Prevention of Human Papillomavirus Infection. Beyond Cervical Cancer: A Brief Review

Prevenção da Infeção pelo Vírus do Papiloma Humano. Para Além do Cancro do Colo do Útero: Uma Breve Revisão

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ABSTRACT

Introduction: Human papillomavirus is responsible for almost all cases of cervical cancer, an important portion of anogenital and oropharyngeal invasive and preinvasive lesions, as well as genital warts (condyloma acuminatum) and recurrent respiratory papillomatosis. Currently, three prophylactic vaccines against high-risk Human papillomavirus are commercialized in many countries worldwide.

Methods: To this non-systematic review the authors searched in MEDLINE/PubMed for systematic reviews, meta-analysis and randomized controlled trials, published in the last six years, using the terms “HPV”, “non-cervical cancer” and “vaccine”. Non-cervical cancers caused by human papillomavirus are less common lesions. However, its incidence has been increasing, while cervical cancer has declined, due mainly to highly effective screening programs. There are no formal screening programs for non-cervical cancers, so universal vaccination could have an important impact. The preventive effect of the vaccine is mainly studied and established in relation to cervical cancer, although it has also been demonstrated in the development of vulvar and vaginal lesions. To date, the efficacy in preventing anal and oropharyngeal diseases related with human papillomavirus is uncertain due to scarce supporting data and low vaccination coverage in men. The prevalence of injuries and subsequent absolute benefit of vaccination is lower in men, but it provides an additional benefit to the herd immunity achieved with the vaccination of women.

Conclusion: The total fraction of malignant and pre-malignant lesions attributed to Human papillomavirus genotypes contained in the nonavalent vaccine is significant in both women and men, which turns this vaccine into a great asset in terms of Public Health.

Keywords: Papillomavirus Infections; Papillomavirus Vaccines; Uterine Cervical Neoplasms

RESUMO

Introdução: O vírus do papiloma humano é responsável por quase todos os casos de cancro do colo do útero, de uma importante fração de lesões anogenitais e orofaringeas pré-invasivas e invasivas bem como de condilomas genitais e da papilomatose respiratória recorrente. Atualmente existem três vacinas profiláticas contra o vírus do papiloma humano de alto risco comercializadas em vários países do mundo.

Métodos: Para esta revisão não-sistemática, os autores pesquisaram na MEDLINE/PubMed revisões sistemáticas, metanálises e ensaios clínicos randomizados, publicados nos últimos seis anos, utilizando os termos “HPV”, “cancro não cervical” e “vacina”. Os cancros não cervicais causados pelo vírus do papiloma humano são lesões menos comuns. Contudo, a sua incidência tem aumentado, a par de uma diminuição do cancro do colo do útero, devido principalmente à implementação de programas de rastreamento altamente eficazes. Uma vez que não existem programas oficiais de rastreamento para cancros não cervicais, a vacinação universal pode ter um impacto importante. O efeito preventivo da vacina é principalmente estudado e estabelecido em relação ao cancro do colo do útero, embora também tenha sido demonstrado no desenvolvimento de lesões vulvares e vaginais. Até ao momento, a eficácia na prevenção de doenças anais e orofaringeas relacionadas com o vírus do papiloma humano é incerta, devido à escassez de dados na literatura e baixa cobertura de vacinação em homens. A prevalência de lesões e o consequente benefício absoluto da vacinação é inferior nos homens, porém proporciona um benefício adicional à imunidade de grupo alcançada com a vacinação de mulheres.

Conclusão: A fração total de lesões malignas e pré-malignas atribuídas aos genótipos de vírus do papiloma humano contidos na vacina nonavalente é significativa tanto em mulheres quanto em homens, o que confere a essa vacina um grande potencial em termos de Saúde Pública.

Palavras-chave: Infecções por Papilomavírus; Neoplasias do Colo do Útero; Vacinas contra Papilomavírus

INTRODUCTION

Human papillomavirus (HPV) is a sexually transmitted double-stranded DNA virus responsible for the development of anogenital (cervical, vaginal, vulvar, penile and anal) and oropharyngeal diseases in both women and men. The International Agency for Research on Cancer (IARC) considers it a human carcinogen and classifies HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 66 as high-risk (HPV-hr) and HPV 6, 11, 42, 43, 44, 54, 61, 70, 72, 81 as low-risk (HPV-lr) types. Some genotypes have an uncertain oncogenic potential. High-risk types 16 and 18 account for almost 70% of all cervical cancers, as well as about 90% of the anal cancers and a variable fraction of vulvar, vaginal, penile and oropharyngeal cancers. HPV genotypes 31, 33, 45, 52 and 58 are the etiological agent for more than 20% of cervical cancers. Low-risk genotypes 6 and 11 mainly cause cervical, vulvar and vaginal low-grade lesions, and
Vaccination represents one of the most cost-effective public health measures. The development of the prophylactic vaccine against HPV, with the aim of preventing the initial infection and subsequent neoplastic transformation, has generated some controversy. Therapeutic vaccines capable of inducing the regression of existing lesions are under development.

Currently, three different vaccines are commercialized, varying in the number of HPV genotypes contained. All vaccines protect against HPV types 16 and 18. The quadrivalent vaccine also targets types 6 and 11. The nonavalent vaccine, available in Europe since 2015, in addition to the genotypes present in the quadrivalent vaccine, also covers types 31, 33, 45, 52, and 58, predicting 90% efficacy in reducing the overall incidence of cancers associated with high-risk genotypes present in the quadrivalent vaccine, also co-
vaccine, available in Europe since 2015, in addition to the nonavalent vaccine in men and women, updated for the population of 2015.3 Within the total number of new cases, estimated as 29% - 43% and 70%, respectively. 13 HPV16 positivity increases with lesion severity in both HIV negative and positive individuals. However, the fraction of anal cancer attributable to HPV16 is smaller in the HIV-positive population, as this virus influences the natural history of HPV.11

Anal cancer
Anal cancer is relatively rare, but recent studies show an increase in incidence in some developed countries, which may be associated with changes in sexual behaviour, estimated to be related with HPV infection in nearly 90% of the cases.11 Men who have sex with men, particularly if infected by the human immunodeficiency virus (HIV), represent a high-risk group, as well as HIV-infected women. Its natural history resembles that of cervical cancer: both share identical risk factors and transmission mechanisms and emerge from the same type of cells that occur in the transformation zone, that is, between stratified squamous and columnar epithelium. HPV16 is the most frequently implicated genotype, followed by HPV18, representing in total 84.3% of HPV positive cases.12 HPV16 positivity increases with lesion severity in both HIV negative and positive individuals. However, the fraction of anal cancer attributable to HPV16 is smaller in the HIV-positive population, as this virus influences the natural history of HPV.11

Vulvar and vaginal cancer
Vulvar and vaginal cancer are rare neoplasias, being associated with HPV infection in a variable fraction of cases, estimated as 29% - 43% and 70%, respectively.13 Considering the subgroup of HPV-related cases, it is presumed that 94.3% of vulvar cancers and 87.1% of vaginal cancers are attributed to the genotypes present in the nonavalent vaccine.3 Unlike HPV-negative cancers, virus-associated lesions tend to occur at a younger age, exhibit basaloid instead of keratinizing characteristics, lack p53 mutations and are associated with sexual risk factors.
These characteristics are present both in cases of vulvar and vaginal cancers, although vaginal lesions are more frequently associated with HPV infection.\textsuperscript{14}

**Penile cancer**

Penile cancer is a rare condition globally, yet in some areas of Africa, South America and Asia it represents about 10\% of all cancers in men.\textsuperscript{1} Similarly to female external genital neoplasia, it is not always associated with HPV infection, but with genotypes 16 and 18 responsible for 35\% to 40\% of cases of penile cancer in general and 70\% to 80\% of those related with HPV. Alike vulvar and vaginal cancer, cases of penile cancer associated with the virus tend to occur at a younger age, exhibit basaloid characteristics, lack p53 mutations and are associated with sexual risk factors.\textsuperscript{14} Among cases of penile cancer, it is estimated that the fraction attributable to the genotypes contained in the nonavalent vaccine is 90.7\%.\textsuperscript{3}

**Recurrent respiratory papillomatosis**

HPV infection has been considered a sexually transmitted disease, but there is increasing evidence pointing to the existence of other transmission routes. Vertical transmission occurs more frequently during vaginal delivery through contact of the fetus with infected maternal cells or during a caesarean section after premature rupture of membranes; ascendant infections have also been described.\textsuperscript{15} Recurrent respiratory papillomatosis represents the most frequent benign laryngeal tumor in children, with 90\% to 95\% of the cases being caused by HPV genotypes 6 and 11. Although it is a benign condition, it can lead to obstructive symptoms, causing significant morbidity. It also has a potential for malignant transformation, particularly to squamous cell carcinoma about 1\% in children and 3\% to 7\% of adults.\textsuperscript{16}

**Vaccination in men**

Although the natural history and prevalence of HPV infection in men is difficult to assess due to the high rate of silent infections, it is estimated that the prevalence is higher than 50\%. Most recent studies report that vaccination of young men seems to cause a reduced direct benefit in the incidence of the disease due to the group immunity achieved with the vaccination of girls. However, this immunity entails a scarce benefit in the era of globalization, due to the circulation between countries and areas with low vaccination coverage rates. On the other hand, even if vaccination coverage in girls was sufficiently high, this would be non-existent in men who have sex with men, who present particularly high rates of HPV-associated lesions.\textsuperscript{17} It is estimated that vaccination in boys may prevent about 94\% of the head and neck cancers attributed to HPV infection and 90\% of penile cancers. 3

**Vaccination challenges**

One of the main obstacles to vaccination is the cost associated with its implementation in an immunisation schedule, and this limitation is greater in countries where the financial burden is not borne by the patient. However, several studies have shown that the strategy is cost-effective, considering the economic impact of diseases caused by the virus. The efficacy of the vaccine also depends on access and attitudes towards it, with lower coverage rates being due to cultural beliefs and stigmatization of HPV as a sexually transmitted infection, with a tendency to delay vaccination until the teenager is sexually active. Similarly, there is a tendency to minimize the impact of the infection, associating it only with the development of cervical cancer, and therefore overlooking the need to extend the recommendation of vaccination to males. However, as mentioned above, group immunity achieved with the vaccination of girls carries a reduced benefit in the era of globalization, being non-existent in particularly vulnerable groups, as is the case of men who have sex with men.

At this point, health professionals play an essential role in transmitting information and awareness about HPV infection and its prevention.

**CONCLUSION**

HPV is a sexually transmitted pathogen responsible for almost all cases of cervical cancer, as well as an important fraction of preinvasive and invasive anogenital and oro-pharyngeal lesions in both sexes. The total fraction of malignant and pre-malignant lesions attributed to HPV genotypes contained in the nonavalent vaccine is significant in both women and men, which turns this vaccine into a great asset in terms of Public Health.

**PROTECTION OF HUMANS AND ANIMALS**

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association.

**DATA CONFIDENTIALITY**

The authors declare having followed the protocols in use at their working center regarding patients’ data publication. Patient consent obtained.

**CONFLICT OF INTEREST**

The authors declare that they have no conflict of interest with regard to this article.

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