NECA National Evidence-based Healthcare Collaborating Agency
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National Evidence-based Healthcare Collaborating Agency

THE EVIDENCE

Economic Evaluation of HPV Vaccination

Introduction

Governments and local organizations in America, Europe, and Australia are now beginning to fund vaccinations against human papilloma virus (HPV) program, following the WHO recommendation in 2009 that all women aged 9 to 13 years be vaccinated.

The HPV vaccines Gardasil (Merck&Co., Inc.) and Cervarix (GSK) have come to market in Korea, after receiving approval from the Korea Food & Drug Administration (KFDA) in June, 2007 and July, 2008, respectively. Korea has not yet introduced HPV vaccination into the national vaccination program, and there is ongoing disagreement on the subject of HPV vaccination among Korean academies.

Two previous cost-benefit studies in Korea showed that the cost of a national HPV vaccination program is high compared with the benefits, leading to the conclusion that the vaccination program is not cost-effective with the current price of HPV vaccines. Considerable uncertainty remains, however, because insufficient data caused the previous studies to rely on some questionable assumptions.

This study was performed with cost-utility analysis that is widely used to estimate the efficiency of HPV vaccination in the healthcare sector. This study also tried to elevate the completeness by incorporating data from the claims to the National Health Insurance (NHI) and from patient survey.

The purpose of this study is to generate useful information for rational healthcare-policy decision-making by conducting the economic evaluation of a national HPV vaccination program from a societal perspective.

HPV infection epidemiology

Ⅰ. Methods

Literature review were conducted to examine sexual behavior, HPV vaccination rate, HPV infection rate, HPV type distribution in cervical intraepithelial neoplasia (CIN) and cervical cancer, disease statistics for CIN and cervical cancer, and survival rate of patients with cervical cancer.

We preferred Korean epidemiologic data in our economic analysis. We used data from other countries to compare with the Korean data, or to substitute for it when necessary.

Ⅱ. Results

Results from Kim et al. (2007), Shin et al. (2010), and the Sixth Health Behavior Online Survey on the Sexual Behavioral Pattern of Korean Adolescents (2010) showed that Korean women tend to have their first sex at a later age and tend to have sex at a lower frequency compared with American, European, and Australian women. Korean women have their first sex at 19 to 21 years of age, on average. A survey of women from 12 to 29 years of age in the six largest Korean cities (Seoul, Busan, Daegu, Inchon, Gwangju, and Daejon) found that 5% had their first sex under the age of 16.

While there are no official statistics on the HPV vaccination rate in Korea, one study (Bang et al., 2011) reported that 12% of a sample of 200 university students had received HPV vaccinations.

The prevalence of HPV infection among Korean women is estimated to be approximately 10-15%, with a higher prevalence typically among younger women (Shin et al., 2007).

This issue paper is written based on the research results performed by the National Evidence-based Healthcare Collaborating Agency (NECA).
The full texts of the research report is available from the website of NECA (www.neca.re.kr).

HPV vaccination significantly decreases the risk of HPV types 16 and 18 related HPV infection and CIN2+.

The infection rate among sexually experienced young women, 28.8%, was especially high compared with that among women in general, 15.2% (Shin et al., 2007). According to research on the HPV infection rate among sexually experienced women in general in 15 countries (Franceschi et al., 2006), African women had the highest rate of infection, 27%, and European women had the lowest rate of infection, 2.7-9.4%; the rate among Korean women was 14.8%. A systematic review of research on HPV types among Korean women found that HPV type 16 was the most common, with an infection rate of 6%, followed by HPV types 18 and 58 (Bae et al., 2008).

The rate of HPV infection was 63.2% among patients with premalignant cervical cancer (ASCUS or CIN 1), and that of high-risk HPV infection among patients with ASCUS or CIN 1 was 56.3%. Among patients with CIN 2, CIN 3, or cervical carcinoma in situ (CIS), the rate of HPV infection was 85.6%, and that of high-risk HPV infection was 83.7%. Among patients with invasive cervical cancer, the HPV infection rate was 88.3%, and that of high risk HPV infection was 84.6%. Data from East Asian countries display a similar trend, with Korea among the top five affected HPV types (Bae et al., 2008).

According to the Central Cancer Registry (2009), the number of new cervical cancer patients in Korea was 4,443 in 1999 and 3,733 in 2009, and the age- standardized incidence rate decreased from 18.6 persons in 1999 to 12.0 persons in 2009. Supposing that the average life span of Korean women is 84 years, the chance of a Korean woman having cervical cancer at some point in her life is 1.4%.

Survival data on Korean patients with cervical cancer are limited, so the survival rate is based mainly on the FIGO Annual Report, which contains Korean data. An analysis of 11,775 patients with cervical cancer found that: the 1-year survival rate was 89.8%; the 2-year survival rate was 80.7%; the 3-year survival rate was 75.5%; the 4-year survival rate was 72.3%; and the 5-year survival rate was 69.3%. The same data found that: the 1-year progression-free survival rate was 92.9%; the 2-year progression-free survival rate was 85.4%; the 3-year progression-free survival rate was 81.4%; the 4-year progression-free survival rate was 79.3%; and the 5-year progression-free survival rate was 77.7% (Quinn et al., 2006).

Clinical efficacy of HPV vaccines

Ⅰ. Methods

We conducted a systematic review of the latest evidence on the clinical efficacy and safety of all types of HPV vaccines. We do not limit age, race, region, HPV infection and sexual experience. HPV types 16 and 18 related CIN2+, CIN3+ and persistent infection rate of 6/12months were reviewed as primary outcome.

We searched the domestic database such as KoreaMed, KISS, KMBASE, NDSL and international database such as Ovid-Medline, Ovid-EMBASE, CENTRAL (Cochrane Library). We conducted the risk of bias assessment on the selected literatures by first and second selection/exclusion process, using Cochrane's Risk of Bias (RoB). Meta-analysis was performed categorizing the data by ITT (intent-to-treat), mITT (modified-intent-to-treat), and PP (per protocol) criteria.

Ⅱ. Results

Nine clinical studies were selected among 5,661 literatures. It was estimated that the risk of bias in each study was almost low. The relative risk (RR) of HPV types 16 and 18 relating CIN 2+ was 0.52 [95% CI: 0.37-0.7] in ITT analysis, 0.09 [95% CI: 0.04-0.22] in mITT analysis, 0.06 [95% CI: 0.03-0.12] in PP analysis. Thus, all three analyses suggested that HPV vaccination significantly decreases the risk of HPV types 16 and 18 relating to CIN 2+ (Figure 1).

The RR in ITT analysis, representing the efficacy for all the vaccinated subjects regardless of their HPV infection, was 0.52, which leads us to conclude that the clinical risk of HPV types 16 and 18 related CIN 2+ is reduced by 48%. The clinical risk of developing HPV types 16 and 18 related CIN 2+ among the only HPV uninfected subjects vaccinated more than once is reduced by 91% based on the mITT analysis and that of developing HPV types 16 and 18 related CIN 2+ among the HPV uninfected subjects vaccinated entirely three times is reduced by 94% based on the PP analysis.

It was found that the persistent infection rate of HPV types 16 and 18 was decreased by 56% (RR = 0.44; 95% CI: 0.34-0.57) according to the combined analysis of ITT and mITT analysis, and by 92% (RR = 0.08; 95% CI: 0.04-0.15) according to the PP analysis. In the ITT and mITT combined analysis, the RR for the 12 month-persistent infection rate was 0.45 [95% CI: 0.34-0.58] and in the PP analysis, the RR for the 12 month-persistent infection rate was 0.09 [95% CI: 0.06-0.13] (Figure 2).

More studies are necessary for the conclusion that HPV vaccination provides cross protection against multiple virus types; because we currently do not have enough data on cross protection, and the data described here is only for the quadrivalent HPV vaccine.

There is no clear evidence based on post-marketing analyses and safety data from clinical trials that HPV vaccines are not safe. Thus, we conclude that HPV vaccines currently appear to be safe. However, it is necessary to monitor the long-term outcomes of vaccinations and the results of post-marketing analyses.

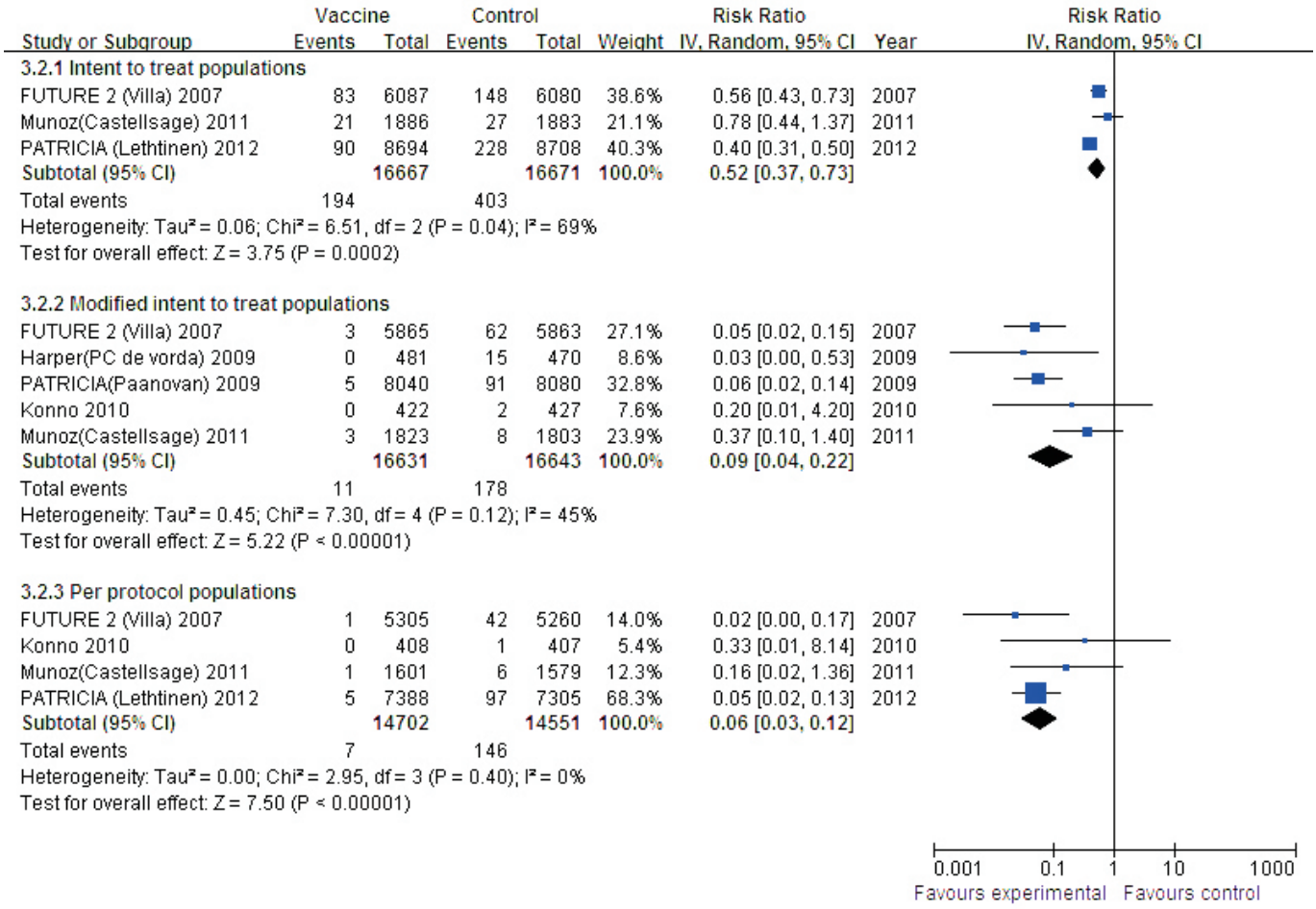

Figure 1. HPV types 16 and 18 related CIN 2+ (ITT, mITT, PP analysis)

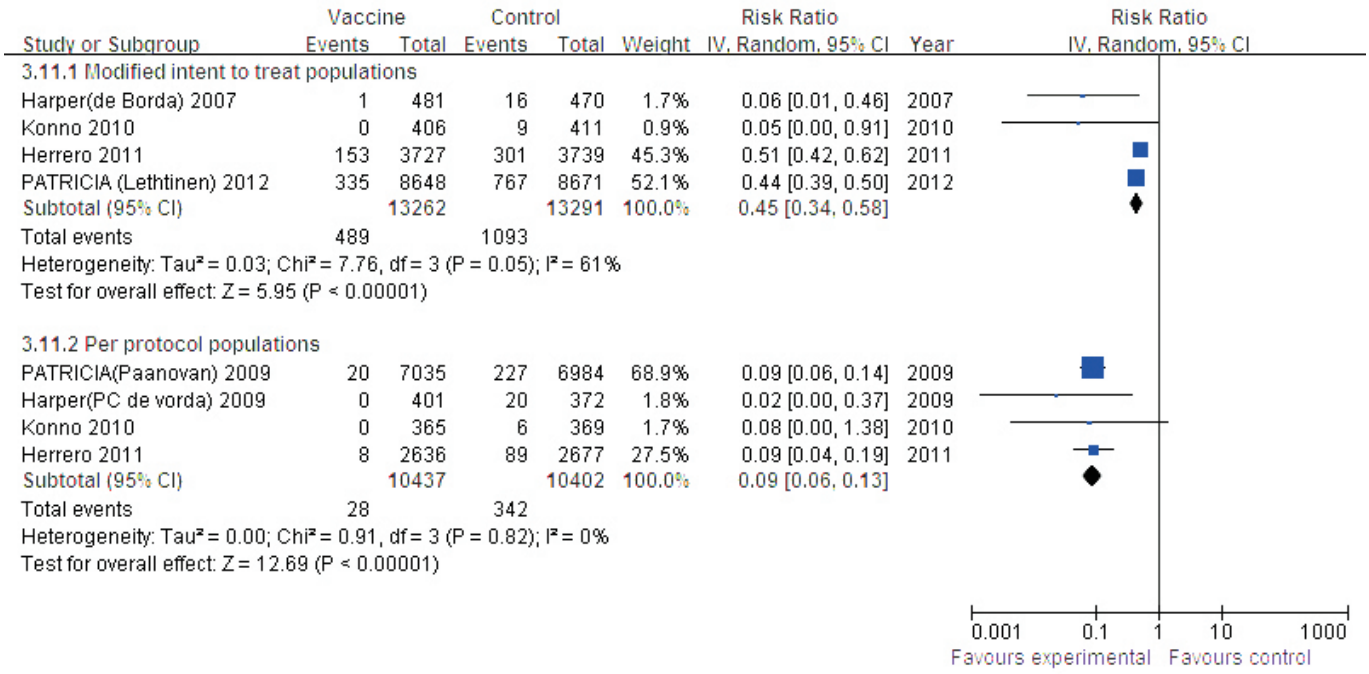

Figure 2. HPV types 16 and 18 related 12 month-persistent infection rate (ITT and mITT combined, PP analysis)

The prevalence rate of cervical cancer was 90.8 per a population of 100,000 with a decreasing trend over recent years.

The number of patients and the medical costs of HPV-related diseases

Ⅰ. Methods

NHI claims data provided by Health Insurance Review & Assessment Service (HIRA) was used to estimate the number of patients and the medical costs of HPV-related diseases. We included the patients with primary disease or first sub-ordinate disease related HPV infection, as classified by ICD-10 code.

We then conducted a more detailed analysis of patients with CIN 1, CIN 2/3, or cervical cancer, which were used in our economic model. We defined new patients as those who did not utilized medical services with CIN 1, CIN 2/3, or cervical cancer for the previous two years, and we used data from 2007 and 2008 as a wash-out period. After consulting a clinician, we defined the ICD-10 code N870 as being CIN1, the ICD-10 code N871 as being CIN2, and the ICD-10 code N872/D06 as being CIN3. We calculated the number of new patients with CIN separately, because there is no sub-code for N87, and the frequency of uncategorized ICD-10 codes, like N879, was around 50%.

Cervical cancer (C53) was analyzed with more specific health condition separating following up of stable condition and suffering a recurrent/persistent condition in next year after initial cervical cancer diagnosis. For this specific classification, patients suffering a recurrent/persistent condition are defined as patients who had got a surgery, chemotherapy, or radiation therapy at next year after initial cervical cancer diagnosis. Procedure codes for surgery, chemotherapy, and radiation therapy are also used along with claims code of HIRA with the consultation of clinicians.

Ⅱ. Results

(1) Prevalence rate and medical costs of cervical cancer (C53)

The prevalence rate of cervical cancer was 90.8 per a population of 100,000 with a decreasing trend over recent years. It was most prevalent among women at the age of 40s to 60s, and the count of cervical cancer prevalent patients among women at 60s per 100,000 persons was 194.9. The average treatment cost per patient with cervical cancer was KRW 3,482,030 and it was found that the treatment cost per patient is increasing annually, while the number of the prevalent patients is decreasing annually.

(2) Incidence rate, recurrence rate, and medical cost of new patients

Depending on whether patients with uncategorized CIN were included, the number of patients for CIN 1 ranged from 25,946 (incidence rate 104.4 per 100,000 women) to 46,463 in 2009 (incidence rate 187.0 per 100,000 women), and it had a trend to increase from 35,018 (incidence rate 139.9 per 100,000 women) to 69,431 (incidence rate 277.4 per 100,000 women) in 2011.

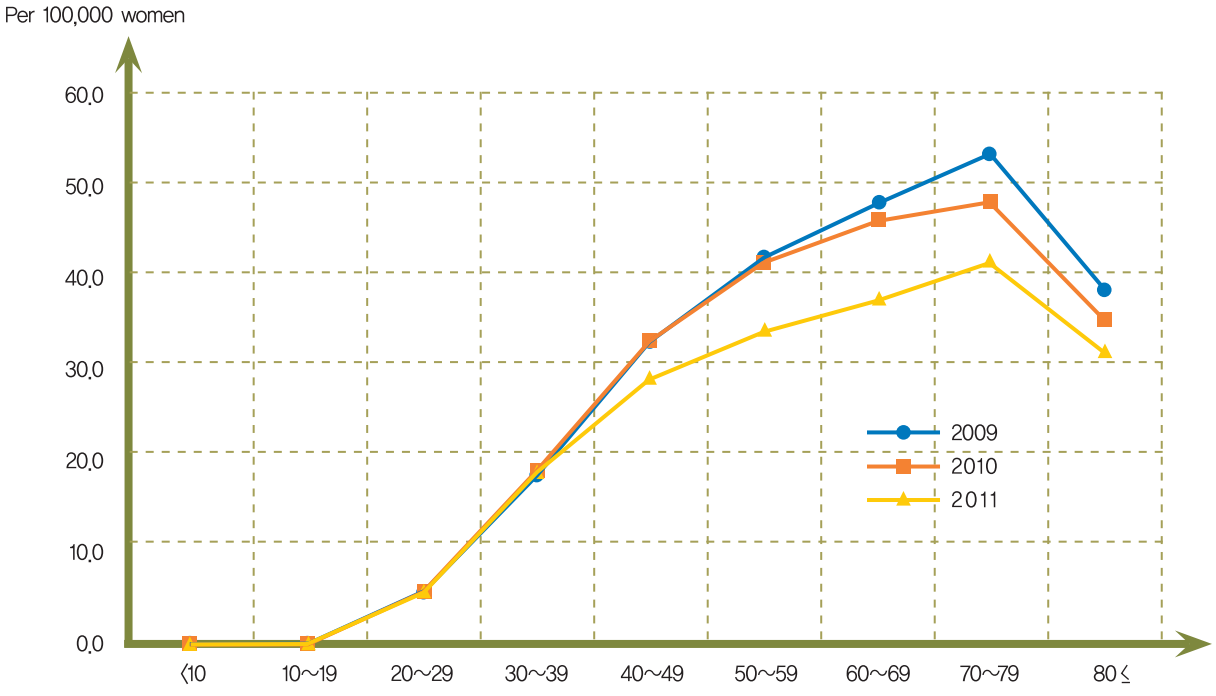

Figure 3. Incidence rate of cervical cancer (C53)

The utility weight was highest among CIN 1 patients at a valuation of 0.933, followed by those among patients with CIN 2/3, at a valuation of 0.933, among patients with cervical cancer, at a valuation of 0.874, and among patients with recurrent cervical cancer, at a valuation of 0.784. Thus, the severity of the disease was in inverse proportion to the quality of life.

Depending on the estimation methods, the estimated range of CIN 2/3 incidence rates per 100,000 women was 97.8-175.1 in 2009, decreasing to 88.1-174.8 in 2011.

The number of new patients with cervical cancer decreased from 5,593 (22.5 per 100,000 women) in 2009 to 4,958 (19.8 per 100,000 women) in 2011. The incidence rate of cervical cancer increased with age, peaking at 70 years of age (Figure 3). The rate of recurrence/persistence in next year after initial cervical cancer diagnosis was 5.44%. The rate of recurrence in the third year after diagnosis was 1.8%, and the rate of recurrence/persistence after an initial recurrence was 25.8%.

Excluding the highest and lowest 3% of total patient costs as outlier, we estimated that in 2009 the average treatment cost per new patient with CIN 1 was KRW 209,979, while the average treatment cost per patient with CIN 2/3 was more than three times higher at KRW 679,291. The average treatment cost per patient in the first year following diagnosis of cervical cancer was KRW 6,570,000 while the average cost per follow-up patient without recurrence was KRW 1,000,000 and that per patient with recurrence was 16 times higher at KRW 16,220,000.

Cost analysis of cervical cancer relevant diseases

Ⅰ. Methods

With the approval of the IRB of the NECA and other medical institutions, we performed a retrospective analysis of the 3-year medical costs for new patients diagnosed with CIN or cervical cancer in 2009 in six medical institutions.

Ⅱ. Results

We identified 1,705 patients who had medical expenses recorded in 2009. We excluded 17 patients who had no medical expenses recorded during the first year following diagnosis. Among the 1,692 remaining patients, 288 had CIN 1, 675 had CIN 2/3, and 729 had cervical cancer; 655 (89.8%) of the patients with cervical cancer had a first-time diagnosis and not a recurrence. The average treatment amount per patient in the first year following CIN 1 diagnosis was about KRW 560,000 and the average medical costs was about KRW 850,000. The average amount of non-health insurance benefit was KRW 290,000 and the average out-of-pocket payment was about KRW 510,000. The percentage of out-of-pocket payment was 72.5% on average per patient and the percentage of non-health insurance benefit was 37.5% on average per patient. The average treatment amount per patient of a first year CIN 2/3 diagnosed patients was about KRW 820,000 and the average medical costs was about KRW 1,200,000. The average amount of non-health insurance benefit was about KRW 370,000 and the average out-of-pocket payment was about KRW 630,000. The percentage of out-of-pocket payment was 58.5% on average per patient and that of non-health insurance benefit was 35% on average per patient.

The average medical cost per patient following a non-recurrent cervical cancer diagnosis was KRW 18,400,000 in the first year, KRW 1,700,000 in the second year, KRW 1,200,000 in the third year. Thus, the annual medical costs gradually decreased among non-recurrence patients. The frequencies of hospital stays and outpatient visits and the average length of hospital stays also decreased from year to year.

The average medical cost per patient following a recurrent cervical cancer was KRW 30,000,000 in the first year, KRW 6,560,000 in the second year and KRW 1,650,000 in the third year.

Survey on cervical cancer patients

Ⅰ. Methods

With the approval of the IRB of the NECA and other medical institutions, we conducted a survey from Oct. to Dec. in 2012. The quality of life and medical expenses of 452 patients with CIN or cervical cancer who were treated in department of gynecology at one of six medical institutions in Seoul and the surrounding metropolitan areas. We measured the patients' quality of life using the EQ-5D tool. The questionnaires included demographic information, quality of life, unofficial medical costs, time costs, and caregiver costs.

Ⅱ. Results

The utility weight was highest among CIN 1 patients at a valuation of 0.933, followed by those among patients with CIN 2/3, at a valuation of 0.933, among patients with cervical cancer, at a valuation of 0.874, and among patients with recurrent cervical cancer, at a valuation of 0.784. Thus, the severity of the disease was in inverse proportion to the quality of life.

The informed medical costs for the first year were highest among patients with cervical cancer (including recurrent cervical cancer), and tended to decrease as the treatment period became longer. The more severe the cervical cancer was and the shorter the treatment period was (less than one year after diagnosis), the more caregiving days and caregiving hours were required. The average time required to visit a hospital was 1.7 hours for patients with CIN 1, 4.2 hours for patients with CIN 2/3, 4.7 hours for patients with first-diagnosis cervical cancer, and 5.6 hours for patients with recurrent cervical cancer.

Economic evaluation of HPV vaccination

Ⅰ. Methods

(1) Model overview

Economic evaluation was conducted to compare a national HPV vaccination program that vaccinates 12-year-old girls with cervical cancer screening and the current system that provides only cervical cancer screening and no HPV vaccination program. We analyzed the effect of the vaccination program on the rates of HPV infection and cervical cancer and conducted a cost-utility analysis applying quality adjusted life years (QALYs), which take into account the extension of life span and the quality of life. We took a societal perspective, considering patient time costs, caregiver costs, and transportation costs, in addition to medical costs. We used a Markov model with a 1-year cycle and lifetime analysis period. The Markov states were: well, HPV infection, CIN 1, CIN 2/3, cervical cancer (initial cancer), follow-up cervical cancer, recurrent/persistent cancer, follow-up recurrent/persistent cancer, and death. We limited the HPV infections caused by HPV types 16 and 18 (Figure 4).

We conducted the analysis with the assumptions that vaccination does not affect the current cervical cancer-screening rate and that the effect of the vaccine lasts for a lifetime. We did not consider any herd-immunity effects or cross-protection effects.

(2) Transition probability

We estimated the rate of HPV infection by calibrating using the age-specific HPV prevalence, frequency of sexual activity, and HPV infection-regression rate. The annual rate of cervical cancer screenings among Korean women was used as the proportion of CIN treatment and management. Claims data from the NHI was analyzed to estimate the transition probabilities from CIN 1 to CIN 2/3 and from CIN 2/3 to cervical cancer. The FIGO annual report (Quinn et al., 2006) and a review of previous research were used to estimate death rate for each health state.

(3) Costs

We estimated the annual cost of vaccines to be KRW 343,144, using equal proportion of the two vaccines on the Korean market, Gardasil and Cervarix, and assuming that the costs would be 70% less than the current market price once a national vaccination program is implemented. We calculated the cost of screening for cervical cancer using the age-specific national cancer-screening rate and the private cancer-screening rate. We computed the annual medical costs per patient diagnosed with CIN or cervical cancer from the NHI claims data, and we estimated the unofficial medical costs based on the results of the patient surveys. We estimated the transportation costs, time costs, and caregiver costs from the NHI claims data, the patient surveys, and the unit costs reported in previous research.

(4) Effects

We used the persistent infection rates of HPV types 16 and 18 obtained from our meta-analysis of the systematic review. We applied the result of the mITT combined analysis, RR 0.45 [CI: 0.34-0.58], to estimate the effect of subjects being vaccinated more than once.

(5) Sensitivity analysis

Sensitivity analysis was conducted to reflect the uncertainty among the variables for the vaccine cost, vaccination rate, vaccine efficacy, discount rate, medical costs, and death rate among patients with recurrent cervical cancer.

Ⅱ. Results

(1) Total effectiveness

Our model showed that for a cohort of 12-year-old girls (n=300,405), a national HPV vaccination and cervical cancer screening program would result in 2,042 patients developing cervical cancer, whereas the current screening program would result in 3,709 patients developing cervical cancer. Thus, the number of cases of cervical cancer would be reduced by about 45%. From this, we estimated that the cohort would get a total of 1,648 life years gained (LYG) and an additional 1,849 QALYs.

(2) Total costs

We estimated that a national HPV vaccination program would cost KRW 90.9 billion to implement, assuming the vaccine cost is reduced to 70% of the current price and 86% of eligible women receive vaccinations, and reduce the costs associated with CIN and cervical cancer by KRW 17.4 billion and KRW 13.9 billion, respectively. We estimate that the total cost of a national HPV vaccination program would be KRW 167 billion (with a discount rate of 5%) compared with the current screening program cost of KRW 107.2 billion, thus requiring an additional KRW 59.8 billion.

(3) Incremental Cost-Effectiveness Ratio

According to cost-utility analysis, the KRW 59.8 billion implementation of a national HPV vaccination program would generate an additional 1,849 QALYs. providing an incremental cost-utility ratio of KRW 32 million/QALY (Table 1). Considering the threshold of Korean cost-effectiveness, which is KRW 20 million to 30 million (Ahn et al., 2010), we conclude that the vaccination program is not cost-effective.

Although the HPV vaccination program for 12-year-old girls was not cost-effective under the current conditions in Korea, the cost-effectiveness is very sensitive to changes in certain variables.

(4) Sensitivity analysis

Sensitivity analysis showed that the vaccination rate, medical costs, and death rate among the patients with recurrent cervical cancer did not affect the result significantly, whereas the vaccine cost, the vaccine efficacy, and the discount rate strongly impacted on the cost-effectiveness of the vaccination program. A national HPV vaccination program would be cost-effective if the vaccine cost drops by 50% or when individuals are fully vaccinated three times after the program is implemented, thus maximizing the effectiveness of the vaccine. The number of patients with cervical cancer and a discount rate for future costs and health outcomes had especially strong effects on the results of the economic evaluation.

Conclusion and Policy suggestion

Although the HPV vaccination program for 12-year-old girls was not cost-effective under the current conditions in Korea, the cost-effectiveness is very sensitive to changes in certain variables. The WHO recommends introducing national HPV vaccination programs when: 1) the prevention of cervical cancer is a priority for public health policy, 2) sustainable financing is available, and 3) the introduction of a national vaccination program is cost-effective. This study will help to prioritize and validate plans to introduce national HPV vaccination programs.

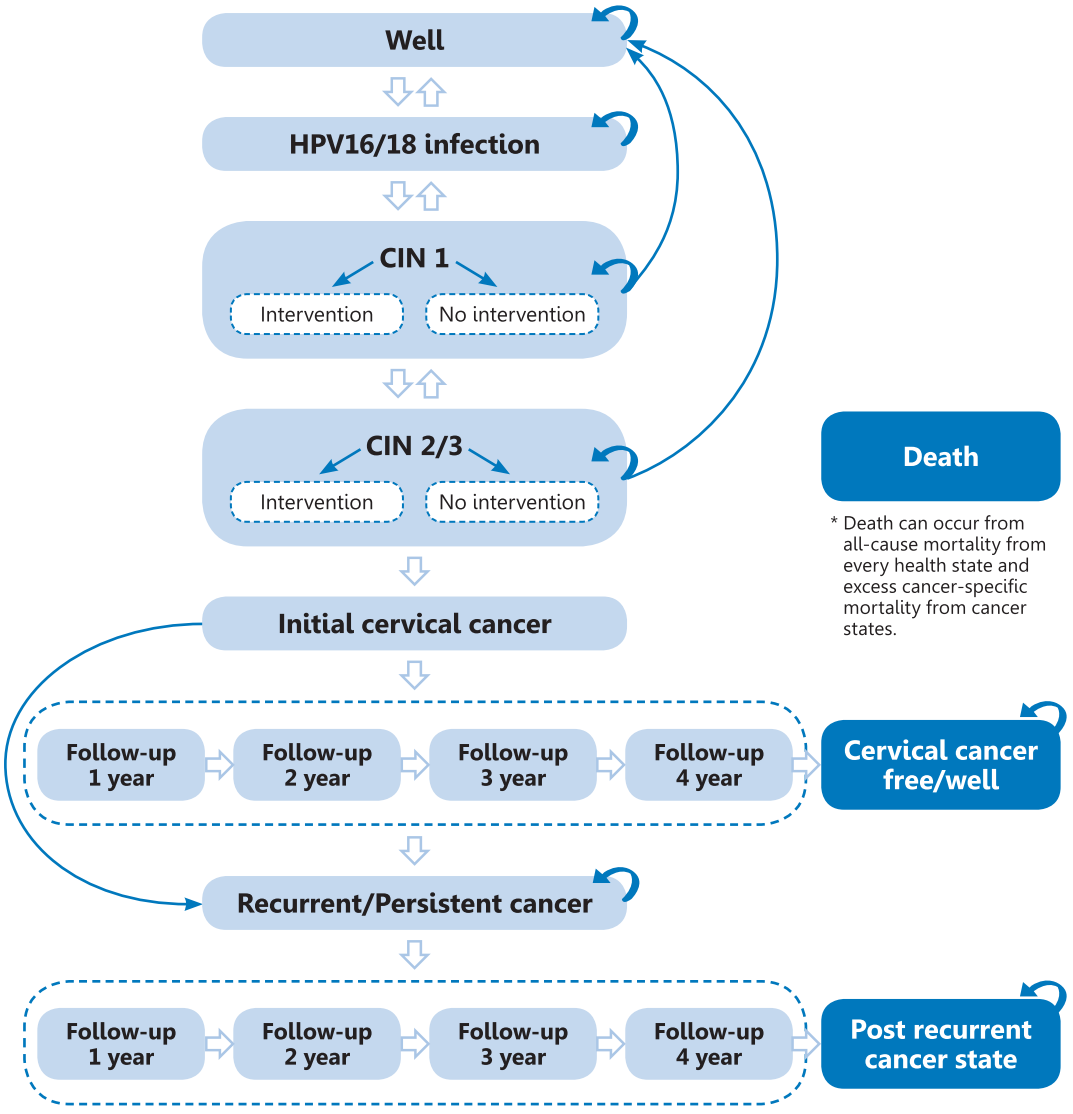

Figure 4. Decision analytic model of economic evaluation: Markov model

Table 1. The result of economic evaluation

Cost-utility analysis			
	Cost (KRW)	QALYs	Incremental cost-utility ratio (ICUR)
HPV vaccination program	167,041,109,046	5,689,390	
Only screening program	107,230,164,873	5,687,541	
Difference	59,810,944,173	1,849	**32,350,288 KRW/QALY**
Cost-effectiveness analysis			
	Cost (KRW)	LYG	Incremental cost-effectiveness ratio (ICER)
HPV vaccination program	167,041,109,046	5,920,325	
Only screening program	107,230,164,873	5,918,677	
Difference	59,810,944,173	1,648	**36,290,804 KRW/LYG**

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