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Epidemiology and prevention of *Human Papillomavirus*

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Key words: Cervical cancer, Prevention, 9-valent HPV vaccine
Parole chiave: Cancro della cervice uterina, Prevenzione, vaccino HPV 9 valente

Abstract

Human papillomavirus is the most common sexually transmitted infection, and skin-to-skin genital contact is sufficient for virus transmission.
Cervical cancer is the second-most common cancer in women living in less developed regions, with an estimated 445,000 new cases in 2012 and 230,000 deaths every year. Until now, more than 200 types of HPV have been identified, and about 15 types (HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66, -68, -82) have been shown to cause cervical cancer because they are able to transform infected cells into malignant tumor cells. The bivalent vaccine containing the serotypes 16 and 18 and the quadrivalent vaccine containing the serotypes 16, 18, 6 and 11, have been used in Italy for many years. The European Medicines Agency authorized marketing of the Gardasil 9 vaccine in the European Union on June 2015. Today, Public Health targets the immunization of adolescents of both genders based on new and important scientific evidence for maximum protection from all HPV related pathologies directly preventable with vaccination.

Introduction

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Papillomavirus is a relatively small virus containing circular double-stranded DNA belonging to the *Papillomaviridae* family, which replicate their genomes by using the host's enzymatic machinery. HPVs infect

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the cutaneous epithelium (skin) and mucosal epithelium (e.g. cervical and other anogenital mucosae). Generally, lesion formations, like micro-wounds or micro-abrasions, on the surface of the epithelium allow the virus to enter and insert the viral genome into the basal cells. The virus uses the host's cells to replicate viral DNA and express virally encoded proteins, so new virus particles are assembled and released in the cervical canal. The deregulation of the host's gene expression leads to abnormal growth of squamous cells on the surface of the cervix (1).

During the process of cervical carcinogenesis the cervix is infected with HPV. Infection may cause mild Pap abnormalities and/or mild cervical intraepithelial neoplasia (CIN), which usually disappear spontaneously.

The persistence of high-risk HPV is a key factor in precancerous lesions or high-grade dysplasia (CIN 2/3) progression, which has a greater likelihood of progressing to invasion and cancer (2). In the precancer phase the probability of returning to a normal cervix is 57% in the presence of CIN 1, 43% with CIN 2 and only 32% with CIN 3. If CIN 3 persists for more than 20 years the risk of invasion and likelihood of a cervical cancer is higher. Worldwide, 570,000 cases in females and 60,000 in males are attributable to HPV annually, which markedly represent 8.6% and 0.8% of all cancer cases occurring globally (3). The prevalence of HPV was estimated at 157,897 women with normal cytology worldwide in a meta-analysis study published in 2007. On all continents, HPV-16 is most common with an estimated point prevalence of 2.6% (95% CI: 2.5–2.8), followed by HPV-18 in Europe, Central and South America (4). The prevalence of HPV by age groups and continent, including both high and low-risk types, is up to 30% in young women in all regions except in Asia. The prevalence declines in middle-aged groups, and a second rise is observed in women in the 35-44 or 45-54-year age groups. Instead, in an HPV (any type) prevalence study in men residing in Brazil, Mexico and the USA in 2009, age does not appear to be as strongly associated with HPV prevalence or duration of infection in men, as it typically affects women (5). A 9-valent vaccine has been recently developed containing serotypes 31, 33, 45, 52, 58 in addition to serotypes 6, 11, 16, 18. Epidemiological data from HPV infection in Italy also emphasizes the importance and possible role of this vaccine. The burden of diseases attributable to HPV in Italy is shown by 2,918 new cases of cervical cancer, 2,065 cases of neck cancer in both genders, and about 100 new cases of penile cancer per year. Mortality data for all HPV cancers is still high, despite the service of free pap-test screening for uterine cervix cancer prevention. Cervix cancer has a case to death ratio of 24% within 5 years. It significantly increases up to 75% in both genders for oropharynx cancer; the highest rate is observed in anal cancer at 86% in women and 89% in men, meaning that after 5 years only 14% of affected women and 11% of the affected men survive (6).

In the classification of most oncogenic viral papilloma serotypes, at the first and second places are 16 and 18, respectively, and responsible for cancer of the cervix, vulva, vagina, penis, anus and oropharynx. In the third place of frequency are serotypes 6 and 11, which are associated with a minor oncogenic risk of the vagina and penis, but are fourth in vulvar cancer and fifth in anus cancer. The bivalent vaccine containing serotypes 16 and 18, and the quadrivalent vaccine containing serotypes 16, 18, 6 and 11, have been in use in Italy for many years. There are other serotypes: 31, 33, 45, 52 and 58, with less oncogenic power. On average, they are in the last position, but are equally important because, for example, serotype 33 is second in oropharyngeal cancer and third in cervical, vulvar and anus cancer. For this reason, a 9-valent vaccine has been recently developed, adding these last serotypes to

the first four serotypes (7). Gardasil was the first HPV vaccine to be authorized by the European Medicines Agency (EMA) in September 2006 for the European Union, while Cervarix was authorized exactly one year later. Both vaccines are constituted by an L1 surface antigen of the human papilloma viruses. Gardasil is a quadrivalent VLP (virus like particles) vaccine consisting of serotypes 6, 11, 16 and 18, adjuvanted with AAHS aluminum salts (amorphous aluminum hydroxyphosphate sulphate) (8). Cervarix is a bivalent VLP vaccine consisting of serotypes 16 and 18, adjuvanted with aluminum salts AS04 ($Al(OH)_3$) (9).

Due to the severity of infections and the high mortality rate of some forms of cancer, a new 9-valent vaccine has been developed containing also serotypes 31, 33, 45, 52 and 58, with a double adjuvant dose compared to Gardasil in order to extend the spectrum of protection. The possible cross-protection of serotypes not present in the bivalent vaccine has also been studied, since serotype 16 is very close to 31 from a phylogenetic point of view, similar to serotypes 18 to 45. The cross-protection study showed that after 4 years of vaccination a cross-protection against serotypes 31, 33 and 45 is present, and after 6.4 years of protective efficacy is no longer significant (10). The Gardasil 9 vaccine was granted marketing authorization in the EU on the 10th of June 2015 (11).

Five main clinical studies demonstrate the benefits of the vaccine. The first study, a phase III study, conducted on 14,000 females aged 16 through 26 years looked at the effectiveness of Gardasil 9. This study showed that only 1 out of 6,016 women vaccinated with 3 doses of Gardasil 9 developed diseases related to HPV types 31, 33, 45, 52 and 58, compared to 30 out of 6,017 who were vaccinated with 3 doses of Gardasil (12). In the second study, 3,066 subjects between 9 and 15 years of age, both females and males, confirmed the effects of the vaccine. The study demonstrated that the vaccine stimulates the production of adequate levels of antibodies against HPV for all 9 viral types, in girls and boys between the ages of 9 and 15 when compared with women 16-26 years of the first study. The third study looked at the development of antibodies one month after the third dose in 600 girls aged 9 to 15 years. The study showed that girls vaccinated with Gardasil 9 have similar levels of protection against types 6, 11, 16 and 18 as girls vaccinated with Gardasil. The fourth main study conducted in 1,419 young men and 1,101 young women aged 16 to 26 found that Gardasil 9 stimulates similar levels of protection against all 9 virus types in both young men and women one month after the third dose. The last study looked at the development of antibodies one month after the last dose in two-dose schedule of Gardasil 9 compared to three-dose vaccination schedule.

The adverse events most observed in the studies were local pain at the injection site and headache. These side effects were generally of mild to moderate intensity. The Gardasil 9 vaccine may be administered concomitantly with a recall vaccine containing diphtheria (d) and tetanus (t), together with the pertussis (acellular) and / or poliomyelitis (IPV): dTap, dT-IPV, DTap-IPV vaccines, and the meningococcal conjugated vaccine (MCV4), with no significant interference in antibody response for both vaccines (13, 14).

An epidemiological study conducted in Europe in 2015 tried to estimate the benefits of the 9-valent vaccine against the 4-valent. The results show that the 9-valent vaccine can cover 19% more cervical cancers than the 4-valent vaccine, and vaccine coverage is estimated at 75% regarding precancerous lesions of the vagina, vulva, cervix and anus (15, 16). Since 2007/2008 in all regions of Italy, the HPV vaccination has been free and actively offered to all girls at twelve years of age. In the New National Vaccinal Prevention Plan 2017-2019 (PNPV 2017-

2019) and in the new essential levels of assistance (LEA), free vaccination is also offered to 12-year old males. The 9-valent vaccine is aligned with the new Public Health objective, offering anti-HPV vaccination to males and females for maximum protection from all related HPV diseases which are directly preventable with vaccination, as expressed in the New PNPV 2017-2019 (17). Although vaccine coverage in females shows a decline in recent years (from 64.59% in 2002 to 56.26% in 2003, with a complete vaccination cycle) the PNPV 2017-2019 aims to achieve 75% vaccine coverage in 2018 and 95% in 2019 for males.

Riassunto

Epidemiologia e prevenzione del Papillomavirus umano

Il virus del papilloma umano si trasmette più comunemente per via sessuale, il contatto della pelle e delle mucose genitali è sufficiente per la trasmissione del virus. Il cancro del collo dell'utero è il secondo tumore più diffuso nelle donne che vivono in regioni meno sviluppate, con circa 445.000 nuovi casi nel 2012 e 230.000 morti ogni anno. Fino ad oggi sono stati identificati più di 200 tipi di HPV e circa 15 tipi (HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, 58, -59, -66, -68, -82) possono causare il cancro della cervice perché sono in grado di trasformare le cellule infette in cellule tumorali maligne. Il vaccino bivalente contenente i sierotipi 16 e 18 e il vaccino quadrivalente contenente i sierotipi 16, 18, 6 e 11 sono usati in Italia da molti anni. Nel giugno 2015 l'Agenzia Europea per i Medicinali ha autorizzato la commercializzazione del vaccino HPV 9-valente nell'Unione Europea. Il vaccino anti-HPV 9-valente è attualmente il vaccino anti-papilloma virus umano con la più alta copertura. Questo nuovo vaccino, in linea con il nuovo obiettivo di Sanità Pubblica per la vaccinazione anti-HPV vuole offrire agli adolescenti di entrambi i sessi la massima protezione da tutte le patologie HPV correlate, così come espresso nel nuovo Piano Nazionale di Prevenzione Vaccinale 2017-2019.

References

1. Berti FCB, Pereira APL, Cebinelli GCM, Trugilo KP, Brajão de Oliveira K. The role of interleukin 10 in human papilloma virus infection and progression to cervical carcinoma. Cytokine Growth Factor 2017; **34**: 1-13. doi: 10.1016/j.cytogfr.2017.03.002.
2. Schiffman M, Castle PE. Human papillomavirus: epidemiology and public health. Arch Pathol Lab Med 2003; **127**: 930-4. doi: 10.1043/1543-2165.
3. de Martel C, Plummer M, Vignat J, Franceschi S. Worldwide burden of cancer attributable to HPV by site, country and HPV type. Int J Cancer 2017; **141**: 664-70. doi: 10.1002/ijc.30716.
4. Bosch FX, Burchell AN, Schiffman M, et al. Epidemiology and natural history of human papillomavirus infections and type-specific implications in cervical neoplasia. Vaccine 2008; 19; **26**(Suppl 10): K1-16. doi: 10.1016/j.vaccine.2008.05.064.
5. Giuliano AR, Tortolero-Luna G, Ferrer E, et al. Epidemiology of Human Papillomavirus Infection in Men, Cancers other than Cervical and Benign Conditions. Vaccine 2008; 19; **26**(Suppl 10): K17-28. doi: 10.1016/j.vaccine.2008.06.021.
6. Azzari C, Ricci S, Canessa C, Ghiori F, Lippi F. 10 anni di protezione anti-HPV: verso nuove frontiere. RIAP. Rivista di Immunologia e Allergologia Pediatrica 2016; **3**: 38-45.
7. De Sanjosé S, Serrano B, Castellsagué X, et al. Human papillomavirus (HPV) and related cancers in the Global Alliance for vaccine and Immunization (GAVI) countries. A WHO/ICO HPV information Centre Report. Vaccine 2012; **30**(Suppl 4): D1-83. doi: 10.1016/S0264-410-X(12)01435-1.
8. European Medicines Agency. Gardasil human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed. Available on: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/000703/WC500021146.pdf [Last accessed 2018, Apr 10].
9. European Medicines Agency. Cervarix human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed]. Available on: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/000721/WC500024634.pdf [Last accessed 2018, Apr 10].
10. Tabrizi SN, Brotherton JM, Kaldor JM, et al. Assessment of herd immunity and cross-protection after a human papillomavirus vaccination pro-

gramme in Australia: a repeat cross-sectional study. Lancet Infect Dis 2014; **14**: 958-66. doi: 10.1016/S1473-3099(14)70841-2.
11. European Medicines Agency. Gardasil. Available on: http://www.ema.europa.eu/docs/it_IT/document_library/EPAR_-_Product_Information/human/003852/WC500189111.pdf [Last accessed 2018, Apr 10].
12. Petrosky E, Bocchini JA Jr, Hariri S, Chesson H, et al. Use of 9-Valent Human Papillomavirus (HPV) Vaccine: Updated HPV Vaccination Recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep 2015; **64**(11): 300-4.
13. Schilling A, Parra MM, Gutierrez M, et al. Coadministration of a 9-Valent Human Papillomavirus Vaccine with Meningococcal and Tdap Vaccines. Pediatrics 2015; **136**: 563-72. doi: 10.1542/peds.2014-4199.
14. Kosalaraksa P, Mehlsen J, Vesikari T, et al. An open-label, randomized study of a 9-valent human papillomavirus vaccine given concomitantly with diphtheria, tetanus, pertussis and poliomyelitis vaccines to healthy adolescents 11-15 years of age. Pediatr Infect Dis J 2015; **34**: 627-34. doi: 10.1097/INF.0000000000000694.
15. Zuccotti GV, Mameli C. I vaccini contro HPV: evoluzione e prospettive. Rivista di Immunologia e Allergologia Pediatrica 2015; **4**: 32-41.
16. Hartwig S, Baldauf J, Dominiak-Felden G, et al. Estimation of the epidemiological burden of HPV-related anogenital cancers, precancerous lesions, and genital warts in women and men in Europe: Potential additional benefit of a nine-valent second generation HPV vaccine compared to first generation HPV vaccines. Papillomavirus Res 2015; **1**: 90-100. doi: 10.1016/j.pvr.2015.06.003.
17. \Piano Nazionale Prevenzione Vaccinale 2017-2019. Available on: http://www.salute.gov.it/imgs/C_17_pubblicazioni_2571_allegato.pdf [Last accessed 2018, Apr 10].

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