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# Burden of Human papillomavirus (HPV)-related disease and potential impact of HPV vaccines in the Republic of Korea

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ABSTRACT

*Background:* We aimed to review the burden and the potential impact of human papillomavirus (HPV) vaccines on HPV-related diseases in the Republic of Korea and to discuss cervical cancer prevention practices in this country.

*Methods:* Cancer burden statistics were retrieved from GLOBOCAN-2018 and Statistics Korea. HPV disease burden was assessed via systematic review. Vaccine types relative contribution (RC) was estimated using data from an international project using formalin-fixed paraffin-embedded specimens.

*Results:* Despite a downtrend in cervical cancer in recent years, Korean rates remain high. In contrast, oropharyngeal cancer incidence has gradually increased and other anogenital cancers remain rare.

In Korea, HPV prevalence in general population is around 20%. In cervical cancer, RC of HPVs 16/18 (74.0%) increased to 92.0% when including HPVs 31/33/45/52/58. Limited information was available for other HPV-related cancer sites.

Regarding prevention, since the inclusion of the HPV vaccine into the National Immunization Program, almost half (49%) of the target cohort in 2016 had received the first dose of vaccine. Further, percentage of women screened with pap has increased from 41.1%-2009 to 53.0%-2016.

*Conclusions:* HPV-related disease burden in Korea is significant. Results suggest that the combination of effective and high coverage HPV vaccination and screening programmes could substantially impact on HPV-related disease in Korea.

## 1. Introduction

Cancer is the leading cause of death in the Republic of Korea (hereinafter also referred to as Korea) and was responsible for 28.1% of all deaths in 2017 [1]. In Korea, more than 277,000 new cancer cases more than 86,000 new cancer deaths are reported annually (estimates for 2018) [2]. Further, cancer burden is expected to increase in Korea with an aging population and westernized lifestyles.

Human papillomavirus (HPV) infection is an important contributor to cancer-related morbidity and mortality in the country, accounting for 11.3% of new infection-related cancer cases and 6.0% of infection-related cancer deaths in 2007 [3]. Although the majority of HPV infections (70–90%) do not cause symptoms and resolve spontaneously within 2 years, persistent infection with oncogenic HPV types, also

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known as high-risk (HR) HPVs may lead to precancerous lesions and cancers [4]. HR HPVs are not only responsible for virtually all cervical cancers cases, but also causally related with a variable fraction of other anogenital cancers (vulvar, vaginal, penile and anal) and a subset of head and neck cancers, particularly base of tongue cancer, tonsil cancer and other oropharyngeal cancer sites [4,5]. The last classification of the International Agency of Research in Cancer (IARC) defined 12 HPV types as carcinogenic to humans, namely HPVs 16/18/31/33/35/39/45/51/52/56/58/59 (Group 1) [6]. Within them, HPV16 and HPV18 stand out for their highest carcinogenic capacity [6].

In recent years, several studies have examined the prevalence and the burden of HPV-related diseases within the Korean population; however, variations in the prevalence and type distribution have been observed. Further, the arrival of the 4-valent HPV vaccine (Gardasil®) in 2007 and the 2-valent HPV vaccine (Cervarix™) in 2008 marked a change in strategy in HPV prevention. Finally, the recent introduction of the 9-valent HPV vaccine (Gardasil®9) could significantly impact on HPV-related disease burden in Korea.

The aim of this review is therefore to provide an overview of the global burden of HPV infection and HPV-related disease in Korea and to estimate the potential public health impact of HPV vaccines on HPV-related cancer in the country. In addition, we aimed to discuss current cervical cancer preventive practices in the country. Special emphasis is given to cervical cancer, as it accounts for more than 80% of cancers attributable to HPV infection [7]. Consideration is also given to genital warts, one major cause of morbidity worldwide, caused mainly by low-risk (LR) HPV6 and HPV11.

## 2. Material and methods

The purpose of this review was to describe and discuss the state of knowledge regarding the burden of HPV infection and HPV-related disease in Korea.

**Cancer burden statistics** were retrieved from GLOBOCAN 2018 and from Statistics Korea [1,2]. Region-specific rates and information regarding time trends were based on data from Statistics Korea and from Cancer in Five Continents (CI5C Volume XI) [1,8]. The CI5C includes information from: a) Korea Central Cancer Registry (KCCR): The KCCR began as a hospital-based nationwide cancer registry, initiated by the Ministry of Health and Welfare in 1980. It is responsible for collecting and managing nationwide cancer registry data, providing technical and financial support to the regional cancer registries, providing training for cancer registers, and providing annual nationwide cancer statistics; b) the following population-based regional cancer registries: 1. Busan Cancer Registry (BSCR), 2. Daegu Cancer Registry (DCR), 3. Daejeon Cancer Registry (DJCR), 4. Gwangju Cancer Registry (GCR), 5) Incheon Cancer Registry (ICR), 6) Jejudo Cancer Registry (JCR), 7) Kangwha Cancer Registry (KCR), 8) Seoul Cancer Registry (SCR), 9) Ulsan Cancer Registry (UCR).

A comprehensive search of peer-reviewed biomedical literature was conducted to assess the burden of HPV-related disease and HPV type distribution by using MEDLINE (1950 to present), Asian Pacific Journal of Cancer Prevention (APJCP), KoreaMed Synapse (1933 to present) and Google Scholar. Journal articles, reports, and various other types of communication published between January 1933 and October 2018 pertaining to “HPV”, and “Korea” were considered. In addition, the reference lists of retrieved articles were evaluated and included when appropriate.

In addition, in order to assess the potential impact of the nine types (HPVs 16/18/31/33/45/52/58/6/11) included in HPV vaccines (2-valent, 4-valent and 9-valent) to HPV-related cancer cases in the Korean population, we used data from an international project on HPV-related lesions designed and coordinated by the Catalan Institute of Oncology (ICO) (Barcelona-Spain) in collaboration with DDL Diagnostic Laboratory (Rijswijk-Netherlands) [9–14]. Briefly, formalin-fixed paraffin-embedded (FFPE) specimens from consecutive cases were obtained from hospital pathology archives in 50 countries worldwide. HPV DNA detection and typing was performed by polymerase chain reaction (PCR) with SPF10 broad spectrum primers followed by DNA detection using a DNA enzyme immunoassay (DEIA) and HPV genotyping using a reverse hybridization line probe assay (LiPA25) [15]. More detailed descriptions can be found in previous reports [9–14]. Specifically for Korea, the project includes information from 742 cases of cervical cancer, 28 cases of female anal cancer, 16 cases of male anal cancer, 10 cases of vaginal cancer, 23 cases of vulvar cancer, 28 cases of penile cancer, 12 cases of female oropharynx cancer, 7 cases of male oropharynx cancer and 3 cases of male larynx cancer. However, due to the limited number of cases included for several locations, data were supplemented using information from several countries in Eastern Asia–including data from China, Japan, the Philippines, Thailand and Taiwan. Prevalence was calculated as the proportion of women positive for a given type among all tested samples. The relative contribution (RC) of the types included in HPV vaccines was expressed as the proportion of cases positive for a given type among all HPV DNA positive samples. Type-specific information included information on multiple infections, which were added to single types in accordance with a proportional weighting attribution [16,17].

To complete the section of cervical cancer screening and HPV vaccination programme in Korea, the Korean Centre of Disease Control (KCDC) and the Ministry of Food and Drug Safety (MSD Korea) were consulted, together with other relevant publications.

## 3. Burden of HPV infection and HPV-related disease in Korea

### 3.1. HPV infection in women with normal cytological findings

HPV infection is commonly found in the anogenital tract of women with and without clinical lesions. The most updated data estimating HPV infection among women with normal cervical cytology is based on systematic reviews and meta-analysis performed by the ICO/IARC Information Centre on HPV and Cancer. Crude and adjusted prevalence of HPV infection is estimated at 12.6% (12.3–12.9) and 10.7% (10.4–10.9) in Eastern Asia [18].

However, limited data regarding specific HPV prevalence among Korean women have been published. A meta-analysis conducted in 2008, reported crude and adjusted HPV prevalence of 20.4% and 23.9% in Korean women with normal cytological findings [19]. Similar HPV prevalence (21.9%) was observed in a recent retrospective cross-sectional study among 18,815 women visited in 13 cities in Korea between January 2014 and October 2015 [20]. However, substantial variations are observed among individual studies (Table 1) – the largest Korean study reported an overall HPV prevalence of 34.2% in women with normal cytological findings [21]. These variations could be explained by differences in HPV detection methods but also because some of these studies have focused on women living in localized areas or on risk groups; hence, are unlikely to be representative of all Korean women.

Globally, HPV prevalence in Korea peaks in women less than 25 year old (28.6%; 8.2–64.1), in which the majority of HPV infections (70–90%) are asymptomatic and transient, and then declines to 10.0–12.0% in other age groups [22]. Individual studies agree with this decrease with age [20,23–25].

Regarding HPV type distribution in women with normal cytological findings, HPV16 is the dominant type in Korea, followed by HPVs 70/58/52/66/18/56/51/35/68 in specific rank order, although differences are observed from study to study [22] (Table 1). Particularly in Korea, the prevalence of HPV52 (2.3%) and HPV58 (0.9%) was higher than in other countries and regions [19].

### 3.2. HPV infection in women with cervical precancerous lesions

HPV DNA prevalence in Korea increases with lesion severity, in accordance with Eastern Asia data. In Korea, Bae et al. [19] meta-

**Table 1**
HPV prevalence in women with normal cervical cytology in the Republic of Korea, by study.

| Reference | Study design | HPV detection and targeted HPVs | Age range (years) | N | Prevalence "any HPV" % (95%CI) | 5 most frequent reported HPVs (%) |
|---|---|---|---|---|---|---|
| **Hwang T, J Korean Med Sci 1999; 14: 593** | Cohort study among women attending the Department of Obstetrics and Gynecology, Inha University Hospital (Incheon). | Other PCR–Consensus primers; TS HPVs 16/18/31/33/35/52b/58 | – | 130 | 10.0 (5.4–16.5) | HPV16 (3.9%), HPV18 (1.5%), HPV58 (2.3%), HPV52 (1.5%) |
| **Oh YL, Cytopathology 2001; 12: 75** | Cross–sectional study among women attending routine cervical cancer screening in healthcare centres in Seoul (1996). | Other PCR–E6, E7 consensus primers; TS HPVs 16/18/31/33 | 23–72 | 1144 | 0.7 (0.4–1.4) | HPV16 (0.6%), HPV18 (0.1%) |
| **An HJ, Cancer 2003; 97: 1672** | Cohort study among women visited at the Department of Gynecologic Oncology at Bundang CHA Hospital (Kyonggi–do) (2001–2002). | PCR–DNA CHIP (GPd5 +/GP6d+); TS HPVs 6/11/16/18/31/33/34/35/39/40/42/43/44/45/51/52/56/58/59/66/68/69 | – | 1143 | 35.1 (32.4–37.9) | HPV16 (22.4%), HPV56 (1.8%), HPV18 (1.8%), HPV56 (1.6%), HPV58 (1.1%) |
| **Cho NH, Am J Obstet Gynecol 2003; 188: 56** | Case control study among women visited at the outpatient clinic of the Yonsei University College of Medicine and at the Pundang CHA Hospital (Kyonggi–do) (2000). | PCR–DNA CHIP (GPd5 +/GP6d+); TS HPVs 6/11/16/18/31/33/34/35/39/40/42/43/44/45/51/52/56/58/59/66/68/69 | 22–70 | 414 | 31.9 (27.6–36.5) | HPV16 (22.9%), HPV18 (3.8%), HPV52 (2.2%), HPV39 (1.4%), HPV35 (0.7%), HPV45 (0.7%) |
| **Lee SA, Cancer Lett 2003; 198: 187** | Case control study among women visited for routine cervical cancer screen at the Department of Obstetrics and Gynecology in Seoul National University Hospital (1992–1995). | PCR–DNA CHIP (GPd5 +/GP6d+); TS HPVs 6/11/16/18/31/33/34/35/39/40/42/43/44/45/51/52/56/58/59/66/68/69 | – | 746 | 7.2 (5.6–9.3) | HPV16 (4.3%), HPV56 (0.7%), HPV58 (0.5%), HPV52 (0.5%), HPV18 (0.4%), HPV35 (0.4%) |
| **Shin HR, Int J Cancer 2003; 103: 413** | Cohort study (population–based survey) in Busan (1999–2000). | PCR–GP5 + /6 + , EIA HPVs 6/11/16/18/26/31 /33/34/35/39/40/42/43/44/45/51/52/53/54/55/56/57/58/59/61/66/68/70/71/72/73/81/82/83/84 | 20–74 | 821 | 8.5 (6.8–10.6) | HPV70 (1.1%), HPV33 (1.1%), HPV16 (0.7%), HPV81 (0.7%), HPV56 (0.5%) |
| **Hwang HS, Cancer Epidemiol Biomarkers Prev 2004; 13: 2153** | Cross–sectional study among consecutive women visited at Department of Obstetrics & Gynecology, Inha University Hospital, (Incheon) (2002–2003). | PCR–DNA CHIP (hpv1/2); TS HPVs 6/11/16/18/31/33/34/35/39/40/42/43/44/45/51/52/56/58/59/66/68/69 | 18–62 | 1609 | 37.4 (35.0–39.7) | HPV16 (6.3%), HPV58 (3.7%), HPV52 (3.4%), HPV51 (2.9%)[a] |
| **Shin HR, J Infect Dis 2004; 190: 468** | Cross–sectional survey among subjects from 3 institutions of higher education: DB College; D University, and the Institute for Continuing Education (Busan) (2002) | PCR–SPF10, EIA HPVs 6/11/16/18/31/33/34/35/39/40/42/43/44/45/51/52/53/54/56/58/59/66/68/73/70/74 | 16–29 | 672 | 15.2 (12.7–18.1) | HPV51 (1.8%), HPV56 (1.5%), HPV53 (1.5%), HPV16 (1.3%), HPV52 (1.3%)[a] |
| **Lee HS, Int J Gynecol Cancer 2007; 17: 497**[b] | Cohort study among women referred to the Department of Gynecologic Oncology at Chonnam National University Hospital (Gwangju) | PCR–DNA CHIP (GPd5 +/GP6d+); TS HPVs 6/11/16/18/31/33/34/35/39/40/42/43/44/45/51/52/53/54/56/58/59/66/68/70 | 20–82 | 1650 | 23.5 (21.5–25.6) | HPV16 (6.8%), HPV58 (4.8%), HPV53 (3.3%), HPV18 (2.6%), HPV66(1.6%) |
| **Bae J, Gynecol Oncol 2009; 115: 75** | Cohort study among women attending cervical cancer screening at the National Cancer Center (Seoul) (2003–2004). | HC2 | 30–84 | 4111 | 6.5 (5.8–7.3) | |
| **Bae JH, J Microbiol Biotechnol 2009; 19: 1051**[c] | Cohort study for a hospital–based cervical cancer screening program (2002–2006). | PCR–DNA CHIP (L1,E2,E6,E7 Consensus primers); TS HPVs 6/11/16/18/31/33/34/35/39/40/42/43/44/45/51/52/56/58/59/66/68/69 | 15–75 | 1750 | 27.0 (25.0–29.2) | |
| **Oh JK, Eur J Cancer Prev 2009; 18: 56**[b] | Cross–sectional survey study among women participating in The National Cervical Cancer Screening Program (Busan&Suwon) (2004–2006). | HC2 & Linear Array; HPVs 6/11/16/18/26/31/33/35/39/40/42/45/51 /52/53/54/55/56/58/59/68/61/62/64/66/67/69/70/71/72/73/81/82/83/84/IS39/CP6108 | 20–69 | 4467 | 7.0 (6.3–7.8) | HPV52 (1.1%), HPV58 (09%), HPV39 (0.7%), HPV16 (0.7%), HPV56 (0.7%)[a] |
| **Kang WD, Int J Gynecol Cancer 2009; 19: 924** | Cohort study among women visited for routine cervical screening at the Department of Obstetrics and Gynecology of Chonnam National University Hospital (Gwangju) (2002–2006). | HC2, PCR-SPF10, EIA HPVs 6/11/16/18/31/33/40/45/51/53/54/58/59/66/68/70 | 21–69 | 136 | _ | HPV58 (11.8%), HPV53 (11.8%), HPV16 (10.3%), HPV52 (6.6%), HPV18 (5.1%) |
| **Kim MA, Obstet Gynecol 2010; 116: 932**[b,c] | Cross–sectional (population based) study among women visiting the Department of Obstetrics and Gynecology, Gangnam Severance Hospital, Yonsei University College of Medicine (Seoul) for a regular medical checkup (2008–2009). | HC2 and PCR–GP5/6; TS VPHs 16/18/31/33/35/39/45/51/52/56/58/59/68 | 20–59 | 902 | 12.6 (10.6–15.0) | HPV56 (1.9%), HPV18 (1.8%), HPV52 (1.7%), HPV16 (1.3%), HPV31 (1.3%), HPV33 (1.3%) |
| **Cho EJ, J Med Microbiol 2011; 60: 162**[c] | Cross sectional study among clinical samples collected at the Catholic Medical University (Seoul) (2006). | PCR–DNA CHIP (GPd5 + /GP6d+); TS HPVs 6/11/16/18/31/33/34/35/39/40/42/43/44/45/51/52/53/54/56/58/59/66/68/70 | – | 624 | 47.3 (43.4–51.2) | |
| **Lee HP, J Med Virol 2011; 83: 471** | Case control study among women visited for cervical cancer screening (Seoul) (2008–2010). | PCR–PGMY09/11, TS HPVs 6/11/16/18 /31/33/34/35/39/40/43/44/45/51/52/53/54/55/56/58/61/62/66/68/69/72/74/81/82/83/84 | – | 101 | 20.8 (14.0–29.7) | |

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Table 1 (*continued*)

| Reference | Study design | HPV detection and targeted HPVs | Age range (years) | N | Prevalence "any HPV" % (95%CI) | 5 most frequent reported HPVs (%) |
|---|---|---|---|---|---|---|
| **Um TH, Ann Clin Lab Sci 2011; 41: 48** | Cross–sectional study among residual samples of liquid–based Pap tests (–2008). | HC2 | – | 122 | 23.0 (16.4–31.2) | |
| **Hwang Y, Ann Lab Med 2012; 32: 201**[c] | Cross–sectional study among women visited at the gynecology clinic at Ewha Womans University Mokdong Hospital (Seoul) (2010). | HC2 | 21–77 | 177 | 54.8 (47.4–62.0) | |
| **Kim J, Int J Gynecol Cancer 2012; 22: 1570**[b] | Case–control (hospital based) study among women evaluated and treated at Center for Uterine Cancer, Research Institute & Hospital, National Cancer Center (Goyang) (2002–2004). | PCR–GP5 + /6 + & MY09/11; TS HPVs 16/18/31/33/35/39/45/51/52/53/56/58/59/66/68/69 | 25–75 | 1214 | 14.6 (12.7–16.7) | HPV16 (9.9%), HPV66 (1.9%), HPV33 (1.0%), HPV58 (1.0%), HPV18 (0.9%) |
| **Kim K, Asian Pac J Cancer Prev 2012; 13: 269** | Cross–sectional study among women visited at the healthcare center located in the Gangnam area of Seoul, (2003–2008). | HC2 | – | 11,800 | 6.2 (5.8–6.6) | |
| **Lee SJ, Int J Med Sci 2012; 9: 103** | Cross–sectional study among women visited at the Department of Gynecologic Oncology at Saint Vincent Hospital of the Catholic University of Korea (Kyungki–do) for routine gynecologic examinations (1999–2009). | HC2 | – | 26,980 | 20.3 (19.9–20.8) | |
| **Lee EH, J Korean Med Sci 2012; 27: 1091**[c] | Cross–sectional study among residual samples after liquid–based pap test (2006–2011) | PCR–PGMY09/11, HPVs 6/11/16/18/26/30/31/33/34/35/39/40/42/43/44/45/51/52/53/54/55/56/58/59/61/62/66/68/70/72/73/74/81/82/83/84/89/90 | 18–79 | 60,775 | 34.2 (33.8–34.6) | HPV16 (4.5%), HPV52 (4.4%), HPV58 (2.0%), HPV18 (1.3%), HPV31 (0.9%)[d] |
| **Kim JH, Oncol Rep 2013; 29: 1645** | Cross–sectional study among women visited at the Department of Obstetrics & Gynecology at the Medical College, Chosun University (Gwangju) (–2010). | HC2 | – | 206 | 8.3 (5.2–12.8) | |
| **Kim MJ, Obstet Gynecol Sci 2013; 56: 110** | Retrospective cross–sectional study among women visited at Seoul National University Hospital Healthcare System Gangnam Center (Seoul) for routine health check–up (2008–2010) | PCR–DNA CHIP; TS HPVs 6/11/16/18/31/33/34/35/39/40/42/43/44/45/51/52/53/54/56/58/59/66/68/70 | – | 6681 | 17.3 (16.4–18.2) | HPV16 (1.6%), HPV52 (1.1%), HPV18 (0.9%), HPV35 (0.7%), HPV34 (0.5%) |
| **Kim YJ, J Microbiol 2013; 51: 665** | Cross–sectional study among women visited at the Total Health Care Center, Kangbuk Samsung Hospital (Seoul) (2012). | Real-time PCR; HPVs 6/11/16/18/26/31/33 /35/39/40/42/43/44/45/51/52/53/54/56/58/59/61/66/68/69/70/73/82 | 21–76 | 2146 | 18.1 (16.6–19.8) | |
| **Bae JM, Arch Virol 2014; 159: 1909** | Case–control study among women referred for cervical cancer screening at the KonKuk Medical Center (Seoul) (2011). | HC2 | 18–85 | 471 | 21.0 (17.6–24.9) | |
| **Kim JK, J Microbiol Biotechnol 2014; 24: 1143**[c] | Cross–sectional study among women attending Dankook University Hospital Health Improvement Center (Cheonan)(2006–2012). | PCR–DNA CHIP (GPd5 +/GP6d+); TS HPVs 6/11/16/18/31/33/34/35/39/40/42/43/44/45/51/52/54/56/58 | 19–78 | 5494 | 14.4 (13.5–15.3) | HPV16 (1.5%), HPV53 (1.5%), HPV56 (1.4%), HPV58 (1.1%), HPV35 (1.1%) |
| **Kim TE, Korean J Pathol 2014; 48: 24**[c] | Cross–sectional study among women visited for gynecological examination in Busan (2011). | PCR–DNA CHIP; HPVs 6/11/16/18/26 /30/31 /32/33/34/35/39/40/42/43/44/45/51/52/53/54/55/56/58/59/61/62/66/67/68/68/69/70/72/73/81/82/83/84/90/91 | 22–83 | 315 | 70.2 (64.9–74.9) | HPV16 (19.7%), HPV58 (12.4%), HPV52 (7.3%), HPV18 (5.1%), HPV56 (5.1%) |
| **Kim Y, J Infect Chemother 2014; 20: 74**[c] | Cross–sectional study among healthy Korean women who visited Gangnam Severance Hospital (Seoul) for general medical check–ups (2012–2012). | HC2 | 25–81 | 799 | 12.1 (10.1–14.6) | |
| **Lee H, Epidemiol Infect 2014; 142: 1579**[c] | Cohort study among cervico–vaginal smear samples from the female participants in the Healthy Twin Study at Samsung Medical Center (Seoul), Busan Paik Hospital (Busan), and Dankook University Hospital (Cheonan) (2005–2009). | PCR–GP5/6(+) & (PG)MY09/11 | 25–79 | 912 | 7.9 (6.3–9.8) | |
| **Park EK, J Korean Med Sci 2014; 29: 32**[c] | Retrospective case control study among women attending Health Promotion Centres of Pusan National University Hospital and Yangsan Pusan National University Hospital (2009–2012) | PCR–DNA CHIP; HPVs 6/11/16/18/31/33/34/35/39/40/42/43/44/45/51/52/53/54/56/58/59/66/68/70 | 43–57 | 1938 | 14.1 (12.7–15.8) | HPV16 (1.0%), HPV70 (0.8%), HPV51 (0.7%), HPV54 (0.7%), HPV58 (0.6%) |
| **So KA, J Cancer Prev. 2016;21(2):104** | Cohort study among women examined at a health promotion center of the Korea University Guro Hospital (Seoul) (2013). | Real-time PCR; HPVs 6/11/16/18/26/31/33 /35/3940/42/43/44/45/51/52/53/54/56/58/59/61/66/68/69/70/73/82 | – | 610 | 33.6 (29.9–37.5) | |

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**Table 1** (*continued*)

| Reference | Study design | HPV detection and targeted HPVs | Age range (years) | N | Prevalence "any HPV" % (95%CI) | 5 most frequent reported HPVs (%) |
|---|---|---|---|---|---|---|
| **Nah EH, Ann Lab Med 2017;37:426** | Retrospective cross-sectional study among women attending Health Promotion Centers for cervical cancer screen in 13 Korean cities (2014–2015). | Real-time PCR; HPVs /6/11/16/18/26/31/33 /35/39/40/ 42/43/44/45/51/5253/54/56/58/59/61/66/68/69/70/ 73/82 | 20–99 | 15,426 | 21.9 (21.2–22.6) | HPV53 (2.8%), HPV70 (2.4%), HPV52 (1.9%), HPV58 (1.6%), HPV56 (1.3%)[d] |
| **Ouh YT, J Gynecol Oncol. 2018; 29(1): e14**[b] | Retrospective cross-sectional study among women attending 7 centres nationwide from a private Korean Medical Institute for ginecological examination. Specimens and data from Korea University Guro Hospital ( (2014–2016). | PCR Microarray; HPVs 6/11/16/18/26/31/32/33/34/35/ 39/40/42/43/44/45/51/52/53/54/55/56/58/59/62/66/ 68/69/70/73/81/83 Or Real-time PCR; HPVs 6/11/16/ 18/26/31/33/35/39/40/42/43/44/45/51/52/53/54/56/ 58/59/61/66/68/69/70/73/82 | 17–83 | 17,717 | 11.4 (10.9–11.8) | HPV53 (14.9%), HPV52 (11.6%), HPV58 (11.1%); HPV39 (8.6%), HPV16 (8.4%), |

"HPV": Human papillomavirus; "95% CI": 95% Confidence Interval; "N": number of women tested.
The samples for HPV testing come from cervical specimens (fresh/fixed biopsies or exfoliated cells).

[a] Only type specific prevalence for these HR HPV.
[b] Any HPV prevalence and type specific prevalence for HR HPV.
[c] Women from the general population, including some with cytological cervical abnormalities.
[d] Type specific prevalence for HR HPV.

analysis reported an adjusted HPV prevalence of 23.9% (23.8–24.1) in women with normal cytology, 60.0% (59.5–60.2) in low-grade cervical lesions (including ASCUS, low-grade squamous intraepithelial lesion (LSIL) and cervical intraepithelial neoplasia grade 1 (CIN1)), 85.8% (85.2–86.5) in high-grade cervical lesions (including high grade squamous intraepithelial lesion (HSIL), CIN2/CIN3 and Carcinoma in situ (CIS)) and 95.8% (95.4–96.2) in cervical cancer lesions.

This meta-analysis confirmed HPV16 as the most frequently detected genotype in all stages of the disease. The strong enrichment in HPV16 prevalence (6.0% in normal cytology, 20.0% in low-grade cervical lesions, 40.6% in high-grade cervical lesions and 53.2% in cervical cancer) confirms its higher carcinogenic potential compared to other HPV types [19]. Even though, differences are observed among individual studies (Table 2).

### 3.3. Cervical cancer

#### 3.3.1. Incidence and mortality rates

Current estimates indicate that every year 3348 women are diagnosed with cervical cancer and 1029 die from the disease in Korea (estimates for 2018) [2]. This figure is similar to the 3582 cases (2015) and 868 deaths (2017) recorded in the KCCR [1].

Based on crude incidence rates, cervical cancer ranks as the ninth most frequent reported cause of cancer among females in Korea (13.1 new cases per 100,000 women in 2018), and the fourth among women aged 15–44. Cervical cancer also ranks as the ninth most frequent reported cause of cancer deaths among females in Korea (4.0 new deaths per 100,000 women in 2018), and the third among women aged 15–44. Age-standardized rates (ASR) in Korea (ASR-incidence (2018): 8.4 per 100,000 and ASR-mortality (2018): 2.0 per 100,000) were slightly lower than that observed in Eastern Asia (ASR-incidence: 10.9 per 100,000 and ASR-mortality: 4.1 per 100,000) (Table 3) [2]. Similar to other developed countries, decreasing trends in incidence and mortality rates of cervical cancer have been reported in the country [1,8,26].

Cervical cancer age-specific incidence uniformly increases with age in Korea, with 74.8% of cases reported in women aged 30–64 in 2015 [1]. By contrast, although cervical cancer mortality increases with age, the peak in mortality is observed among women older than 50 years (80.0% of cases in 2015) (Fig. 1).

In Korea, most of cases are squamous cell carcinomas (SCC) (approximately 80%) followed by adenocarcinomas (ADC), although an increase in the proportion of ADC was reported (from 8.9% in 1993 to 16.1% in 2009). Unlike a downtrend in ASR-incidence of SCC (from 14.1 per 100,000 in 1993–7.0 per 100,000 in 2012), ASR-incidence of ADC has remained fairly stable over time (Fig. 2) [1,26]. These could be explained by several factors including duration and quality of screening programmes and changes in cervical cancer risk factors, such as sexual behaviour and HPV exposure.

In relation to carcinoma in situ, 62,300 cases (96.3% SCC) were reported between 1993 and 2009. Unlike rates of invasive cervical cancer, Korean rates of CIS have increased steadily over time across all age groups (ASR-incidence has increased from 7.5 per 100,000 women in 1993–19.0 per 100,000 women in 2009) [27].

#### 3.3.2. HPV prevalence and type distribution

According to Bae et al. [19] meta-analysis, HPV16 is the main type among cases of cervical cancer (53.2%), followed by HPV18 (11.9%) and HPV58 (8.6%).

Similarly, pooled data on HPV prevalence estimated by ICO/IARC Information Centre on HPV and Cancer reports HPV16 as the dominant type in cervical cancer in Korea (56.3%, 53.9–58.6), followed by HPV18 (11.7%, 10.2–13.3), HPV33 (4.7%, 3.8–5.9), HPV58 (3.7%, 2.9–4.8), HPV31 (2.5%, 1.7–3.4) and 45 (2.0%, 1.4–2.9). HPV16 is detected more often in cases of SCC (59.3%, 56.3–62.1) than in cases of ADC (36.5%, 30.7–42.7), while HPV18 and 45 are detected more often in ADC (35.2%, 29.5–41.4% and 3.3%, 1.7–6.3, respectively) than in

**Table 2**
HPV prevalence in the Republic of Korea, by lesion severity and study.

| Reference | Study design | HPV detection and targeted HPVs | Age range (years) | HPV Prevalence | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Low–grade lesions | | High–grade lesions | | Cervical cancer | |
| | | | | Any HPV (%) | 5 most frequent reported HPVs (%) | Any HPV (%) | 5 most frequent reported HPVs (%) | Any HPV (%) | 5 most frequent reported HPVs (%) |
| **Kim KH, Yonsei Med J 1995; 36: 412** | Retrospective cross–sectional study on FFPE cervical cancer specimens from pathology archives from the Department of Pathology of the Yonsei University colleague of Medicine (Seoul). | Other PCR–p53, E6 consensus primers; TS HPV16/18/31/33 | – | – | – | – | – | 21/30 (70.0%) | HPV16 (53.3%), HPV18 (16.7%) |
| **Hwang T, J Korean Med Sci 1999; 14: 593** | Cohort study among women attending the Department of Obstetrics and Gynecology, Inha University Hospital (Inchon). | Other PCR–Consensus primers; TS HPVs 16/18/31/33/35/52b/58 | – | 6/8 (75.8%) | HPV18 (37.5%), HPV52 (25.0%) | 20/27 (74.1%) | HPV16 (18.6%), HPV33 (11.1%), HPV31 (7.4%), HPV52 (7.4%), HPV58 (7.4%) | 38/41 (92.7%) | HPV16 (36.6%), HPV58 (14.6%), HPV18 (9.8%), HPV33 (9.8%), HPV31 (7.3%) |
| **Oh YL, Cytopathology 2001; 12: 75** | Cross–sectional study among women attending routine cervical cancer screening in healthcare centres in Seoul (1996). | Other PCR–E6, E7 consensus primers; TS HPVs 16/18/31/33 | 23–72 | 7/28 (25.0%) | HPV16 (17.9%), HPV33 (7.1%), HPV18 (3.6%) | 26/33 (78.8%) | HPV16 (51.5%), HPV33 (24.2%), HPV18 (3.0%), HPV31 (3.0%) | 3/3 (100%) | – |
| **An HJ, Cancer 2003; 97: 1672** | Cohort study among women visited at the Department of Gynecologic Oncology at Bundang CHA Hospital (Kyonggi–do)(2001–2002). | PCR–DNA CHIP (GPd5 +/GP6d+); TS HPVs 6/11/16/18/31/33/34/35/39/40/42/43/44/45/51/52/56/58/59/66/68/69 | – | 157/200 (78.5%) | HPV16 (36.5%), HPV18 (6.0%), HPV58 (5.0%), HPV35 (4.0%), HPV68 (1.5%) | 146/151 (96.0%) | HPV16 (45.0%), HPV58 (12.6%), HPV18 (6.6%), HPV35 (3.3%), HPV68 (0.6%) | 48/50 (96.0%) | HPV16 (64.0%), HPV18 (16.0%), HPV58 (10.0%), HPV68 (2.0%) |
| **Cho NH, Am J Obstet Gynecol 2003; 188: 56** | Case control study among women visited at the outpatient clinic of the Yonsei University College of Medicine and at the Pundang CHA Hospital (Kyonggi–do) (2000). | PCR–DNA CHIP (GPd5 +/GP6d+); TS HPVs 6/11/16/18/31/33/34/35/39/40/42/43/44/45/51/52/56/58/59/66/68/69 | 22–70 | 110/150 (73.3%) | HPV16 (26.7%), HPV18 (7.3%), HPV51 (5.3%), HPV39 (6.0%), HPV52 (2.7%) | 60/72 (83.3%) | HPV16 (51.4%), HPV18 (9.7%), HPV51 (5.6%), HPV52 (5.6%), HPV33 (2.8%), HPV35 (2.8%), HPV39 (2.8%) | 43/49 (87.8%) | HPV16 (61.2%), HPV18 (4.1%), HPV39 (4.1%), HPV33 (2.1%), HPV51 (2.1%), HPV52 (2.1%) |
| **Lee SA, Cancer Lett 2003; 198: 187** | Case control study among women visited for routine cervical cancer screen at the Department of Obstetrics and Gynecology in Seoul National University Hospital (1992–1995). | PCR–DNA CHIP (GPd5 +/GP6d+); TS HPVs 6/11/16/18/31/33/34/35/39/40/42/43/44/45/51/52/56/58/59/66/68/69 | – | – | – | – | – | 52/68 (76.5%) | HPV16 (42.6%), HPV18 (8.8%), HPV35 (5.9%), HPV58 (4.4%), HPV 31 (2.9%), HPV33 (2.9%), HPV45 (2.9%), HPV58 (2.9%) |
| **Shin HR, Int J Cancer 2003; 103: 413** | Cohort study (population–based) survey in Busan (1999–2000). | PCR–GP5 + /6 + , EIA HPVs 6/11/16/18/26/31/33/34/35/39/40/42/43/44/45/51/52/53/54/55/56/57/58/59/61/66/68/70/71/72/73/81/82/83/84 | 20–74 | 9/17 (52.9%) | HPV66 (17.6%), HPV16 (5.9%), HPV 33 (5.9%), HPV35 (5.9%) | – | – | – | – |
| **Hwang TS, Gynecol Oncol 2003; 90: 51** | Cohort study among consecutive women visited at the Department of Obstetrics and Gynecology, Inha University Hospital, (Incheon). | PCR–GDP5 + /GDP6D+ , TS HPVs16/18/31/33/35 /52b/58 and PCR–DNA CHIP (GPd5 +/Gp6d+); TS HPVs 6/11/16/18/31/33/34/35/39/40/42/43/44/45/51/52/56/58/59/66/68/69/ | – | 17/24 (70.8%) | HPV16 (16.7%), HPV18 (16.7%), HPV39 (8.4%), HPV35 (4.2%), HPV51 (4.2%), HPV52 (4.2%), HPV56 (4.2%), HPV66 (4.2%) | 59/73 (80.8%) | HPV16 (24.7%), HPV58 (13.7%), HPV31 (12.3%), HPV33 (11.0%), HPV35 (6.8%) | 65/72 (90.3%) | HPV16 (52.8%), HPV33 (12.5%), HPV58 (8.3%), HPV18 (4.2%), HPV35 (4.2%) |

(*continued on next page*)

Table 2 (*continued*)

| Reference | Study design | HPV detection and targeted HPVs | Age range (years) | HPV Prevalence | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Low–grade lesions | | High–grade lesions | | Cervical cancer | |
| | | | | Any HPV (%) | 5 most frequent reported HPVs (%) | Any HPV (%) | 5 most frequent reported HPVs (%) | Any HPV (%) | 5 most frequent reported HPVs (%) |
| **Hwang HS, Cancer Epidemiol Biomarkers Prev 2004; 13: 2153** | Cross–sectional study among women visited at regional hospitals in Korea for Pap smear (2002–2003). | PCR–DNA CHIP (hpv1/2); TS HPVs 6/11/16/18/31/33/34/35 /39/40/42/43/44/45/51/52/56/58/59/66/68/69/ | 18–62 | 116/168 (69.0%) | HPV16 (8.9%), HPV51 (10.7%), HPV52 (7.1%), HPV58 (6.0%)[a] | 59/66 (89.4%) | HPV16 (34.8%), HPV58 (13.6%), HPV52 (6.1%), HPV51 (4.6%)[a] | – | – |
| **An HJ, Mod Pathol 2005; 18: 528**[b] | Cross–sectional retrospective (population–based) study including cervical cancer specimens retrieved from 15 korean institutes (1997–2001). | Other PCR–E6, E7 consensus primers; TS HPVs 16/18/31/33 and PCR–DNA CHIP ( GPd5 +/Gp6d+); TS HPVs 6/11/16/18/31/33/34/35 /39/40/42/43/44/45/51/52/56/58/59/66/68/69/ | – | – | – | – | – | 121/135 (90.0%) | HPV16 (44.4%), HPV18 (32.5%), HPV33 (4.4%), HPV45 (0.7%), HPV59 (0.7%), HPV68 (0.7%) |
| **Lee HS, Int J Gynecol Cancer 2007; 17: 497**[c] | Cohort study among women referred to the Department of Gynecologic Oncology at Chonnam National University Hospital (Gwangju) | PCR–DNA CHIP (GPd5 +/GP6d+); TS HPVs 6/11/16/18/31 /33/34/35/39/40/42/43/44/45/51/52/53/54/56/58/59/66/68/69/70 | 20–82 | 124/167 (74.2%) | HPV16 (19.2%), HPV53 (11.4%), HPV52 (10.8%), HPV18 (10.2%), HPV58 (7.1%) | 322/381 (84.5%) | HPV16 (41.7%), HPV58 (17.1%), HPV33 (11.3%), HPV31 (7.9%), HPV18 (5.3%) | 133/160 (83.1%) | HPV16 (51.9%), HPV18 (18.8%), HPV58 (5.6%), HPV33 (3.1%), HPV35 (2.4%) |
| **Tong SY, Int J Gynecol Cancer 2007; 17: 1307** | Retrospective cross–sectional study among women with cervical cancer treated at the Department of Obstetrics and Gynecology of the KangnamSt Mary's Hospital, Catholic University (2001–2004). | PCR–DNA CHIP; TS HPVs 6/11/16/18/31/33/34/35/39/40/42/43/44/45/51/52/56/58/59/66/68/69 | 25–79 | – | – | – | – | 79/97 (81.5%) | HPV16 (51.5%), HPV18 (11.3%), HPV33 (8.2%), HPV35 (5.2%), HPV66 (30.9%) |
| **Song ES, J Korean Med Sci 2007; 22: 99** | Cohort study among consecutive women visited the Department of Obstetrics and Gynecology, Inha University Hospital (Incheon)(2003). | PCR–DNA CHIP; TS HPVs 6/11/16/18/31/33/34/35/39/40/42/43/44/45/51/52/56/58/59/66/68/69 | 26–77 | – | – | – | – | 26/29 (89.7%) | HPV16 (65.5%), HPV18 (6.9%), HPV33 (6.9%), HPV31 (3.4%), HPV51 (3.4%) |
| **Kim JY, J Clin Oncol 2009; 27: 5088** | Cohort study among women with cervical cancer, treated at the National Cancer Center, (Goyang–Gyeonggi) (2003–2006). | HC2, PCR-SPF10, EIA HPVs 6/11/16/18/31 /33/40/45/51/53/54/58/59/66/68/70 | 23–80 | – | – | – | – | 154/169 (92.2%) | HPV16 (66.5%), HPV18 (11.2%)[a] |
| **Kang WD, Int J Gynecol Cancer 2009; 19: 924**[d] | Cohort study among women visited for routine cervical screening at the Department of Obstetrics and Gynecology of Chonnam National University Hospital (Gwangju) (2002–2006). | HC2, PCR-SPF10, EIA HPVs 6/11/16/18/31 /33/40/45/51/53/54/58/59/66/68/70 | 21–69 | 90 | HPV16 (17.8%), HPV53 (12.2%), HPV58 (8.9%), HPV18 (7.8%), HPV52 (6.7%) | 317 | HPV16 (39.7%), HPV58 (22.7%), HPV31 (9.5%), HPV18 (7.6%), HPV33 (7.6%) | 198 | HPV16 (53.5%), HPV18 (24.7%), HPV58 (17.7%), HPV33 (2.5%), HPV31 (2.0%), HPV53 (2.0%) |
| **Oh JK, Asian Pac J Cancer Prev 2010; 11: 993** | Retrospective cross–sectional study on FFPE cervical cancer specimens from pathology archives from National Medical Center (Seoul) and Dong–A University Hospital (Busan) (1958–2004). | PCR–SPF10, EIA HPVs 6/11/16/18/31/33/34/35/39/40/42/43/44/45/51/52/53/54/56/58/59/66/68/70/74 | – | – | – | – | – | 674/742 (90.8%) | HPV16 (59.1%), HPV18 (8.4%), HPV33 (5.4%), HPV31 (4.2%), HPV58 (3.9%) |
| **Kim J, Int J Gynecol Cancer 2012; 22: 1570**[c] | Case–control (hospital based) study among women attending a healthcare center in the Gangnam area of Seoul (2003–2008). | PCR–GP5+/6+ & MY09/11; TS HPVs 16/18 /31/33/35/39/45/51/52/53/56/58/59/66/68/69 | 25–75 | – | – | – | – | 100/104 (96.2%) | HPV16 (66.3%), HPV18 (13.5%), HPV31 (7.7%), HPV33 (6.7%), HPV58 (3.8%), HPV66 (3.8%) |

(*continued on next page*)

**Table 2** (*continued*)

| Reference | Study design | HPV detection and targeted HPVs | Age range (years) | HPV Prevalence | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Low–grade lesions | | High–grade lesions | | Cervical cancer | |
| | | | | Any HPV (%) | 5 most frequent reported HPVs (%) | Any HPV (%) | 5 most frequent reported HPVs (%) | Any HPV (%) | 5 most frequent reported HPVs (%) |
| **Kim MJ, Obstet Gynecol Sci 2013; 56: 110**[c] | Retrospective cross–sectional study among consecutive women visited at Seoul National University Hospital Healthcare System Gangnam Center for a routine health check–up (2008–2010). | PCR–DNA CHIP; TS HPVs 6/11/16/18/31/33/34/35/39/40/42/43/44/45/51/52/56/58/59/53/54/66/68/70 | – | 208/311 (68.0%) | HPV52 (8.4%), HPV16 (7.4%), HPV58 (6.8%), HPV56 (4.1%), HPV18 (3.2%), HPV39 (3.2%) | 19/22 (86.4%) | HPV31 (13.6%), HPV58 (13.6%), HPV18 (9.1%), HPV16 (4.5%), HPV33 (4.5%), HPV35 (4.5%), HPV45 (4.5%), HPV51 (4.5%), HPV56 (4.5%)[e] | – | – |
| **Quek SC, Int J Gynecol Cancer 2013; 23: 148** | International cross–sectional (hospital–based) study on FFPE cancer specimens from 5 Asian countries, including South Korea (2007–2009). | PCR–SPF10, EIA HPVs 6/11/16/18/31/33/34/35/39/40/42/43/44/45/51/52/53/54/56/58/59/66/68/70/74 | > 21 | – | – | 100/100 (100.0%) | HPV16 (39.0%), HPV52 (17.0%), HPV58 (16.0%), HPV31 (12.0%), HPV51 (12.0%) | 93/97 (95.9%) | HPV16 (56.4%), HPV18 (12.4%), HPV33 (6.2%), HPV52 (5.1%), HPV31 (3.1%) |
| **Kahng J, Ann Lab Med 2014; 34: 127** | Cohort study among patients treated at the Catholic University Bucheon St. Mary's Hospital (2011–2012). | PCR–DNA CHIP (MY and gp); TS HPVs 6/11/16/18 /31/34/33/35/39/40/42/43/44/45/51/52/56/58/59/66/68/69 | 16–78 | – | – | – | HPV16 (43.0%), HPV58 (18.0%), HPV52 (9.0%), HPV18 (8.0%), HPV33 (8.0%)[g] | – | – |
| **So KA, J Cancer Prev. 2016 Jun;21(2):104** | Cohort study among women examined at a health promotion center of the Korea University Guro Hospital (Seoul) (2013). | Real-time PCR; HPVs 6/11/16/18/26/31/33/35/39/40/42/43/44/45/51/52/53/5456/58/59/61/66/68/69/70/73/82 | 20–99 | 55/67 (82.1%) | – | 14/15 (93.3%) | – | – | – |
| **Nah EH, Ann Lab Med 2017;37:426**[d] | Retrospective cross–sectional study among women attending Health Promotion Centres for cervical cancer screen in 13 Korean cities (2014–2015). | Real-time PCR; HPVs 6/11/16/18/31/33/35/39/40/42/43/44/45/51/52/54/56/58/59/61/68/66/26/53/69/70/73/82 | 20–99 | 160/178 (89.9%) | HPV53 (19.1%), HPV51 (12.9%), HPV56 (12.9%), HPV52 (10.7%), HPV66 (10.7%), | 93/94 (98.9%) | HPV58 (22.3%), HPV16 (18.1%), HPV33 (17.0%), HPV52 (12.8%), HPV 31 (8.5%), HPV51 (8.5%), HPV53 (8.5%)[e] | – | – |
| **Ouh YT, J Gynecol Oncol. 2018; 29(1): e14**[c] | Retrospective study among women attending 7 centres nationwide from a private Korean Medical Institute for ginecological examination. Specimens and data from Korea University Guro Hospital ( (2014–2016). | PCR Microarray; HPVs 6/11/16/18/26/31/32/33/34/35/39/40/42/43/44/45/51/52/53/54/55/56/58/59/62/66/68/69/70/73/81/83 Or Real-time PCR; HPVs 6/11/16/18/26/31/33/35/39/40/42/43/44/45/51/52/53/54/56/58/59/61/66/68/69/70/73/82 | 17–83 | 113/151 (74.8%) | HPV58 (17.4%), HPV53 (13.2%), HPV56 (12.0%), HPV51 (8.4%), HPV39 (7.8%) | 45/50 (90.0%)[h] | HPV6 (24.6%), HPV52 (13.9%), HPV58 (12.3%), HPV31 (7.7%), HPV35 (7.7%) | | |

"HPV": Human papillomavirus; "95% CI": 95% Confidence Interval; "Low–grade lesions": LSIL or CIN–1; "High–grade lesions": CIN–2, CIN–3, CIS or HSIL; "HR": High risk.
The samples for HPV testing come from cervical specimens (fresh/fixed biopsies or exfoliated cells).
(f) Women from the general population, including some with cytological cervical abnormalities.
[a] Only type specific prevalence for these HR HPV.
[b] Only cases of cervical adenocarcinoma.
[c] Any HPV prevalence and type specific prevalence for HR HPV.
[d] Type specific prevalence for HR HPV.
[e] Includes 2 cases with squamous cell carcinoma.
[g] Includes carcinoma.
[h] Includes 11 cases with ASC-H.

**Table 3**
Burden of cancer in anatomical sites related to HPV, in the Republic of Korea, compared to Eastern Asia.
Data sources: [2].

| | | | Republic of Korea | | | Eastern Asia | | |
|---|---|---|---|---|---|---|---|---|
| | | | N | Crude rate[a] | ASR[a] | N | Crude rate[a] | ASR[a] |
| **Cervix** | **Incidence** | | 3348 | 13.10 | 8.40 | 126,874 | 15.70 | 10.90 |
| | **Mortality** | | 1029 | 4.00 | 2.00 | 54,547 | 6.80 | 4.10 |
| **Anus** | **Incidence** | **Overall** | 334 | 0.65 | 0.34 | 6464 | 0.39 | 0.24 |
| | | **Female** | 182 | 0.71 | 0.35 | 3222 | 0.40 | 0.23 |
| | | **Male** | 152 | 0.59 | 0.34 | 3242 | 0.38 | 0.25 |
| | **Mortality** | **Overall** | 90 | 0.18 | 0.08 | 2900 | 0.18 | 0.10 |
| | | **Female** | 51 | 0.20 | 0.07 | 1104 | 0.14 | 0.08 |
| | | **Male** | 39 | 0.15 | 0.08 | 1796 | 0.21 | 0.13 |
| **Vagina** | **Incidence** | | 96 | 0.38 | 0.19 | 2121 | 0.26 | 0.16 |
| | **Mortality** | | 24 | 0.09 | 0.04 | 843 | 0.10 | 0.06 |
| **Vulva** | **Incidence** | | 143 | 0.56 | 0.28 | 4512 | 0.56 | 0.31 |
| | **Mortality** | | 35 | 0.14 | 0.05 | 1495 | 0.19 | 0.10 |
| **Penis** | **Incidence** | | 86 | 0.34 | 0.19 | 5082 | 0.60 | 0.39 |
| | **Mortality** | | 20 | 0.08 | 0.05 | 1792 | 0.21 | 0.13 |
| **Oropharynx** | **Incidence** | **Overall** | 735 | 1.40 | 0.81 | 10,195 | 0.62 | 0.39 |
| | | **Female** | 84 | 0.33 | 0.18 | 1914 | 0.24 | 0.14 |
| | | **Male** | 651 | 2.50 | 1.50 | 8281 | 0.98 | 0.64 |
| | **Mortality** | **Overall** | 176 | 0.34 | 0.18 | 4659 | 0.28 | 0.17 |
| | | **Female** | 17 | 0.07 | 0.03 | 763 | 0.09 | 0.05 |
| | | **Male** | 159 | 0.62 | 0.35 | 3896 | 0.46 | 0.29 |
| **Lip, Oral cavity** | **Incidence** | **Overall** | 1543 | 3.00 | 1.70 | 47,532 | 2.90 | 1.08 |
| | | **Female** | 594 | 2.30 | 1.20 | 16,458 | 2.00 | 1.20 |
| | | **Male** | 949 | 3.70 | 2.20 | 31,074 | 3.70 | 2.40 |
| | **Mortality** | **Overall** | 586 | 1.10 | 0.56 | 21,062 | 1.30 | 0.75 |
| | | **Female** | 225 | 0.88 | 0.36 | 7310 | 0.91 | 0.47 |
| | | **Male** | 361 | 1.40 | 0.08 | 13,752 | 1.60 | 1.00 |
| **Larynx** | **Incidence** | **Overall** | 1120 | 2.20 | 1.20 | 34,409 | 2.10 | 1.30 |
| | | **Female** | 50 | 0.20 | 0.09 | 3478 | 0.43 | 0.25 |
| | | **Male** | 1070 | 4.20 | 2.40 | 30,931 | 3.70 | 2.40 |
| | **Mortality** | **Overall** | 369 | 0.72 | 0.33 | 17,630 | 1.10 | 0.62 |
| | | **Female** | 43 | 0.17 | 0.06 | 2618 | 0.32 | 0.18 |
| | | **Male** | 326 | 1.30 | 0.69 | 15,012 | 1.80 | 1.10 |

"N": number of cases; "ASR": Age-standardized rate.
[a] Rates per 100,000 persons.


**Fig. 1.** Age–specific incidence and mortality rates from cervical cancer in the Republic of Korea, in 2015..
Data sources [1]

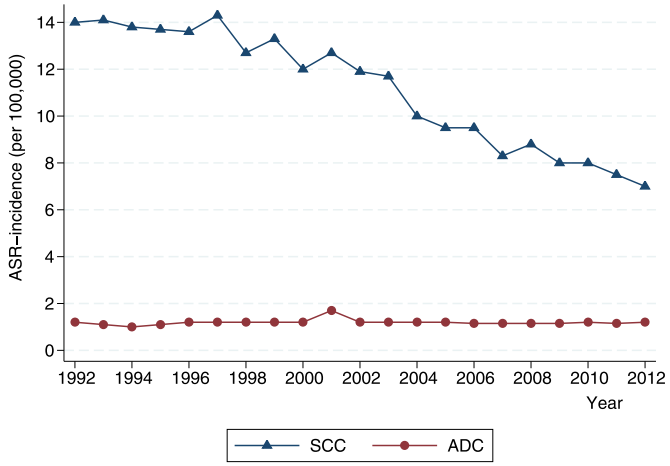


**Fig. 2.** Trends in cervical cancer incidence in the Republic of Korea, by histology. "SCC": Squamous cell carcinoma; "ADC": Adenocarcinoma; "ASR": Age-standardized rate..
Data sources: Adapted from [1,26]

SCC (7.0%, 5.7–8.7% and 1.9%, 1.2–2.9, respectively) [22]. Variations in prevalence and type distribution have been observed among individual studies (Table 2).

### 3.3.3. Survival

Population-based cancer survival estimates reflect the average prognosis for a given cancer type, but data on cancer survival is scarce in Korea. Data from the KCCR reports an overall 5-year relative survival rate for all cancers increasing from 41.2% in 1993–1995, to 70.7% in 2011–2015. Specifically for cervical cancer, the 5-year relative survival has remained quite stable since 1993, (77.5% in 1993–1995, to 80.0% in 1996–2000, 81.4% in 2001–2005, 80.5% in 2006–2010 and 79.9% in 2011–2015) [1]. These data are in accordance with SurCan database [28].

Considerable variation in cervical cancer survival rates are observed

across age, stage at diagnosis and histology in Korea. Five-year relative survival is highest for localized disease (91.1%) and lowest for distant stage cancers (25.8%) and remains consistent across age groups. With regard to age at the diagnosis, 5-year relative survival is highest in women aged 20–64 (> 90.0% for localized stage, > 70.0% for regional stage and > 30.0% for distant stage), and lowest in women aged 75 and older (63.2% for localized stage, 48.6% for regional stage and 9.4% for distant stage). In addition, 5-year relative survival is higher in SCC than in ADC regardless of stage at diagnosis [26,29].

### 3.4. Other anogenital cancers and precancerous lesions

In addition to cervical cancer, HPV is responsible for a substantial number of other anogenital cancers. Globally, low age-standardized incidence rates are observed for these cancers in Korea (0.7 cases per 100,000), although data is still limited [7].

#### 3.4.1. Anal cancer and precancerous lesions

Anal cancer is rare in the general population but is reported to be increasing in more developed regions [7]. This is probably linked to several risk factors such as changes in sexual behaviour that increases the risk of HPV exposure in the anal canal [30]. An estimated 334 new cases and 90 new deaths are diagnosed annually in Korea, with differences by sex (estimates for 2018). Crude incidence and mortality rates of anal cancer were 0.65 and 0.18 per 100,000, respectively. Age-standardized incidence and mortality rates of 0.34 and 0.08 per 100,000 were observed in Korea, compared to 0.24 and 0.10 per 100,000 in Eastern Asia (Table 3) [2].

Anal cancer is similar to cervical cancer with respect to overall HPV DNA positivity, with approximately 88.0% (85.1–91.0%) of anal cancer cases and 95.3% (84.2–99.4%) of high-grade precancerous anal lesions (AIN2/3) associated with HPV infection worldwide [12]. Worldwide, HPV16 is the most common type in both lesions. Limited data is available in Korea, with HPV prevalence in anal cancer ranging from 74.5% to 100.0% and with HPV16 being the dominant type [12,31,32] (Table 4).

Regarding survival of anal cancer, data from a recent population-based study in Korea showed that overall 5-year survival increased from 38.9% (period 1993–1995) to 65.6% (period 2006–2010) [33]. The increase was consistent across histological types.

#### 3.4.2. Vaginal cancer and precancerous lesions

Vaginal cancer is also a rare malignancy that shares similar risk factors with cervical cancer. It is generally accepted that both carcinomas share the same aetiology of HPV infection although limited evidence is available. Most vaginal cancers are classified as SCC (90–95% of cases). An estimated 96 new vaginal cancer cases and 24 new deaths are diagnosed annually in Korea (estimates for 2018), with crude incidence and mortality rates of 0.38 and 0.09 per 100,000 women, respectively. Age-standardized incidence and mortality rates in Korea (0.19 and 0.04 per 100,000) were similar to those in Eastern Asia (0.16 and 0.06 per 100,000) (Table 3) [2].

Worldwide, HPV DNA is detected among 74.3% (69.7–78.4) of vaginal carcinomas and 95.8% of high-grade vaginal intraepithelial neoplasia (VaIN2/3), with HPV16 being the most common type [11]. Information at this cancer site is scarce in Korea, limited to one study that estimated an HPV prevalence of 71.7% (57.5–82.7) in vaginal cancer and 100.0% (77.2–100.0) in VaIN2/3, with HPV16 being the most common type [11] (Table 4).

At the time of the review, no large-scale population-based studies of incidence, mortality, or survival of vaginal cancer has been conducted in Korea.

#### 3.4.3. Vulvar cancer and precancerous lesions

Malignancies of the vulva are also rare among women worldwide. About 60.0% of all vulvar cancer cases occur in more developed countries. Regarding histology, basaloid/warty lesions generally affect young women, and are very often associated with HPV DNA detection (75–100%). Keratinizing vulvar carcinoma is the most frequent histology (over 60%), occurs more often in old women and is more rarely associated with HPV [34]. An estimated 143 new vulvar cancer cases and 35 new deaths are diagnosed annually in Korea (estimates for 2018), with crude incidence and mortality rates of 0.56 and 0.14 per 100,000 women, respectively. In Korea, age-standardized incidence and mortality rates were 0.28 and 0.15 per 100,000, compared to 0.31 and 0.10 per 100,000 in Eastern Asia (Table 3) [2].

Worldwide, HPV DNA is detected in 28.6% (26.5–30.8) of vulvar carcinomas and 86.7% (84.0–89.4) in high-grade vulvar intraepithelial neoplasia (VIN2/3), with HPV16 being the most common type [10]. Particularly in Korea, only one study estimated an HPV prevalence of 28.7% (22.7–35.6) in vulvar cancer and 100.0% (83.9–100.0) in VIN2/3, with HPV16 being the most common type [10] (Table 4).

No population-based study of incidence, mortality or survival of vulvar cancer has been conducted in Korea.

#### 3.4.4. Penile cancer and precancerous lesions

Malignancies of the penis are rare among men worldwide. Incidence rates are higher in less developed countries and generally affect men aged 50–70. Over 95% of invasive penile cancers are SCC (subtypes: 49% keratinizing, 17% mixed warty-basaloid, 8% verrucous, 6% warty and 4% basaloid). HPV is most commonly detected in basaloid and warty tumours [34]. In Korea, an estimated 86 new penile cancer cases and 20 new deaths are diagnosed annually (estimates for 2018), with crude incidence and mortality rates of 0.34 and 0.08 per 100,000 men, respectively. Age-standardized incidence and mortality rates in Korea (0.19 and 0.05 per 100,000, respectively) were lower than those in Eastern Asia (0.39 and 0.13 per 100,000, respectively) (Table 3) [2].

Worldwide, HPV DNA is detected in approximately 33.1% (30.2–36.1) of all penile cancers and 87.1% (78.0–93.4) of high-grade penile intraepithelial neoplasia (PeIN2/3), with HPV16 being the most common type [13]. Particularly in Korea, only one study estimated an HPV prevalence of 10.7% (2.3–28.2) in penile cancer and 100.0% (29.2–100.0) in PeIN2/3, with HPV16 being the most common type [13] (Table 4).

No population-based study of incidence, mortality or survival of vulvar cancer has been conducted in Korea.

### 3.5. Head and neck cancer

Although smoking and alcohol consumption has been classically regarded as the major etiological factors in head and neck cancers, HPV has been recently found to cause an epidemiologically and clinically distinct form of head and neck cancer, particularly at the oropharynx, and to a weaker extent, oral cavity and larynx [34]. Moreover, the incidence of HPV-related head and neck cancers is sharply increasing worldwide, and is associated with lifestyle, including sexual behaviour, and is rapidly changing in Korea from a “conservative Asian” to a more open “Western” style.

Particularly in Korea, an estimated 735 new cases and 176 new deaths are diagnosed annually at the oropharynx (estimates for 2018), 1120 new cases and 369 new deaths at the larynx, and 1543 new cases and 586 new deaths at the lip and oral cavity, with differences by sex (Table 3). Crude incidence and mortality rates at the oropharynx were 1.4 and 0.34 per 100,000 respectively, at the larynx were 2.2 and 0.72 per 100,000 respectively, and at the lip and oral cavity were 3.0 and 1.1 per 100,000 respectively. In Korea, age-standardized incidence and mortality rates were 0.81 and 0.18 per 100,000 respectively, at the oropharynx, 1.70 and 0.56 at the lip and oral cavity, and 1.20 and 0.33 at the larynx. In Eastern Asia, age-standardized incidence and mortality rates were 0.39 and 0.17 per 100,000 respectively, at the oropharynx, 1.08 and 0.75 at the lip and oral cavity, and 1.30 and 0.62 at the larynx [2].

**Table 4**
HPV prevalence among anogenital cancer cases and precancerous high–grade lesions in the Republic of Korea, by study.

| Reference | Study design | HPV detection and targeted HPVs | Sex | N | Prevalence | | |
|---|---|---|---|---|---|---|---|
| | | | | | % | 95%CI | 5 most frequent HPVs (%) |
| **ANAL CANCER** | | | | | | | |
| Alemany L, Int J Cancer 2015; 136: 98[a] | Retrospective cross–sectional study. FFPE specimens (496) from pathology archives in 24 countries (1986–2011). | PCR–SPF10, EIA HPVs 6/11/16/18/26/30/31/33/34/35/39/40/42/43/44/45/51/52/53/54/56/58/59 /61/66/67/68/69/70/73/74/82/83/87/89/91 | Both | 52 | 80.8 | (68.1–89.2) | HPV16 (67.3%), HPV18 (3.8%), HPV35 (3.8%), HPV56 (1.9%), HPV58 (1.9%) |
| Yhim HY, Int J Cancer 2011; 129: 1752 | Retrospective cross–sectional study. FFPE specimens from patients from four Korean institutions (1998–2009). | PCR–DNA CHIP, TS HPVs 6/11/16/18/31/33/34/35/39/40/42/43/44/45/51/52/56/58/59/66/68/69 | Both | 47 | 74.5 | (60.5–84.7) | HPV16 (66.0%), HPV58 (6.4%), HPV35 (2.1%) |
| Youk EG, Dis Colon rectum 2001; 44: 236 | Retrospective cross–sectional study. FFPE specimens from patients treated at Seoul National University Hospital (1989–1998). | PCR–MY09/11, PCR–L1C1/C2, PCR–E6, PCR–E7, TS HPVs 16/18 | Both | 21 | 100 | (84.5–100.0) | HPV16 (100.0%) |
| **VULVAR CANCER** | | | | | | | |
| de Sanjosé S, Eur J Cancer 2013; 49: 3450[b] | Retrospective cross–sectional study. FFPE specimens (1709) from pathology archives in 39 countries (1980–2011). | PCR–SPF10, EIA HPVs 6/11/16/18/26/30/31/33/34/35/39/40/42/43/44/45/51/52/53/54/56/58/59/61/66/67/68/69/70/73/74/82/83/87/89/91 | Female | 188 | 28.7 | (22.7–35.6) | HPV16 (18.1%), HPV18 (1.6%), HPV44 (1.6%), HPV45 (1.1%), HPV52 (1.1%) |
| **VIN2/3** | | | | | | | |
| de Sanjosé S, Eur J Cancer 2013; 49: 3450[b] | Retrospective cross–sectional study. FFPE specimens (587) from pathology archives in 39 countries (1980–2011). | PCR–SPF10, EIA HPVs 6/11/16/18/26/30/31/33/34/35/39/40/42/43/44/45/51/52/53/54/56/58/59/61/66/67/68/69/70/73/74/82/83/87/89/91 | Female | 20 | 100 | (83.9–100.0) | HPV16 (80.0%), HPV6 (5.0%), HPV18 (5.0%), HPV33 (5.0%), HPV35 (5.0%) |
| **VAGINAL CANCER** | | | | | | | |
| Alemany L, Eur J Cancer 2014; 50: 2846[c] | Retrospective cross–sectional study. FFPE specimens (408) from pathology archives in 31 countries (1986–2011). | PCR–SPF10, EIA HPVs 6/11/16/18/26/30/31/33/35/39/42/45/51/52/53/56/58/59/66/67/68/69/73/82 | Female | 46 | 71.7 | (57.5–82.7) | HPV16 (41.3%), HPV33 (4.3%), HPV68 (4.3%), HPV18 (2.2%), HPV26 (2.2%) |
| **VaIN2/3** | | | | | | | |
| Alemany L, Eur J Cancer 2014; 50: 2846 | Retrospective cross–sectional study. FFPE specimens (189) from pathology archives in 31 countries (1986–2011). | PCR–SPF10, EIA HPVs 6/11/16/18/26/30/31/33/35/39/42/45/51/52/53/56/58/59/66/67/68/69/73/82 | Female | 13 | 100 | (77.2–100.0) | HPV16 (53.8%), HPV52 (15.4%), HPV59 (15.4%), HPV45 (7.7%), HPV73 (7.7%) |
| **PENILE CANCER** | | | | | | | |
| Alemany L, Eur Urol. 2016;69:953 | Retrospective cross–sectional study. FFPE specimens (1010) from pathology archives in 25 countries (1983–2011). | PCR–SPF10, EIA HPVs 6/11/16/18/26/30/31/33/35/39/42/45/51/52/53/56/58/59/66/67/68/69/73/82 | Male | 28 | 10.7 | (2.3–28.2) | HPV16 (3.6%), HPV33 (3.6%), HPV35 (3.6%) |
| **PeIN2/3** | | | | | | | |
| Alemany L, Eur Urol. 2016;69:953 | Retrospective cross–sectional study. FFPE specimens (85) from pathology archives in 25 countries (1983–2011). | PCR–SPF10, EIA HPVs 6/11/16/18/26/30/31/33/35/39/42/45/51/52/53/56/58/59/66/67/68/69/73/82 | Male | 3 | 100 | (29.2–100.0) | HPV16 (100.0%) |

"HPV": Human papillomavirus; "95% CI": 95% Confidence Interval; "EIA": Enzyme ImmunoAssay; "PCR": Polymerase Chain Reaction; "SPF": Short Primer Fragment; "TS": Type Specific; "FFPE": formalin-fixed paraffin-embedded; "RT": radiotherapy; "CCRT": concurrent chemoradiotherapy.

[a] Includes cases from Bangladesh, India and The Republic of Korea.

[b] Includes cases from Bangladesh, India, Israel, The Republic of Korea, Kuwait, Lebanon, Philippines, Taiwan and Turkey.

[c] Includes cases from Australia, Bangladesh, India, Israel, The Republic of Korea, Kuwait, Philippines, Taiwan and Turkey.

**Table 5**
HPV prevalence among head and neck cancer cases in the Republic of Korea, by study.

| Reference | Study design | HPV detection and targeted HPVs | Sex | N | Prevalence | | |
|---|---|---|---|---|---|---|---|
| | | | | | % | 95%CI | 5 most frequent HPVs (%) |
| **Oral cavity cancer** | | | | | | | |
| Shin KH, Int J Oncol 2002; 21: 297 | Cross–sectional study. Specimens from patients from Seoul National University Dental Hospital. | TS–PCR E6, TS HPVs 16/18/33 | Male | – | 9.2 | (4.5–17.8) | HPV18 (6.6%), HPV16 (1.3%) HPV33 (1.3%) |
| Shin KH, Int J Oncol 2002; 21: 297 | Cross–sectional study. Specimens from patients from Seoul National University Dental Hospital | TS–PCR E6, TS HPVs 16/18/33 | Female | – | 5.3 | (2.1–12.8) | HPV16 (3.9%), HPV18 (3.9%) HPV33 (1.3%) |
| Shin KH, Int J Oncol 2002; 21: 297 | Cross–sectional study. Specimens from patients from Seoul National University Dental Hospital | TS–PCR E6, TS HPVs 16/18/33 | Both | 76 | 14.5 | (8.3–24.1) | HPV18 (10.5%), HPV16 (5.3%), HPV33 (2.6%) |
| **Oropharyngeal cancer** | | | | | | | |
| Oh TJ, J Clin Microbiol 2004; 42: 3272 | Retrospective cross–sectional study. FFPE tonsillar SCC tissues. | PCR–MY09/MY11 (L1) and HMB01 (L1) Microarray hybridization HPVs 6/11/16/18/31/33/34/35/39/40/42/43/44/45/51/52/54/56/58/59/62/66/67/68/69/70/72 | Both | 39 | 64.1 | (48.4–77.3) | HPV16 (59.0%), HPV6 (2.6%) HPV33 (2.6%), HPV58 (2.6%) |
| Kim SH, Int J Cancer 2007; 120: 1418 | Retrospective cross–sectional study. FFPE tonsillar SCC specimens from the Yonsei University Medical College Department of Pathology and Head and Neck Oncology Division of otorhinolaryngology (1995–2005). | RT–PCR E2/E6, DNA CHIP; TS HPVs 6/11/16/18/31/33/34 35/39/40/42/43/44/45/51/52/56/58/59/66/68/69 | Both | 52 | 73.1 | (59.7–83.2) | HPV16 (65.4%), HPV18 (1.9%), HPV33 (1.9%), HPV35 (1.9%), HPV58 (1.9%) |
| Park WS, Head Neck. 2012;34:1408 | Retrospective cross–sectional study. FFPE specimens from patients with resectable oropharyngeal SCC at the National Cancer Center, Goyang (2002–2007). | PCR–DNA CHIP; TS HPVs 6/11/16/18/31/33/34/35/39/40/42/43/44/45/51/52/53/54/56/58/59/66/68/70 | Both | 86 | 43.0a | (32.8–53.7) | – |
| No JH, Cancer. 2015;121:535 | Retrospective cross–sectional study. FFPE tonsillar carcinoma tissues recruited from 3 Seoul National University Hospital (1998–2008), Asan Medical Center (1991–2005) and Korea Cancer Center Hospital (1994–2009) | PCR HPV L1 & E6/E7 (42 HPVs; 14–HR–VPHs 16/18/31/33/35/39/45/51/52/56/58/59/68/82) | Both | 175 | 35.4 | (28.4–43.0) | HPV16 (10.3%), HPV18 (10.3%) |
| Castellsague X, J Natl Cancer Inst. 2016;108 | Retrospective cross–sectional study. FFPE specimens (1090) from pathology archives in 29 countries (1986–2011). | PCR–SPF10, EIA HPVs 6/11/16/18/26/30/31/33/35/39/42/45/51/52/53/56/58/59/66/67/68/69/73/82) | Both | 85 | 23.5 | (15.0–34.0) | HPV16 (22.3%) |

"HPV": Human papillomavirus; "95% CI": 95% Confidence Interval; "PCR": Polymerase Chain Reaction; "TS": Type Specific; "FFPE": formalin–fixed paraffin–embedded; "SCC": squamous cell carcinoma; "HR": High risk; "LR": Low risk.

Regarding data retrieved from the KCCR for the period 1999–2009, oropharyngeal cancer increased significantly over this period (annual percent changes (APC) = 2.4%), particularly in men aged 30–59 (APC = 2.7%), whereas laryngeal and hypopharyngeal cancers markedly decreased in both sexes. Interestingly, tongue cancer increased gradually 2.4% annually in both sexes [35].

Prior studies of head and neck cancers have reported higher incidence rates [36]. However, a broader range of tumour sites was used to define head and neck cancer (including larynx, oral cavity, oropharynx, hypopharynx, nasopharynx, trachea, oesophagus, nasal cavity, and paranasal sinuses).

Globally, in oropharyngeal cancer, variations in HPV DNA detection are observed among countries, with 25.0% (22.5–27.7) of cases attributable to HPV. In oral cavity cancer and laryngeal cancer global HPV DNA detection is 7.4% (6.0–8.9) and 5.9% (4.5–7.5) respectively [14]. At all these cancer sites, HPV16 is the most common type. Limited studies have reported HPV prevalence in head and neck cancers in Korea, ranging from 5.3% to 14.5% in the oral cavity, and from 23.5% to 73.1% in the oropharynx, with HPV16 being the most common type (Table 5) [14,37–41].

### 3.6. Genital warts

Genital warts are common and highly infectious lesions. Although they are not life-threatening, the high infectivity, the high risk of recurrence, and the need of multiple treatments, are associated with a high social and economic impact [42]. Low risk HPV6 and HPV11 are estimated to cause approximately 90.0% of genital warts [4].

Based on the update (until June 2016) of a systematic review of global estimates performed by Patel et al. [43], overall reported annual incidence of new genital warts ranged from 85 to 205 cases per 100,000 in both sexes combined (77–560 in men and 76–790 in women, respectively), with higher incidence in people younger than 30 years (230–790 in both sexes combined, 130–560 in men and 320–1030 in women, respectively) [44]. Particularly in Korea, limited data on the burden of genital warts is available. However, some estimates have been reported recently. A recent cross-sectional study evaluated the prevalence and socio-economic burden of genital warts using national claims data from the Health Insurance Review and Assessment of Korea [45]. In this study the overall prevalence and socio-economic burden of genital warts increased during the last 9 years (in 2015 was 11.6 and 3.6 per 100,000 men and women, respectively), although significant differences were observed by sex. The female prevalence increased until 2012 (highest in females aged 20–29), and decreased thereafter (APC = 3·6%). In contrast, the male prevalence increased continuously over time (APC = 11·6%), especially in those aged 20–49 (Fig. 3). Variations in prevalence have been reported in other Korean studies [46,47].

There is also limited Korean data regarding the prevalence of HPV in genital warts. In a study examining the HPV prevalence in 150 consecutive male patients with histopathologic-confirmed genital warts from a single private clinic, LR-HPV types were detected in 97.0% of cases (only LR-HPV types in 76.5% of cases). In 121 cases (91.7%), HPV6 or HPV11 or both were observed. HPV6 was the most common type (76.5% globally, 50.8% as a single infection and 25.8% as multiple infections) [48].

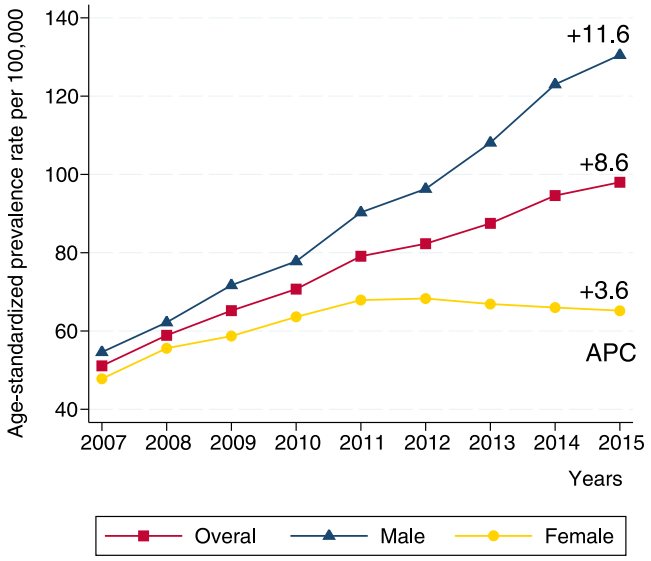


**Fig. 3.** Trends in genital warts prevalence in the Republic of Korea, by sex. "APC": annual percent change Adjusted to residence-registration mid-year population in 2011..
Data sources: Adapted from [45]

## 4. HPV screening and vaccination programme in Korea

### 4.1. Cervical Cancer Prevention Strategies in Korea

#### 4.1.1. Cervical cancer screening programme

In Korea, the Pap smear was first introduced in 1988 in a health examination for industrial workers [49]. In 1999, the National Cervical Cancer Screening Programme (NCCSP) was launched as a part of the National Health Care Screening Programme which supplied Medicaid participants with stomach, breast and cervical cancer screening free-of-charge [49]. The screening programme gradually expanded with including further participants and target cancer sites. Currently, the Korean government operates two population-based cervical screening programmes. The National Health Insurance Service Cancer Screening Programme (NHISCSP), which is offered to National Health Insurance Service (NHIS) beneficiaries in the upper 50% income stratum, and the National Cancer Screening Programme (NCSP), which is offered to NHIS beneficiaries in the lower 50% income stratum and Medical Aid Programme (MAP) recipients. Both programmes use the Pap test as the main screening tool, that is conducted by gynaecologists and provide complimentary biennial cervical cancer screening for all Korean women over the age of 30 [50]. Since 2016, the programme has been expanded to women over the age of 20 [51]. The percentage of women screened, among target population, has increased rapidly, from 41.1% in 2009, 53.0% in 2016 [1,50,52].

#### 4.1.2. National immunization programme (NIP) in Korea and current guidelines for HPV vaccine use

In Korea, the 4-valent HPV vaccine (Gardasil®–VPHs 6/11/16/18) was licensed for females aged 9–26 and males aged 9–15 in June 2007, and expanded for females and males aged 9–26 in December 2011. The 2-valent HPV vaccine (Cervarix™–VPHs 16/18) was licensed for females aged 9–25 in July 2008. In 2014, a 2-dose vaccination schedule was approved for both vaccines for girls and boys aged 9–13 (4-valent HPV) and for girls aged 9–14 (2-valent HPV). The 3-dose schedule was reserved for older subjects and for immunocompromised subjects. In addition, the 9-valent HPV vaccine (Gardasil®9–VPHs 6/11/16/18/31/33/45/52/58) was approved by MFDS in January 2016 [53].

In June 2016, the HPV vaccine (2-valent and 4-valent) was included in the NIP in Korea as a 2-dose schedule (0, 6 months) for 12 year old girls (based on birth cohort). Girls have at least two years to get the opportunity of being vaccinated within the NIP. The selection of the HPV vaccine was based on physician or patient/parent preference [54].

### 4.2. Current status of HPV vaccination in Korea

Since the inclusion of the HPV vaccine into the NIP, 232,203 girls received the first dose of HPV vaccine, which represented almost half (49.9%) of the target cohort in 2016 (data February 2017) [55].

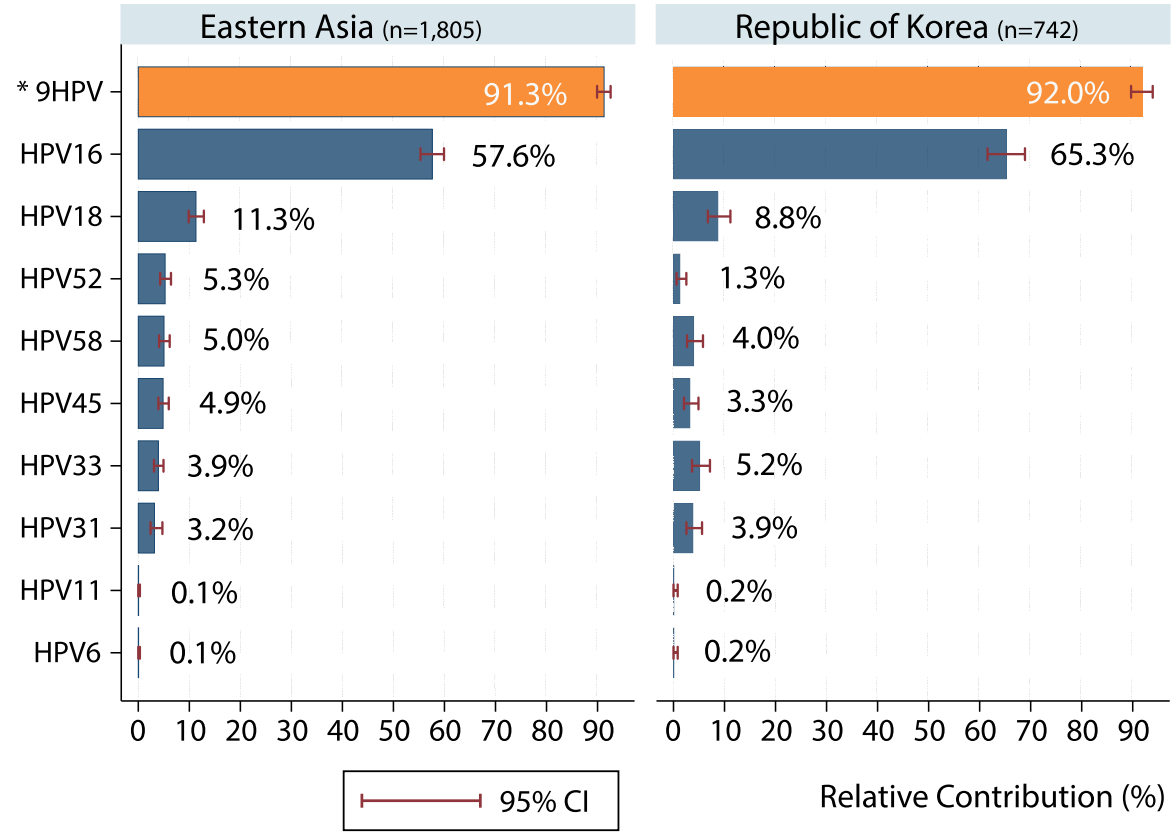


**Fig. 4.** Contribution of HPVs 16/11/18/31/33/45/52/58/6/11 in the Republic of Korea compared to Eastern Asia. "HPV": Human papillomavirus; "95%CI": 95% Confidence Interval; * "9HPV types" includes the ones in 9–valent HPV vaccine: HPVs 16/18/31/33/45/52/58/6/11. Eastern Asia: combined data for the following countries: China, Japan, Philippines, The Republic of Korea, Thailand and Taiwan. Type specific relative contribution estimations: Numerator = single infections + proportional attribution of multiple types; Denominator = HPV DNA positive cancer cases..
Data sources [9–14]

Regarding previous vaccination rates in Korea, a nationwide survey on immunization rates conducted in 2013 (in cohorts born below 1993) reported an HPV vaccine coverage of 28.7% between the ages of 19 and 26 years, 15.9% between 27 and 39 years, and 4.6% between 40 and 59 years [56]. In addition, vaccination is recommended by professional societies, including the Korean Pediatric Society, the Korean Society of Pediatric Infectious Diseases, the Korean Society of Obstetrics and Gynecology and the Korean Society of Gynecology Oncology.

### 4.3. Barriers and facilitators of HPV vaccination introduction in Korea

Globally, awareness and acceptance of vaccines in Korea (including social, cultural, and behavioural barriers and facilitators) is relatively high for childhood vaccines, although differences between NIP vs non-NIP vaccines are observed. A nationwide survey conducted in 2012 among 4374 participants aged 7–83 months showed 95.9–100.0% vaccination rates for NIP vaccines, and 30.7–85.4% for non-NIP vaccines [57]. However, information in other age groups such as adolescents is still scarce.

Regarding HPV vaccination in Korea, limited data is available prior to the inclusion of the HPV vaccine into the NIP in 2016. However, there are some vaccination data among hospital employees and relatives during reduced-price vaccination programmes. HPV vaccine uptake increased from 2009 to 2010–2012 (370 and 515 subjects vaccinated, respectively) and was probably attributed to an increased awareness of the benefits of the vaccine following media coverage and education of health professionals. In contrast, a decrease was observed in 2013 (17 women vaccinated during the programme) following the safety issues of the HPV vaccine in Japan (June 2013). The negative reports from the media could have significantly impact the acceptance of HPV vaccination in Korea [58].

In addition, a nationwide survey conducted in 2007, and updated in 2016, showed a significant increase in the awareness of HPV infection (from 13.3% in 2007 to 35.8% in 2016) and the preventive effect of the HPV vaccine (from 8.6% to 36.9%), and a decrease in the willingness to vaccinate against HPV (from 55.0% to 25.8%). Higher education level, awareness of HPV infection and vaccination, and perception of the seriousness of infection were positively associated with the willingness of respondents to vaccinate their daughters [59,60]. Another nationwide survey in Korea revealed that mothers' awareness of HPV vaccination is the most important method for preventing cervical cancer in their daughters. Further, in this study, mothers understood the importance of undergoing the Pap test regardless the administration of the HPV vaccine [61].

Previous to the inclusion of the HPV vaccine into the NIP in 2016, a survey on the knowledge and acceptability of HPV infection and vaccination was performed among 140 mothers of children aged 9–14. Sixty-six mothers (47.0%) were aware of HPV infection, 67 (48.0%) had knowledge about HPV vaccinations, and 72 (51.0%) were aware of the relation of HPV and cervical cancer. Further, most of them (99 mothers - 70.0%) willed to vaccinate their daughters, referring protection against cervical cancer as the main reason for vaccination (83 mothers). Forty-one mothers had unfavourable opinions or strong opposition to vaccinate their daughters, mainly related to concerns of possible side effects (20 mothers), and poor awareness regarding HPV (18 mothers). Higher education level was negatively associated with the willingness to vaccinate their daughters, while knowledge of HPV and cervical cancer was positively associated [62].

**Table 6**
Relative contribution of HPVs 16/18/31/33/45/52/58/6/11 in HPV–related cancers positive for HPV–DNA, in Eastern Asia, by sex.
Data sources [9–14].

| | Female | | | | | Male | | |
|---|---|---|---|---|---|---|---|---|
| | Cervix N+ = 1805 RC (%) (95%CI) | Vagina N+ = 14 RC (%) (95%CI) | Vulva N+ = 20 RC (%) (95%CI) | Anus N+ = 23 RC (%) (95%CI) | Oropharynx N+ = 3 RC (%) (95%CI) | Anus N+ = 13 RC (%) (95%CI) | Penis N+ = 5 RC (%) (95%CI) | Oropharynx N+ = 17 RC (%) (95%CI) |
| *Combination of HPV types* | | | | | | | | |
| *9HPV | 91.3 (89.9–92.6) | 71.4 (41.9–91.6) | 65.0 (40.8–84.6) | 91.3 (72.0–98.9) | 100.0 (29.2–100.0) | 84.6 (54.6–98.1) | 80.0 (28.4–99.5) | 100.0 (80.5–100.0) |
| HPVs 16/18 | 68.9 (66.7–71.1) | 57.1 (28.9–82.3) | 45.0 (23.1–6.8) | 91.3 (72.0–98.9) | 66.7 (9.4–99.2) | 76.9 (46.2–95.0) | 40.0 (5.3–85.3) | 100.0 (80.5–100.0) |
| HPVs 31/33/45/52/58 | 22.3 (20.4–24.3) | 14.3 (1.8–42.8) | 20.0 (5.7–43.7) | 0.0 (0.0–14.8) | 33.3 (0.8–90.6) | 7.7 (0.2–36.0) | 40.0 (5.3–85.3) | 0.0 (0.0–19.5) |
| **12 oncogenic HPV types | 95.8 (94.8–97.0) | 85.7 (57.2–98.2) | 70.0 (45.7–88.1) | 100.0 (85.2–100.0) | 100.0 (29.2–100.0) | 92.3 (64.0–99.8) | 100.0 (47.8–100.0) | 100.0 (80.5–100.0) |
| *Specific HPV types* | | | | | | | | |
| HPV16 | 57.6 (55.3–59.9) | 50.0 (23.0–76.0) | 45.0 (23.1–6.8) | 91.3 (72.0–98.9) | 66.7 (9.4–99.2) | 76.9 (46.2–95.0) | 40.0 (5.3–85.3) | 100.0 (80.5–100.0) |
| HPV18 | 11.3 (9.9–12.9) | 7.1 (0.2–33.9) | 0.0 (0.0–16.8) | 0.0 (0.0–14.8) | 0.0 (0.0–70.8) | 0.0 (0.0–24.7) | 0.0 (0.0–52.2) | 0.0 (0.0–19.5) |
| HPV31 | 3.2 (2.4–4.7) | 0.0 (0.0–23.2) | 0.0 (0.0–16.8) | 0.0 (0.0–14.8) | 0.0 (0.0–70.8) | 0.0 (0.0–24.7) | 0.0 (0.0–52.2) | 0.0 (0.0–19.5) |
| HPV33 | 3.9 (3.1–4.9) | 7.1 (0.2–33.9) | 0.0 (0.0–16.8) | 0.0 (0.0–14.8) | 33.3 (0.8–90.6) | 0.0 (0.0–24.7) | 20.0 (0.5–71.6) | 0.0 (0.0–19.5) |
| HPV45 | 4.9 (3.9–6.0) | 0.0 (0.0–23.2) | 0.0 (0.0–16.8) | 0.0 (0.0–14.8) | 0.0 (0.0–70.8) | 0.0 (0.0–24.7) | 20.0 (0.5–71.6) | 0.0 (0.0–19.5) |
| HPV52 | 5.3 (4.3–6.4) | 7.1 (0.2–33.9) | 10.0 (1.2–31.7) | 0.0 (0.0–14.8) | 0.0 (0.0–70.8) | 0.0 (0.0–24.7) | 0.0 (0.0–52.2) | 0.0 (0.0–19.5) |
| HPV58 | 5.0 (4.1–6.2) | 0.0 (0.0–23.2) | 10.0 (1.2–31.7) | 0.0 (0.0–14.8) | 0.0 (0.0–70.8) | 7.7 (0.2–36.0) | 0.0 (0.0–52.2) | 0.0 (0.0–19.5) |
| HPV6 | 0.1 (0.0–0.3) | 0.0 (0.0–23.2) | 0.0 (0.0–16.8) | 0.0 (0.0–14.8) | 0.0 (0.0–70.8) | 0.0 (0.0–24.7) | 0.0 (0.0–52.2) | 0.0 (0.0–19.5) |
| HPV11 | 0.1 (0.0–0.3) | 0.0 (0.0–23.2) | 0.0 (0.0–16.8) | 0.0 (0.0–14.8) | 0.0 (0.0–70.8) | 0.0 (0.0–24.7) | 0.0 (0.0–52.2) | 0.0 (0.0–19.5) |

"HPV": Human papillomavirus; "N+": HPV–DNA positive cases; "RC": Relative Contribution; "95%CI": 95% Confidence Interval; *"9 HPV types" includes the ones in 9–valent HPV vaccine: HPVs 16/18/31/33/45/52/58/6/11 ; ** "12 oncogenic HPV types" tested for were: HPVs 16/18/31/33/35/39/45/51/52/56/58/59/66/68.
Combined data for the following countries: China, Japan, Philippines, Republic of Korea, Thailand and Taiwan.
Type specific RC estimations: Numerator = single infections + proportional attribution of multiple types; Denominator = HPV DNA positive cancer cases.
Oral cavity and larynx cancer were not included due to the limited number of cases included in the study.

Finally, once the HPV vaccine was included into the NIP, the main reason of the parents for not vaccinating their daughters with the HPV vaccine was 'worrying about safety' (73.5% of respondents - mainly those accessing information on HPV vaccine from media) [63].

## 5. Estimation of the potential impact of HPV vaccines in the Korean population

### 5.1. Potential impact of HPV vaccines in cervical cancer in Korea compared to Eastern Asia

According to data from an ICO international project on HPV-related lesions [9–14], 90.8% (88.5–92.9) of Korean cervical cancer cases were positive for HPV DNA. Among HPV DNA positive cases, HPV16 was the most common detected type (RC: 65.3%, 61.6–68.9), followed by HPV18 (RC: 8.8%; 7.3–11.2) and HPV33 (RC: 5.2%; 3.6–7.5). The overall contribution of the combined HPVs 16/18 was 74.0% (70.6–77.3); increasing up to 92.0% (89.7–93.9) with the inclusion of HPVs 31/33/45/52/58/6/11. Further, the combined contribution of the nine HPV types (HPVs 16/18/31/33/45/52/58/6/11) was similar to that of the Eastern Asian region ($p > 0.05$) (Fig. 4).

### 5.2. Potential impact of HPV vaccines in anogenital cancers and head and neck cancers in Eastern Asia

Due to the limited number of cases included for several HPV-related cancer locations, Korean data were supplemented using information from the following countries from Eastern Asia: China, Japan, the Philippines, Thailand and Taiwan. Results from the ICO study indicate that in Eastern Asia, HPV DNA prevalence was 89.5% (88.1–90.8) in cervical cancer, 87.5% (61.7–98.4) in vaginal cancer, 38.5% (25.3–53.0) in vulvar cancer, 82.1% (63.1–93.9) in female anal cancer, 81.2% (54.4–96.0) in male anal cancer, 9.6% (3.2–21.0) in penile cancer, 21.4% (4.6–50.8) in female oropharyngeal cancer and 21.0% (12.7–31.5) in male oropharynx cancer–with most cases identified as SCC.

In females, the combined RC of the nine HPV types (HPVs 16/18/31/33/45/52/58/6/11), among DNA positive cases, was 91.3%

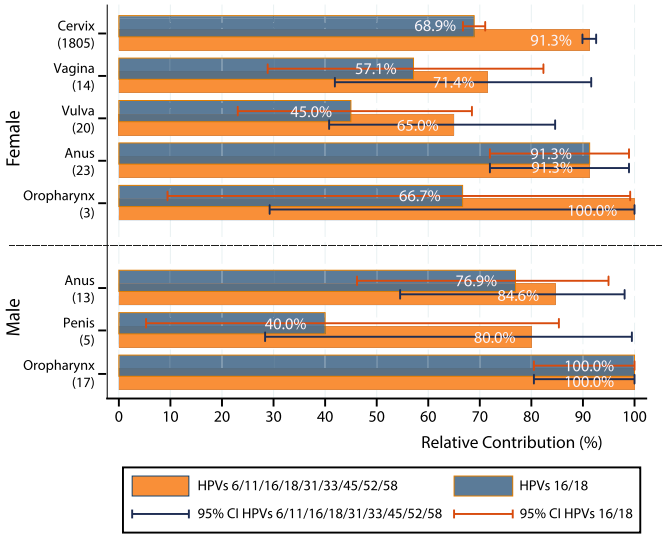


**Fig. 5.** Relative contribution of types included in HPV vaccines in HPV–related cancers positive for HPV–DNA, in Eastern Asia. "HPV": Human papillomavirus; "95% CI": 95% Confidence Interval Combined data for the following countries: China, Japan, Philippines, The Republic of Korea, Thailand and Taiwan. Multiple infections are computed according to a proportional weighting attribution. Type specific relative contribution estimations: Numerator = single infections + proportional attribution of multiple types; Denominator = HPV DNA positive cancer cases. Oral cavity and larynx cancer were not included due to the limited number of cases included in the study..
Data sources [9–14]

(89.9–92.6) in cervical cancer, 71.4% (41.9–91.6) in vaginal cancer, 65.0% (40.8–84.6) in vulvar cancer, 91.3% (72.0–98.9) in anal cancer and 100.0% (29.2–100.0) in oropharyngeal cancer. In males, the RC of the nine HPV types was 84.6% (54.6–98.1) in anal cancer, 80.0% (28.4–99.5) in penile cancer and 100.0% (80.5–100.0) in oropharyngeal cancer (Table 6; Fig. 5).

In Eastern Asia, the combined RC of HPVs 16/18 was especially prominent in anal cancer, for both females (91.3%; 72.0–98.9) and males (76.9%; 46.2–95.0). The additional contribution of HPVs 31/33/45/52/58 was especially prominent in cancer of the cervix (22.3%; 20.4–24.3), penis (40.0%; 5.3–85.3) and female oropharynx (33.3%; 0.8–90.6) (Table 6; Fig. 5).

## 6. Conclusions

HPV infection is an important contributor to cancer-related morbidity and mortality in the Republic of Korea (11.3% of new infection-related cancer cases and 6.0% of infection-related cancer deaths in 2007).

In June 2016, the HPV vaccine (2-valent and 4-valent) was included in the National Immunization Programme in Korea as a 2-dose schedule for girls12 year old. By 2016, 49.9% of the target cohort had received the first dose of the HPV vaccine. The 9-valent vaccine has been licensed concurrently.

The inclusion of HPV vaccines in the Republic of Korea could impact in HPV-related disease, preventing from 70% to 90% of cervical cancer cases, most of anal and vaginal cancers, approximately a quarter of vulvar cancers, a smaller fraction of penile and head and neck cancers and more than 90% of benign genital warts.

However the impact of HPV vaccines on reducing the global burden of HPV-related disease in Korea will greatly depend on HPV vaccine uptake, coverage, availability, and affordability.

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## Potential conflict of interest

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