Cost-Effectiveness Analysis of Prophylactic Cervical Cancer Vaccination in Japanese Women

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Introduction: The incidence of cervical cancer (CC) is high in Japan and is further increasing among women younger than 30 years. This burden could be reduced by the implementation of a CC vaccine, but its cost-effectiveness is unknown.

Methods: We quantified the clinical impact and assessed the cost-effectiveness of adding CC vaccination at age 12 to the current screening in place in Japan with a lifetime Markov model adapted to the Japanese setting. Transition probabilities and utility values were obtained from public databases. Direct costs for treatment and screening were estimated using Japanese medical fees. Annual costs and benefits were discounted at 3%. Sensitivity analyses were conducted on the age at vaccination, the vaccine characteristics, the discount rates, the proportion of human papillomavirus types 16/18 in cancer, and the screening coverage.

Results: Vaccinating a 12-year-old cohort was predicted to reduce CC incidence and deaths from CC by 73%. These clinical effects were associated with an incremental cost-effectiveness ratio of ¥1.8 million per quality-adjusted life year gained. The incremental cost-effectiveness ratio of vaccinating all 10- to 45-year-old women was ¥2.8 million per quality-adjusted life year, still below the threshold value.

Conclusions: The implementation of a CC vaccination in Japan could reduce the CC burden in a very cost-effective manner for women up to 45 years.

Key Words: Cost-effectiveness, HPV vaccination, Japan

Received September 2, 2009, and in revised form December 25, 2009.
Accepted for publication December 27, 2009.

(*Int J Gynecol Cancer* 2010;20: 385–392)

In Japan, the age-standardized cervical cancer (CC) incidence rate is 8 per 100,000 women, and the age-standardized mortality is 2.8 per 100,000 women in 2002, a high level compared with some European countries.[1,2] The medical direct cost (consultation, laboratory, chemotherapy, radiotherapy, surgery, hospital administration, and relief care) due to CC is estimated to be at least ¥3.0 billion per year.[3] The burden on Japanese public health care finances is therefore significant. Moreover, in recent years, the CC incidence has increased in the age group of 20 to 29 years old. It peaks in

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ISSN: 1048-891X
DOI: 10.1111/IGC.0b013e3181d189b8

This study was supported by a grant from GlaxoSmithKline K.K Japan. R. Konno received research and travel grants and honoraria for courses and conferences from GlaxoSmithKline Japan, Merck Japan, and Qiagen Japan. He is a member of the Advisory/Expert Board at GlaxoSmithKline Biologicals. This study was also supported by GlaxoSmithKline Biologicals, where authors Van Kriekinge and Demarteau are currently employed.

the age group of 30 to 39 years old. In 2002, the CC incidence in women aged 20 to 29 was approximately 12 per 100,000 women,[4] and it is estimated that the number of patients with CC will increase by more than 1.5 times in the coming years.[5] Some conceivable reasons for this are a downtrend in the age of sexual debut,[6] an increase in the lifetime risk of high-risk human papillomavirus (HPV) infection, and the low coverage of CC screening, compared with other Organization for Economic Cooperation and Development (OECD) countries.[7]

Persistent infection with an oncogenic HPV type is a prerequisite for CC.[8,9] More than 100 types of HPV have been identified. Among these, 13 are high-risk oncogenic types and particularly closely involved in carcinogenesis; it includes types 16 and 18. HPV types 16 and 18 are cumulatively responsible for more than 70% of all invasive CC cases.[10,11] HPV vaccines represent a new hope for CC reduction.

The economic evaluation of vaccines can provide useful information to decision makers regarding whether to allocate funds from public health care financial resources to a new vaccination program. We undertook an economic evaluation of prophylactic CC vaccination in Japanese women by adapting to the Japanese setting a Markov model estimating the long-term clinical and economic effect of the CC vaccine.

MATERIALS AND METHODS

Model Structure

A cohort model based on the Markov process already adapted to different countries and based on a previously published model[12] was used. This lifetime Markov model is constituted of 12 different health states for each cycle within which transition occurs each year following observed probabilities (Fig. 1). The model was adjusted to the Japanese setting by inputting specific Japanese data on screening and precancerous lesion treatment practice, HPV epidemiology, mortality, and costs. The cancer incidence by age, estimated by the model, was compared against observed statistics for Japan to validate the model. In addition, all input data and model results were validated by a Japanese expert panel.

Vaccination protection against oncogenic HPV infection is applied by means of a reduction of the transition from "no HPV infection" to "HPV-infected." In turn, this results in the reduction of cervical intraepithelial neoplasia (CIN) 1 to 2/3 and CC statuses. Each health state is attributed a specific resource utilization (costs) and utility. Costs and benefits are compared between a nonvaccination strategy and a vaccination strategy.

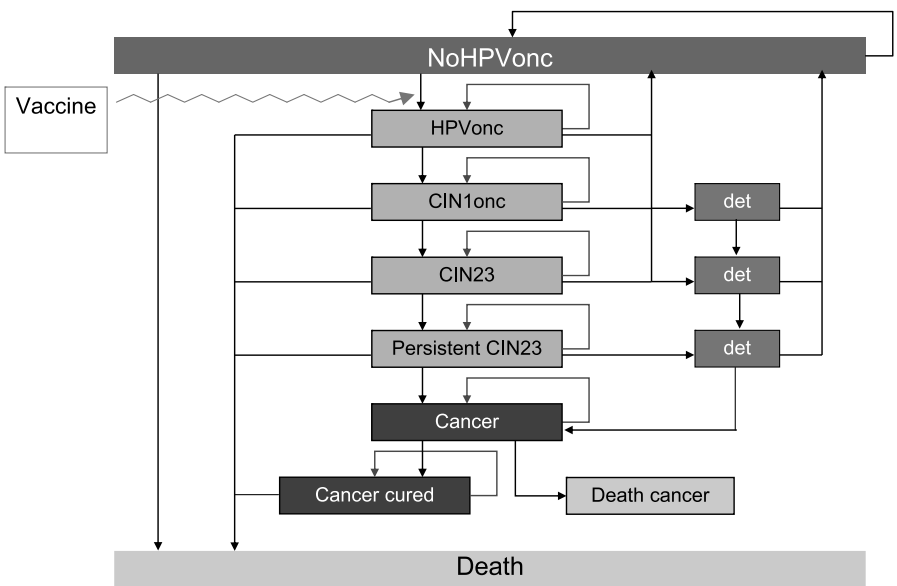
A lifetime time horizon was used (95 yearly cycles) to capture all costs and outcomes associated with HPV disease. Each cohort modeled is therefore followed up until all members reach the death health state.

To account for the time preference, future costs and effects need to be discounted because they are valued less than present costs and effects. Costs and effects were discounted at an annual rate of 3%.

Data Input

The transition probabilities used in the model replicate the natural history from HPV infection to CC; they were derived from literature review.[12] For most of them, Japanese data were not available, but we reasonably assumed that these would not be country-specific; we therefore kept input data included in the original version of the model (Table 1).

Other input data were Japan-specific parameters (Table 1); these refer to HPV infection, mortality, screening



det: women with disease detected through screening – same pathways but different transition probabilities

FIGURE 1. Schematic of Markov model for evaluation of CC vaccination.

TABLE 1. Clinical and economic parameters incorporated into model

Variables	Value	Reference
State: HPVOnc		
HPVOnc to NoHPV	0.2930–0.5530: Age-dependent yearly regression from HPVOnc infection to NoHPV	Debicki et al[12]
HPVOnc to CIN 1	0.049	Debicki et al[12]
HPVOnc to CIN 2/3	0: Spontaneous progression within 1 yr; assumed to be 0; ie, need at least 2 yr to develop CIN 2/3	Assumption
State: CIN 1 and CIN 1 detected		
CIN 1Onc to cured	0.45: Natural yearly regression from CIN 1 to NoHPV	Debicki et al[12]
CIN 1Onc to CIN 2/3	0.091: Spontaneous progression from CIN 1 to CIN 2/3 within 1 yr	Debicki et al[12]
States: CIN 2/3, persistent CIN 2/3 and CIN 2/3 detected		
CIN 2/3 to cured	0.227: Spontaneous regression from CIN 2/3 to NoHPV within 1 yr	Debicki et al[12]
CIN 2/3 to CIN 1Onc	0: Spontaneous regression from CIN 2/3 to CIN 1 within 1 yr; assumed to be 0 all patients cured going to NoHPV	Debicki et al[12]
CIN 2/3 to persistent CIN 2/3	0.114: Spontaneous progression from CIN 2/3 to CIS within 1 yr	Debicki et al[12]
Persistent CIN 2/3 to cancer	Assumed 0.004 yearly increase from 20 to 40 yr and 0.0005 yearly increases thereafter based on calibration to CC incidence in the original model	
HPV infection rate	Yearly incidence of HPVOnc	Inoue et al[13]*
Death rates	Age-specific death rate	Abridged Life Tables for Japan[14]*
Screening practice	13.6% of the women are screened every 2 yr from age 20 to 55 yr	Guideline (Partial Revision) for Health Education on Prevention of Cancer and Performance of Screening[15] and Specified Report of Regional Health and Elderly Health[16]*
	40% of the women are screened on an opportunistic basis at age 30 and 40 yr	Assumption*
CIN 1 detected	0.68	Inoue et al[13]*
CIN 1 treatment practice and efficacy	0% of the CIN 1 detected patients undergoing treatment (watchful waiting)	Assumption*
CIN 2/3 detected	0.72	Inoue et al[13]*
CIN 2/3 treatment practice and efficacy	100% of the CIN 2/3 detected patients undergoing treatment; 90% efficacy of the CIN 2/3 treatment (patients returning to normal [NoHPV] state after treatment)	Assumption*
Cancer death with ICC	Age-specific distribution of CC death rate	Cancer Statistics '05 in Japan[17]*
Population in females	579,000–997,000 (estimated population in October 2006)	Current Population Estimates as of October 1, 2006[18]*
Cancer cured	0.1954†	Cancer Statistics '05 in Japan[17]*
Detection rate of HPV-16/18 in CC patients	71.0%	Clifford et al[19]
Discount rate	3%	Assumption*

(continued on next page)

TABLE 1. *(Continued)*

Variables	Value	Reference
Utility measure		
NoHPV	1	Assumption
HPV	1	Assumption
CIN 1	1	Assumption
CIN 1det	0.128: as decrement from 1	Debicki et al[12]
CIN 2/3	1	Assumption
CIN 2/3det	0.009376: as decrement from 1	Debicki et al[12]
CC	0.273: as decrement from 1	Debicki et al[12]
Cancer cured	0.062: as decrement from 1	Debicki et al[12]
Death (CC or other)	0	Assumption
Cost components		
Screening and CIN treatment newly detected (year 1)	Regular screening + negative Papanicolaou result: ¥1500	Japan National Health Insurance fee tariffs*
	Regular screening + positive Papanicolaou result: ¥7512	
	Treatment of CIN 2/3 detected: ¥78,800	
CIN treatment, year after detection	Treatment of CIN 2/3 detected, year 2: ¥7460	
Cancer treatment	Cancer stage I–IV: weighted cost‡	
Vaccine	Cost of 1 course of vaccination: ¥36,000	Assumption*

*Japan-specific data.

†Formula for 5-year survival rate: stage I, 81.9% (A); stage II: 61.8% (B); stage III, 38.1% (C); and stage IV, 12.6% (D). Distribution: 0.58 (a), 0.19 (b), 0.16 (c), and 0.06 (d) (n = 730). 66.51% = Aa + Bb + Cc + Dd. 19.54% = $1 - (1 - 0.6651)^{1/5}$.

‡Formula for unit cost: stage I, ¥1,000,970 (A); stage II, ¥1,554,460 (B); stage 3, ¥3,222,980 (C); and stage IV, ¥4,421,410 (D). Distribution: 0.582 (a), 0.190 (b), 0.164 (c), and 0.063 (d) (n = 730). Weighted sum of cancer treatment cost = Aa + Bb + Cc + Dd.

ICC, invasive cervical carcinoma.

pattern, and HPV-related lesion treatment. Whenever possible, age-specific data were used. The annual incidence of oncogenic HPV by age was obtained from the study of Inoue et al.[13] Other cause mortality statistics for 2004 were obtained from the Ministry of Health, Labour and Welfare database.[14] The screening algorithm replicates the mix of organized and opportunistic screening in place in Japan. Organized screening corresponds to 1 screening every 2 years among women aged 20 to 45 years old according to the guideline of education on cancer prevention and screening (amended in 2004)[15] and is followed by 13.6% of the women.[16] Opportunistic screening was assumed to occur twice in a lifetime at 30 and 40 years and covers another 40.0% of the women. The diagnosis rate of CIN 1 to 3 and the sensitivity of the Papanicolaou test for CIN 1 and CIN 2 to 3 were derived from the data published by Inoue et al[13] and Sasagawa et al.[20] The treatment rate for CIN 1 was assumed at 0% and that for CIN 2 or 3 was at 90% based on expert opinion. The survival and cure rate of cancer patients were calculated based on the 5-year survival rate and the mortality rate by age group reported in clinical efficacy data at a central hospital of the National Cancer Center between 1993 and 2002.[5] The cohort sizes used in this study were taken from the annual report on the estimated population for 2006 (estimated as of October 1, 2006).[18]

Cost Data

Cost data were determined from a perspective of entire payers (payment by the National Health Insurance and copayment by women). Therefore, these include only direct medical cost. All costs associated with the vaccine, the screening, and the treatment of HPV-related lesion were included. Treatment algorithms were determined by an expert panel. Official medical fee tariffs in Japan were thereafter assigned to the resources used to determine a total cost per event.

The screening program for initiation and follow-up consists of cytological diagnosis by Papanicolaou test and histological verification by colposcopy and biopsy. DNA testing for the detection of HPV was excluded because it is currently paid entirely by the patients themselves in Japan. Using the medical fee schedule for 2006, the costs for the screening program were calculated as follows: at ¥1500 for the initial screening (in case of negative Papanicolaou test result), at ¥7512 for a screening with follow-up procedure (in case of positive Papanicolaou test result), and at ¥78,800 and ¥7460 for the initial and follow-up treatment after a diagnosis of CIN 2 to 3, respectively. No costs were assigned to CIN 1 because these are not treated. Treatment costs for cancer by stage were taken from a published stage-dependent CC cost further weighted by the observed proportion of

cancer cases in each stage to determine a cost per year with CC[17] (Table 1).

Outcomes: Quality-Adjusted Life Year

Quality-adjusted life year (QALY) was determined based on the stage-specific utility weights and the time spent in each status. The utility measures were derived from 2 sources[12,21] (Table 1).

Vaccine Effect

The effectiveness of the vaccine against oncogenic HPV-16/18 was assumed to be 95%.[12] The global effectiveness also includes the effectiveness of the vaccine against non–HPV-16/18 oncogenic HPV types.[12] The resulting overall effectiveness of the vaccine was set at 75.28% and calculated as follows:

$$71\%^{*} \times 95\% \text{ effectiveness} + (100\% - 71\%)^{**} \times 27\% \text{ effectiveness} = 75.28\%$$

where a single asterisk (*) indicates the prevalence of HPV-16/18 type[19] and double asterisks (**) indicate the prevalence of other oncogenic HPV types[19] and vaccine effectiveness.[12]

Base Case Analysis

The lifetime cost and clinical effect of vaccinating 100% of a cohort of 12-year-old girls (equivalent to the first grade of junior high school) was estimated. The expected cost and effectiveness for vaccinated (*V*: vaccination plus screening program) and nonvaccinated (NV: screening program only) groups were calculated under the aforementioned conditions. The incremental cost-effectiveness ratio (ICER) using the outcomes estimated by the model were determined by computing the ratio between the incremental costs and incremental effect (QALY) between the 2 strategies. The ICER stands for the incremental cost in vaccine per incremental QALY gained, and it was calculated using the following formula:

$$ICER = \frac{C_v - C_{nv}}{E_v - E_{nv}}$$

where *C* indicates cost; *E*, effectiveness; v, vaccinated; nv, nonvaccinated.

Sensitivity Analyses

To assess the uncertainties surrounding key variables in the model, a sensitivity analysis on these variables was performed. The variables were tested in univariate (single-variable) sensitivity analyses by varying discount rate from 0% to 5%, the cost of the vaccine from 50% to 150% of the base case value, the proportion of HPV-16/18 in cancer from 50.3%[23] to 80.0%,[24] either cancer or CIN 2/3 treatment costs from −25% to +25% of the base case value, the regular screening rate of 23.7% taken from OECD report,[7] the perspective from entire payers (payment by National Health Insurance and co-payment by women) to health care payer-only perspective (exclusive of co-payments by women), the vaccine uptake rate of 50%, and age at vaccination from 10 to 45 years old.

RESULTS

Impact of Vaccination on Clinical Outcomes

The impact of vaccination on incidence and mortality of CC was estimated as follows:

Vaccination of 100% of a single cohort of 12-year-old girls (n = 589,000) would reduce the number of cancer cases by 73.1% (from 5097 CC cases without vaccine to 1373 CC cases with the vaccine) and the number of CC-related mortality by 73.2% (from 1762 CC deaths without vaccine to 473 CC deaths with the vaccine).

Impact of Vaccination on the Costs and Cost-Effectiveness

The vaccination of 100% of a cohort of 12-year-old girls (n = 589,000) would result in a reduction of HPV lesion treatment–related direct costs of ¥6.5 billion (a 41% reduction in treatment costs compared with the current situation, ie, without vaccination).

However, the analysis estimated that a medical expenditure of approximately ¥21.0 billion would be necessary, assuming a cost of ¥36,000 per course of vaccination (3 injections per full course); thus, the ICER was calculated at ¥1,810,023 per QALY gained (Table 2).

Sensitivity Analyses

Results of the sensitivity analyses are presented in Figures 2 and 3.

Discount Rate

Under the base case when the discount rate was varied from 0% to 5%, the vaccination became dominating

TABLE 2. Cost-effectiveness analysis of CC vaccine for all 12-year-old girls (n = 589,000; discount rate, 3%)

	Unvaccinated, ¥	Vaccinated, ¥	Difference, ¥	% Reduction
Total cost	15,773,181,319	30,504,955,805	14,731,774,486	
Vaccine cost*	0	21,204,000,000	21,204,000,000	
Health care cost	15,773,181,319	9,300,955,805	−6,472,225,514	−41.0
QALYs	17,759,821	17,767,960	8139	
ICER (cost per QALY gained)			1,810,023	

*Vaccine cost was assumed as ¥36,000 per course.
ICER = (cost in vaccinated − cost in unvaccinated) / (QALY in vaccinated − QALY in unvaccinated).

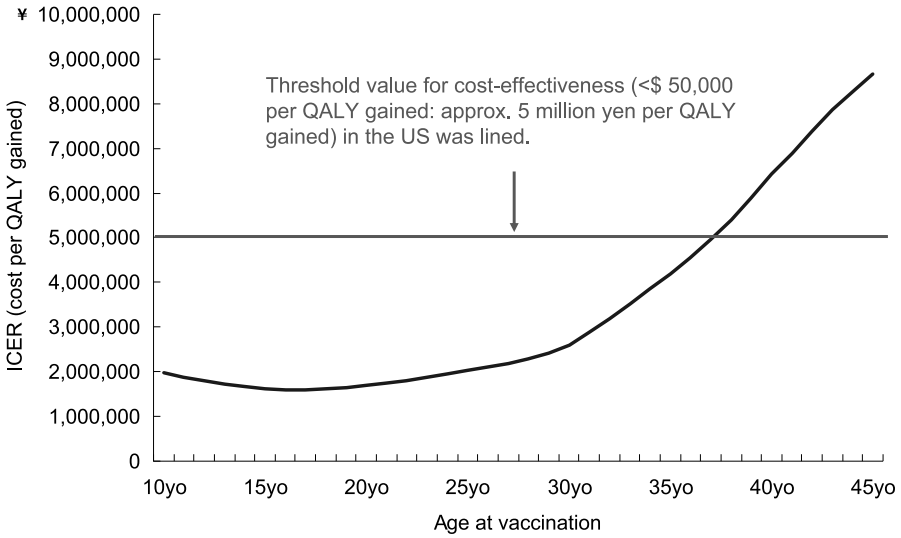


FIGURE 2. Economic impact with age at vaccination.

compared with no vaccination (both cost-saving and yielding more QALY) under a 0% discount rate and yielded an ICER of ¥5,491,457 per QALY gained with a 5% discount rate (Fig. 2).

Vaccine Cost

Under the base case, a vaccine costs from ¥18,000 to ¥56,000 per course, resulting in an ICER of ¥507,416 to ¥3,112,702 per QALY gained, respectively (Fig. 2).

Proportion of HPV-16/18 in CC

Under the base case, a proportion of HPV-16/18 in CC ranging from 50.3% to 80% resulted in an overall efficacy from 61% to 81% and an ensuing ICER of ¥1,603,263 to ¥2,438,965 per QALY gained, respectively (Fig. 2).

Cancer Treatment Cost

Under the base case, a cancer treatment cost varied 25% up and down from base case resulted in an ICER of ¥1,613,198 and ¥2,006,920 per QALY gained, respectively (Fig. 2).

Regular Screening Rate

Under the base case, an organized screening coverage raised to 23.7% resulted in an ICER of ¥2,180,879 per QALY gained (Fig. 2).

Health Care Payer Perspective (Excluding Women Co-Payment)

When the base case analysis is conducted from a health care payer perspective, the ICER changed from ¥1,810,023 (entire payer perspective) to ¥1,977,547 per QALY gained (Fig. 2).

Vaccine Uptake Rate

Under the base case, a vaccine uptake rate of 50% resulted in an ICER of ¥1,943,006 per QALY gained (Fig. 2).

CIN 2/3 Treatment Cost

Under the base case, when the regular cost of treatment of CIN 2/3 was varied from −25% to +25% up of the base case value, the ICER ranged from ¥1,809,890 to ¥1,810,228 per QALY gained, respectively (Fig. 2).

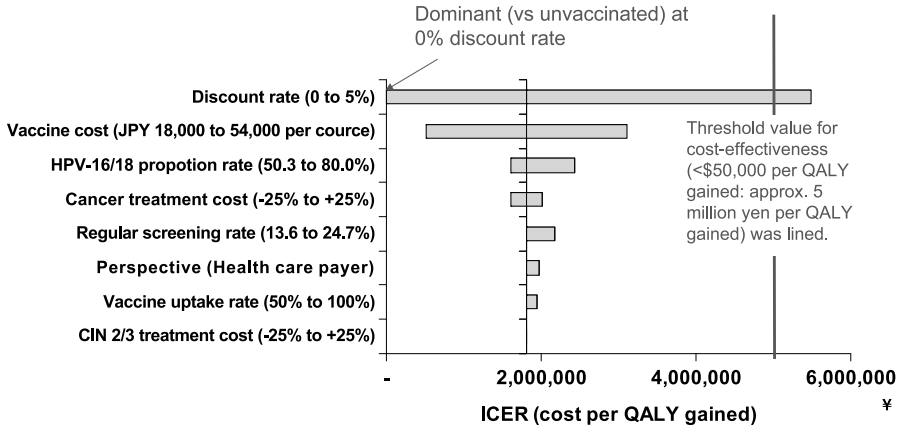


FIGURE 3. Univariate sensitivity analysis to examine variables that impact base case.

TABLE 3. Cost-effectiveness analysis of CC vaccine for all 10- to 45-year-old women

	Unvaccinated	Vaccinated	Difference	ICER
Total cost, ¥	944,397,321,957	1,694,570,864,445*	750,173,542,488	
QALYs	752,144,038	752,413,864	269,826	2,780,215

*Vaccine cost was assumed as ¥36,000 per course.
ICER = (cost in vaccinated − cost in unvaccinated) / (QALY in vaccinated − QALY in unvaccinated).

Age at Vaccination

We estimated the ICER for a vaccination from 10 to 45 years. For vaccination up to 37 years, the ICERs were lower than a $50,000 (¥5 million) threshold corresponding to the accepted US threshold figure (Fig. 3).[25,26] The ICER of vaccinating all cohorts from the age of 10 to 45 years was ¥2,780,215 per QALY gained, respectively (Table 3).

DISCUSSION

We assessed the cost-effectiveness of HPV vaccination to prevent CC in Japan using a lifetime Markov model. Cervical cancer vaccination was projected to reduce the disease burden by reducing the incidence of cases and CC deaths by approximately 73.1% and 73.2% over a lifetime. With a vaccine cost at ¥36,000 per course, it was estimated that the ICER for CC vaccination of all 12-year-old girls would be ¥1.8 million per QALY gained from the perspective of entire payers.

The cost-effectiveness threshold in Japan can be set to ¥5.0 million,[26] a figure corresponding to the $50,000 per QALY gained threshold used in the United States.[25] Given this threshold, vaccination can be considered as cost-effective in Japan. Moreover, the estimated ICER is substantially lower than the ICER for mammography for breast cancer screening for women in their 40s (¥3,102,000 per life year saved).[27] These results hold true when women from age 10 to 45 years were vaccinated because the ICER of ¥2,780,215 estimated for this scenario is still substantially lower than the aforementioned threshold value. The present results do advise the vaccination of women up to the age of 45 using public funds because this would be cost-effective from the health care perspective.

When comparing this result for Japan (approximately ¥1.8 million per QALY gained when vaccinating 12-year-old girls taking into account a 3% annual discount rate) to published results in the United States, introducing vaccination into the Japanese society is more cost-effective than that in the United States because it was reported that vaccination of the 12-year-old girls in the United States was approximately $20,000 to 24,000 per QALY gained (approximately ¥2–2.4 million per QALY gained).[22] The reasons why the results for Japan are better than for the United States could be (1) the low coverage of screening for CC observed in Japan and (2) the high level of disease burden in the younger generation in Japan. The OECD dossier reported that screening coverage in Japan is approximately 24%, which is much lower than the screening coverage observed in the United States and in European countries (up to 80%).[7,28] Also, the number of new CC cases is increasing among the younger generation in Japan. National statistics reported in 2001[29] that 10 new CC cases per 100,000 population (aged 20–29 years) and approximately 55 new CC cases per 100,000 population (aged 30–39 years) compared with 32 CC cases per 100,000 in 1992.

This study has limitations in the interpretation of the analyzed results, although it has provided evidence to support implementation of CC vaccination in all women in the age group of 10 to 45 years using public funds. The proportion of HPV-16/18 among CC has been reported in a wide range from 50.3% to 80.0% for Japanese women with CC based on different age groups studied and different detection methods used[23,24]; however, HPV-16/18 types seem to be highly prevalent in young women with CC because the detection rate of HPV-16/18 type in CC patients in their 20s and 30s was approximately 80%.[24] Nevertheless, we used the worldwide average value reported by Clifford et al[19] in our model, which had a rate of 71.0%, but a sensitivity analysis conducted on this parameter showed that the vaccine was still cost-effective even when a low HPV-16/18 proportion was used.

We used a discount rate of 3% taking into consideration the current economic growth and interest rate. An investigator at the Bank of Japan reported that the trend in time preference for Japanese people has been stable at a range of −1% to 1% for approximately 30 years from 1970 to 1997, much lower than those observed in European countries and in the United States.[30] Many health economists and policy makers around the world, however, commonly use a rate of 3% or more, in particular, the National Institute for Health and Clinical Excellence in the United Kingdom commonly uses an annual rate of 3.5%. As we identified that the base case result is sensitive to discount rate independently, we attempted to present the results using a discount rate ranging from 0% to 5% from the perspective of entire payers.

The utility measures reported from overseas were used for the present analysis because corresponding suitable parameters could not be obtained in Japan.

CONCLUSIONS

Cervical cancer vaccination has a large potential to reduce CC burden in Japan. From the perspective of entire payers, the ICER for CC vaccination at 12 years old was estimated at ¥1.8 million per QALY gained and approximately ¥2.8 million per QALY gained for vaccinating all 10 to 45-year-old women, still well below the threshold value. The implementation of CC vaccination is predicted to be cost-effective in Japan.

ACKNOWLEDGMENT

The authors thank Professor Koinuma at Tohoku University for his cooperation in gathering information.

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