended questionnaire that is easy to respond to, while SG is difficult to respond to for those individuals who are unfamiliar with considering preferences using bets (Gold et al., 1996). For this reason, the SG measurements are usually conducted face-to-face, and interviews are conducted using visual instruments in many cases (Drummond et al., 1997). We used a self-reported questionnaire for this study because the face-to-face investigation required an infeasible investment of time and effort. However, we believe that this reliance on self-reporting may have affected our results.

The preference measures obtained by EQ-5D tended to become smaller than those obtained by SG (Table 1, Figure 4). Accordingly, we can see how it has been reported in Japan (Tamura et al., 1996) that SG directly assesses individual preferences as the probability of death avoidance rate, and that the utility was overestimated with a risk-adverse tendency. Moreover, the preference measures obtained with SG tended to be quite variable (Figure 3). We believe that individual risk-adverse, risk-neutral, and risk-seeking attitudes also directly affected the results, because individual preferences obtained by SG are a direct reflection of expected utility theory (Drummond et al., 1997). It has previously been reported that EQ-5D is the most commonly used instrument for obtaining the preference measures that are used in cost-effective analysis (Greenberg et al., 2009). Therefore, we suggest that EQ-5D is an evaluation method that is easy to use.

We expected that the AI preference measures would be higher than the AD preference measures. Otherwise, the preference measures for AI were less than those for AD in stages IB2, IIB, and III with EQ-5D, as well as in CIN1 and stages IIB, III, and IV with SG. However, only stage IIB with EQ-5D showed a significant difference ($p=0.01$) (Table 1). We think that this result was influenced by the scenario for this stage, which included both morbidities following radical hysterectomy and delayed radiation injury.

Furthermore, we studied the influences of various covariates on these preference measures using multiple regression analysis. However, the AD and AI dichotomous variable was not significant. In the advanced stages of cancer diagnosis and treatment (a period that includes the delayed effects of radiation therapy and anxiety about cancer recurrence) clinical outcomes were under expectation, subjects expressed that they, “remain in the same health state with or without medical intervention”, and the effects were possibly counterbalanced. From the tendency of the preference measures after medical intervention were both exceeded in CIN and the early period of cancer, we considered that the importance of the early medical intervention.

The preference measures used for cost-utility analyses of cervical cancer prevention in Japan have referred to the literatures from other nations (Konno et al., 2010; Yamamoto et al., 2011). Konno et al. (2010) used the preference measures, CIN1: 0.87 and CIN2/3: 0.99, as well as cervical cancer: 0.727 and after cervical cancer medical intervention: 0.938. Yamamoto et al. (2011) used CIN1: 0.97, CIN2/3: 0.93, and stage I: 0.65, II: 0.56, III: 0.56, IV: 0.48, I AI: 0.97, stage II AI: 0.9, III AI: 0.9, and IV AI: 0.62. Moreover, in the latest analysis from outside Japan, Westra et al. (2013) used the preference measures for each health state in their simulation model. The specific preference measures that the used were as follows: CIN1: 0.974, CIN2: 0.99, CIN3: 0.92, stage I: 0.97, II-III: 0.9, and IV: 0.62. The preference measures that we obtained were lower than those that have been reported previously. Although we contemplated that this discrepancy may have resulted from between-country differences (Galante et al., 2011), bias may have arisen from the different details of the scenarios that were used in each study. Indeed, such between-scenario differences are always and issue for hypothetical evaluations. We expect that future research in Japan may provide further information to validate our research.

The specific choice of the subjects who are used to evaluate utility has been controversial. Generally, these evaluations may be made by patients and persons who have experience with the diseases in question, or members of the general population (De Wit et al., 2000). In the present study, we evaluated subjects who did not have personal experience with the disease. Accordingly, bias may have resulted from these subjects' insufficient understanding of the exact conditions of the disease. However, as advised by an expert panel that was convened by the U.S. Public Health Bureau in Washington, DC, economic evaluations concerning the effects of resource allocation should be specified by representative samples of the general population(Gold et al., 1996; Hashimoto et al., 1998). Difficulties are posed by using the utility evaluations of actual patients. Further, ethical considerations must be treated very carefully when asking direct questions to patients with cancer (using SG and other systems). Moreover, we anticipate that investigations of patient utility may be limited by the small number of patients who have advanced-stages cancer and can participate in research.

This research was limited by its single-institution design, and its reliance on hypothetical evaluations by students at a nursing university. Accordingly, when the preferences measures from this study are used for cost-utility analyses, appropriate sensitivity analyses should also be performed (Drummond et al., 1997; Gold et al., 1996). We suggest that it is necessary to promote further research based on the results of this study, with the specific goal of accumulating evidence for utility evaluations in Japan.

In conclusion, in this study, we obtained preference measures for CIN1, 2 and 3, and eight stages of cervical cancer, based on healthy female student nurses' hypothetical evaluations. The evaluations themselves were determined following EQ-5D and SG. The variance of EQ-5D preference measures were smaller than those of SG measures for most health states. We found a strong correlation between health state and preference measures that were assessed using EQ-5D. The EQ-5D preference measures obtained in this research are appropriate for economic evaluations of cervical cancer prevention in Japan. When using these results for a cost-utility analysis, we suggest that it may also be necessary to perform an appropriate sensitivity analysis. Future research may provide an economic valuation on strategies for cervical cancer prevention.

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References

Cancer Statistics Japan Editorial Board. Cancer Statistics in Japan (2009). http://ganjoho.jp/professional/statistics/backnumber/2009_jp.html (11st February 2014).

Canfell K, Chesson H, Kulasingam SL, et al (2012). Modeling preventative strategies against human papillomavirus-related disease in developed countries. *Vaccine*, **30**, 157-67.

De Wit GA, Busschbach JJ, De Charro FT (2000). Sensitivity and perspective in the valuation of health status: whose values count? *Health Econ*, **9**, 109-26.

Drummond MF, O'Brien BJ, Stoddart GL, et al (1997). Methods for the Economic Evaluation of Health Care Programmes, Second Edition. Oxford University Press, Oxford, UK.

Ferlay J, Soerjomataram I, Ervik M, et al (2012). GLOBOCAN 2012, Cancer Incidence and Mortality Worldwide, Version 1.0, IARC CancerBase No. 11. http://globocan.iarc.fr (10th December 2013).

Galante J, Augustovski F, Colantonio L, et al (2011). Estimation and comparison of EQ-5D health states' utility weights for pneumococcal and human papillomavirus diseases in Argentina, Chile, and the United Kingdom. *Value Health*, **14**, 60-4.

Gold MR, Siegel JE, Russell LB, et al (1996). Cost-Effectiveness in Health and Medicine. Oxford University Press, Oxford, UK.

Greenberg D, Fang C, Cohen JT, et al (2009). Preferences for Preferences. ISPOR 12th Annual European Congress, PMC56.

Hashimoto H (1998). Economic evaluation of health: theories and underlying assumptions. *Jpn J Health Econ Pol*, **8**, 53-65.

Kobayashi M, Ohno T, Noguchi W, et al (2009). Psychological distress and quality of life in cervical cancer survivors after radiotherapy: do treatment modalities, disease after medical, and self-esteem influence outcomes? *Int J Gynecol Cancer*, **19**, 1264-8.

Korfage IJ, van Ballegooijen M, Wauben B, et al (2012). Having a Pap smear, quality of life before and after cervical screening: a questionnaire study. *BJOG*, **119**, 936-44.

Konno R (2010). Efficient combination of primary and secondary prevention in cervical cancer. *San Fujinkna no Zissai*, **59**, 553-8 (in Japanese).

Konno R, Sasagawa T, Fukuda T, et al (2010). Cost-effectiveness analysis of prophylactic cervical cancer vaccination in Japanese women. *Int J Gynecol Cancer*, **20**, 385-92.

Lang HC, Chang K, Ying YH (2012). Quality of life, treatments, and patients' willingness to pay for a complete remission of cervical cancer in Taiwan. *Health Econ*, **21**, 1217-33.

Matsuda A, Matsuda T, Shibata A, et al (2013). Cancer incidence and incidence rates in Japan in 2007: a study of 21 population-based cancer registries for the monitoring of cancer incidence in Japan (MCIJ) project. *Jap J of Clinic Onc*, **43**, 328-36.

Ministry of Health, Labour and Welfare, Japan. Vital Statistics Japan (2012). http://ganjoho.jp/professional/statistics/statistics. html (26th November 2013).

Ohara-Hirano Y, Kaku T, Hirakawa T, et al (2004). Uterine cervical cancer: a holistic approach to mental health and it's socio-psychological implications. *Fukuoka Igaku Zasshi*, **95**, 183-94 (in Japanese).

Singer S, Kuhnt S, Momenghalibaf A, et al (2010). Patients' acceptance and psychometric properties of the EORTC QLQ-CX24 after surgery. *Gynecol Oncol*, **116**, 82-7.

Suzuki N, Ninomiya M, Maruta S, et al (2011). Psychological characteristics of Japanese gynecologic cancer patients after learning the diagnosis according to the hospital anxiety and

depression scale. *J Obstet Gynaecol Res*, **37**, 800-8.
Tamura M, Nozaki M, Fukuda T (1996). An empirical study on utility assessment methods for quality adjusted life years (QALYs). *Jpn J Health Econ Pol*, **3**, 87-103.
The Japanese EuroQol Translation Team (1998). The development of Japanese EuroQol instrument. *J Health Care Soc*, **8**, 109-24 (in Japanese).
Westra TA, Stirbu-Wagner I, Dorsman S, et al (2013). Inclusion of the benefits of enhanced cross-protection against cervical cancer and prevention of genital warts in the cost-effectiveness analysis of human papillomavirus vaccination in the Netherlands. *BMC Infect Dis*, **13**, 75.
Yamamoto N, Mori R, Jacklin P, et al (2012). Introducing HPV vaccine and scaling up screening procedures to prevent deaths from cervical cancer in Japan: a cost-effectiveness analysis. *BJOG*, **119**, 177-86.
zur Hauzen H (1991). Human papillomaviruses in the pathogenesis of anogenital cancer. *Virology*, **184**, 9-13.