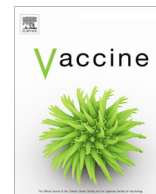


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The economic burden of human papillomavirus infection-associated diseases in the Republic of Korea, 2002–2015

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ABSTRACT

Background: This prevalence-based, cost-of-illness study estimated the health care costs of human papillomavirus (HPV) infection-associated diseases in the era before the introduction of organized HPV vaccination for 12-year-old girls in 2016, South Korea.

Methods: The claims data provided by the National Health Insurance Service was used to estimate the prevalence of HPV-associated diseases and their direct medical costs, including costs related to hospitalizations, outpatient visits, and medications.

Results: A total of 1.3 million men and women used medical services for HPV-attributed diseases between 2002 and 2015. Among women, the most common diseases attributable to HPV were cervical dysplasia (64.4%), anogenital warts (12.9%), cervical carcinoma in situ (10.7%) and cervical cancer (2.6%), whereas anogenital warts (80.6%), benign neoplasms of larynx (14.3%), and anal cancers (8.9%) were most common among men. In 2015, the healthcare cost attributable to HPV was 124.9 million US dollars (USD) representing 69.0% of the annual cost of all HPV-associated diseases. At a cost of 75.1 million USD, cervical cancer contributed the largest economic burden in 2015 followed by cervical dysplasia (19.4 million USD) and cervical carcinoma in situ (10.7 million USD). These three conditions represented 58.2% of the total annual cost of all HPV-associated diseases, while 84.2% of the total annual cost was attributable to HPV. Annual health care costs increased from 42.6 million USD in 2002 to 180.9 million USD in 2015.

Conclusion: The healthcare costs associated with HPV-related diseases in Korea are substantial and increased between 2002 and 2015 mainly caused by increased number of patients. Expanding the target age for HPV vaccination of girls and introducing HPV vaccination for boys are possible ways of reducing the economic burden of HPV-associated disease and should be considered.

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1. Introduction

Human papillomavirus (HPV) is the most common sexually transmitted infection. It is associated with a substantial burden of diseases, including cancer. Non-oncogenic or low-risk HPV types, such as types 6 or 11, can cause benign or low-grade abnormalities of the cervix, anogenital warts, and recurrent respiratory papillomatosis [1]. Oncogenic or high-risk HPV types, including

types 16 and 18, can cause intraepithelial neoplasia of the anogenital region, including cervical, vulvar, vaginal, penile, and anal cancers as well as some oropharyngeal cancers [2]. Along with *Helicobacter pylori*, hepatitis B and C virus, and Epstein-Barr virus, high-risk HPV strains are one of the major causes of infection-related cancers worldwide [3]. Although HPV vaccines have been used in Korea since 2007, HPV vaccination was only included in the fully funded National Immunization Program, which targeted 12-year-old girls, in June 2016 [4].

Cost-of-illness studies identify relevant costs and show the distribution of costs within the health care system [5]. This information, in turn, helps to inform policy decision-makers by giving them knowledge on where the majority of resources in the health care sector and other sectors are being utilized. According to a

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recent Korean cost-of-illness study, the healthcare cost of anogenital warts was \$ 3.9 million US dollars (USD) in 2015, including direct and indirect costs [6]. However, at present there is no published cost-of-illness study from Korea estimating the healthcare costs associated with overall HPV-related diseases.

We performed a prevalence-based, cost-of-illness study to estimate the healthcare costs of HPV-associated diseases (i.e. precancerous lesions; cancers of the cervix, vulva, vagina, anus, penis, and head and neck; anogenital warts; and benign laryngeal neoplasms) in the era before the introduction of organized HPV vaccination in Korea.

2. Methods

2.1. Data source

This study used health insurance claims data provided by the National Health Insurance Service (NHIS). The NHIS is a mandatory insurance and is a single payer that provides benefits for prevention, diagnosis, and treatment of disease and injury, as well as for rehabilitation, births, deaths, and health promotion. All South Korean citizens must either be enrolled in the NHIS (97% of entire population) or must be a recipient of medical aid (3%) [7]. The NHIS database contains information on medical aid subjects as well; therefore, it is based on the entire Korean population. Currently, the NHIS maintains and stores national records for healthcare utilization and prescriptions. The NHIS claims data contain details on the cost of care, the medical institution attended, the income distribution, and the residence of all insurance subscribers [8].

2.2. Study population

This prevalence-based, cost-of-illness study examined all yearly diagnosis-specific events from 2002 to 2015. We estimated prevalence costs (e.g., the costs of treatment incurred in a given year for HPV-associated diseases regardless of when HPV was acquired) as opposed to incidence costs (e.g., the expected lifetime costs of treatment arising from HPV infections acquired in a given year) [9]. We used the NHIS claims data to determine the number of patients and events in the healthcare sector in order to estimate direct medical costs associated with inpatient and outpatient care. The study population was identified from the NHIS based on the following International Classification of Diseases 10th revision (ICD-10) primary disease codes: anogenital warts (A63.0); cancer of the head and neck (C00–C10), anus (C21), vulva (C51), vagina (C52), cervix uteri (C53), and penis (C60); carcinoma in situ (CIS) of the lip, oral cavity and pharynx (D00.0), anus (D01.3), cervix (D06), vulva (D07.1), vagina (D07.2), and penis (D07.4); benign neoplasms of the larynx (D14.1); and dysplasia of the cervix (N87), vagina (N89), and vulva (N90) (Table 1).

In the NHIS data, all patients have a unique identifier, which is an eight-digit de-identified join key that replaces personal identifier (e.g. the resident registration number), to prevent leakage of personal information. We used the unique identifier in identifying individual patients. Patients with the following criteria were used in identifying HPV cases: (1) patients with one HPV-associated disease at time of visit – that HPV diagnosis counted as one case if it was designated as the primary disease; (2) patients with multiple concomitant HPV-associated diseases at time of visit – that HPV

Table 1
Estimated number of patients with HPV-associated diseases in South Korea, 2002–2015.

HPV-associated disease (ICD-10 Code)	Men		Women		Total		Attributable Fraction	Reference
	N of patients (%)	N of attributable to HPV (%)	N of patients (%)	N of attributable to HPV (%)	N of patients (%)	N of attributable to HPV (%)		
<i>Cancer</i>								
Oral cavity (C00–C08)	23,306 (8.9)	513 (0.2)	16,201 (1.2)	356 (0.0)	39,507 (2.5)	869 (0.1)	2.2	[10]
Tonsil (C09)	6,395 (2.4)	1,970 (0.9)	1,966 (0.1)	606 (0.1)	8,361 (0.5)	2,575 (0.2)	30.8	[10]
Oropharynx (C10)	4,985 (1.9)	1,535 (0.7)	1,250 (0.1)	385 (0.0)	6,235 (0.4)	1,920 (0.1)	30.8	[10]
Anus and anal canal (C21)	6,070 (2.3)	5,342 (2.6)	5,060 (0.4)	4,453 (0.4)	11,130 (0.7)	9,794 (0.7)	88.0	[10,11]
Vulva (C51)	–	–	2,421 (0.2)	961 (0.1)	2,421 (0.2)	961 (0.1)	39.7	[12]
Vagina (C52)	–	–	1,810 (0.1)	1,412 (0.1)	1,810 (0.1)	1,412 (0.1)	78.0	[10]
Cervix uteri (C53)	–	–	101,599 (7.6)	101,599 (8.8)	101,599 (6.4)	101,599 (7.5)	100	[10,11]
Penis (C60)	1,529 (0.6)	765 (0.4)	–	–	1,529 (0.1)	765 (0.1)	50.0	[10,11]
<i>CIS</i>								
Lip, oral cavity and pharynx (D00.0)	1,002 (0.4)	<100 (0.0)	814 (0.1)	<100 (0.0)	1,816 (0.1)	<100 (0.0)	2.2	^a
Anus and anal canal (D01.3)	<300 (0.1)	<300 (0.1)	<300 (0.0)	<200 (0.0)	<500 (0.0)	<500 (0.0)	88.0	^a
Cervix uteri (D06)	–	–	123,273 (9.2)	123,273 (10.7)	123,273 (7.7)	123,273 (9.1)	100	^a
Vulva (D07.1)	–	–	893 (0.1)	354 (0.0)	893 (0.1)	354 (0.0)	39.7	^a
Vagina (D07.2)	–	–	859 (0.1)	670 (0.1)	859 (0.1)	670 (0.0)	78.0	^a
Penis (D07.4)	<300 (0.1)	<200 (0.1)	–	–	<300 (0.0)	<200 (0.0)	50.0	^a
<i>Benign/precancerous lesions</i>								
Anogenital warts (A63.0)	185,980 (70.7)	167,382 (80.6)	165,449 (12.4)	148,904 (12.9)	351,429 (22.0)	316,286 (23.3)	90	[13]
Benign neoplasm of larynx (D14.1)	33,101 (12.6)	29,791 (14.3)	20,572 (1.5)	18,515 (1.6)	53,673 (3.4)	48,306 (3.6)	90	[14,15]
CIN (N87, N87.0, N87.1, N87.2, N87.9)	–	–	882,753 (66.2)	741,513 (64.4)	882,753 (55.3)	741,513 (54.6)	84	[11]
VaIN (N89.0, N89.1, N89.2, N89.3)	–	–	5,405 (0.4)	5,189 (0.5)	5,405 (0.3)	5,189 (0.4)	96	[16]
VIN (N90.0, N90.1, N90.2, N90.3)	–	–	3,767 (0.3)	2,874 (0.2)	3,767 (0.2)	2,874 (0.2)	76.3	[12]
Total	262,924 (100)	207,703 (100)	1,334,306 (100)	1,151,270 (100)	1,597,230 (100)	1,358,973 (100)		

HPV, human papillomavirus; CIS, carcinoma in situ; CIN, cervical intraepithelial neoplasia; VaIN, vaginal intraepithelial neoplasia; VIN, vulvar intraepithelial neoplasia. The number of individual patients with HPV-associated disease during the 14-year study period was 1,441,633 (258,062 men; 1,183,571 women). A patient can have two or more HPV-associated diseases as a primary diagnosis between 2002 and 2015. In this case, we counted each HPV-associated disease separately.

The precise number of patients below 500 were masked and reported as <100/<200/<300 < 400/<500 to protect patient confidentiality.

^a These attributable fractions were assumed to be the same as those of cancer at the corresponding anatomical site.

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