

THE IMPACT BEYOND CANCER OF THE HPV VACCINE

O IMPACTO DA VACINA CONTRA O HPV ALÉM DO CÂNCER

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The incidence of 16,370 new cases of cervical cancer was recorded in Brazil during the year of 2018 with 5,000 deaths¹. Regarding the low coverage of HPV vaccination in Brazil, we decided to write this letter to show that maybe there are some benefits of this vaccine beyond the oncogenesis process. This news could be increasing the motivation for vaccination.

Cervical cancer remains as one of the most common causes of malignancies in women, with estimates of 570,000 new cases and 311,000 deaths from the disease in 2018². Cervical cancer is also the leading cause of years of potential life lost (YPLL) among women in south central Asia, Latin America, and sub-Saharan Africa, resulting in a greater reduction of women's life expectancy when compared to AIDS, tuberculosis, or maternal conditions in Latin America and Europe. The causal role of human papillomavirus (HPV) infection in the development of cervical cancer has been extensively evaluated and is universally recognized, with the presence of the virus' DNA being the first necessary factor to develop cancer ever identified³. HPV infection is the most prevalent sexually transmitted disease (STD) in the world, and has become an almost unavoidable consequence of sexual activity and considered a worldwide public health problem of epidemic proportions⁴. At least 50% of sexually active women acquire a genital HPV infection along their lifetime, and most of them do not even get to know they have the virus, given the lack of signs and symptoms. The treatment options available nowadays are far from ideal. The associated pharmacological treatment for genital warts, including podofilox and imiquimod, has showed clearance and recurrence rates from 23% to 88% and 19% to 65%, respectively⁵. The surgical treatments available—such as electro-surgery, surgical excision, cryotherapy, and laser therapy—are not proven more effective or associated with less recurrence, being only more costly.⁵ When cervical cancer itself is in the spotlight, despite modern chemotherapeutic, radiologic, and/or surgical interventions, the mortality rate within 5 years accounts for approximately 30%⁴. Therefore, effective prevention strategies aimed at eliminating HPV-related diseases are the key to decrease the associated morbidity and mortality, and the existence of a vaccine is extremely important in this context. Periodic screening associated with HPV vaccination is the primary strategy for eliminating cervical cancer.

The first regulatory approval for an HPV vaccine came in 2006 and, by the end of 2019, a total of 124 countries and territories had implemented national HPV immunization programs^{6,7}. Several studies have demonstrated the efficacy and effectiveness of HPV vaccines to prevent HPV infection, genital warts and high-grade precancerous cervical lesions. Most recently, a study showed a substantially

reduced risk of invasive cervical cancer among Swedish girls and women aged 10 to 30 years old who had received the quadrivalent HPV vaccine, according to a nationwide registry including 1,672,983 people⁸. Among women who had initiated vaccination before the age of 17 years, the risk of cervical cancer was 88% lower in comparison to those who had never been vaccinated.

Unlike the association with cervical cancer, other non-neoplastic health problems related to HPV infection, such as cardiovascular diseases (CVD) and potential side effects of treatments, are not well established yet and, thus, require further specific studies⁹. Meanwhile, there may be more potential benefits of HPV vaccination that also require further investigation and should be considered.

CVD are the leading cause of death and disability around the world, accounting for approximately one third of all deaths. About 85% of this burden is attributable to ischemic heart diseases or cerebrovascular diseases¹⁰. Given their importance, there are many studies on the most common risk factors, such as high blood pressure, smoking, dyslipidemia and diabetes, and the advances in their management. Nevertheless, in about 20% of the cases, no common risk factor is identified, which point to the need of new studies that can identify other less common risk factors¹¹. HPV infection has been suggested as a potential risk factor, and that is why the focus of this letter is its correlation with CVD and the hypothesis that the benefits of HPV vaccination can go beyond cancer prevention.

The interest in HPV-related mechanisms that could play a role in CVD development has increased after epidemiological evidence supporting the relationship between HPV infection and cardiovascular events was published by Kuo and Fujise¹². Subjects with genital HPV infection had a 2.5-fold increased incidence of severe cardiovascular complications, such as myocardial infarction and stroke, compared to HPV-negative women, despite other traditional risk factors and/or coexisting medical conditions¹². However, these findings are limited by the cross-sectional design of the study, the unknown temporal relationship between HPV infection and cardiovascular events, self-collection of specimen, and self-reporting of data. Positive HPV was also associated with a higher risk of cerebrovascular events compared with negative HPV in patients with head and neck cancer. However, these findings are also limited once we need to consider potential late side effects of radiotherapy besides the potential effect of HPV infection¹³. A recent study reported that high risk of HPV infection among Korean women was a factor independently associated with increased risk of developing CVD, with a hazard ratio (HR) for the incidence of CVD in HPV-positive women of 1.23 (95% confidence interval 1.01–1.50) compared to HPV-negative women, after multivariate adjustment for age, body mass index, smoking status, alcohol intake, physical activity, educational level, family history of CVD, cholesterol and glucose levels, and systolic blood pressure¹⁴. The association was stronger among

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individuals with obesity and metabolic syndrome, which may indicate a synergic effect. This latest prospective cohort study included 63,411 women followed up for a mean time of 4.4 years, which makes data more reliable and supports the findings of previous studies.

The pathophysiological mechanisms that could potentially determine the associations between HPV infection and CVD are not yet convincingly defined. The effects of chronic infections, which may play an important role in the development, progression, or destabilization of atheromatous plaques, seem to be particularly important. There is strong evidence that infectious pathogens could initiate atherosclerosis in childhood¹⁵. The adverse effects of these pathogens on the arteries, specifically on the endothelium and smooth muscle, seem to be mediated predominantly by the increased pro-inflammatory activity and abnormal lipid metabolism. However, one must note that specific mechanisms differ significantly between pathogens¹⁰. Some of the infectious agents linked to this potential role in the atherogenesis process include *Chlamydia pneumoniae*, *Helicobacter pylori*, *Mycoplasma pneumoniae*, *Cytomegalovirus*, *Porphyromonas gingivalis*, the Influenza virus and HIV¹⁶. Hypothesis about the role of HPV include increased levels of circulating inflammatory mediators, expression of E6 and E7 oncoproteins in cells linked to the atherogenesis and an influence in lipid metabolism¹⁰. Although HPV infection is not associated with classical viremia, HPV DNA was found in 55% of atheromatous coronary arteries from 20 deceased donors and in 16 out of 22 cases of biopsy of giant cell arteritis (GCI), confirmed by histology, in the temporal artery^{17,18}. One study reported a significant association between HPV infection and coronary artery disease (CAD) among climacteric women, specially associated with high-risk genotypes of HPV¹⁹. In this study, the HPV-positive group had lower blood levels of HDL cholesterol and elevated blood pressure compared to the HPV-negative group, which may be explained by a possible association between HPV infection and lipid metabolism.

Considering the interaction between infections and CVD, it is important to investigate how treatment and prevention of infections could impact the onset and development of CVD. Several investigators have focused on the effects of vaccination on the atherosclerosis process using animal models. Experimental studies with *P. gingivalis* and *S. pneumoniae* found out that immunization led to the attenuation of atherosclerosis²⁰. Regarding immunization against influenza, many studies have evaluated its relationship with subsequent risk of CVD. A recent meta-analysis concluded that there is a significant decrease in the risk of CVD events as a result of influenza vaccination²¹. The same hypothesis could be raised about HPV vaccination once more knowledge supporting the role of HPV infection on CVD is available.

Since 2011, the HPV vaccine has been recommended for all preadolescents and adolescents by the World Health Organization (WHO). In Brazil, since 2014, this vaccine is offered by the Brazilian Unified Health System (SUS, in the Portuguese acronym) for girls between 9 and 14 years old, and, as of 2017, also for boys. Yet, optimal vaccine coverage has not been achieved¹. This situation is speculated to be related with the belief that the vaccination could stimulate adolescents into early sexual activities or lead them to act recklessly when it comes to safe sex, added to the concern by the population about the safety of the vaccine. A study conducted in 2018 collected interviews with several parents in Roraima, Brazil, and showed

that parental acceptance of the HPV vaccine for daughters and sons 18 years of age or less was high (92% and 86%, respectively) but the understanding about the vaccine was still low. Conclusion was that, one year after its introduction in the national immunization program (NIP), as recommended by The World Health Organization (WHO), most parents surveyed in Brazil accepted HPV vaccination for their daughters and sons. The low coverage in the NIP seemed to stem from challenges in vaccine delivery to adolescents and HPV vaccination barriers in healthcare centers rather than from refusal to vaccination. The study also states that changing back to a school-based vaccine delivery would likely improve vaccine coverage access to it²². Actions aimed at informing the public about the HPV vaccine, including its risks and benefits, are also needed to attain higher vaccination coverage in Brazil and, thus, avoid the numerous complications resulting from HPV infection, such as cervical cancer and CVD²³.

In face of this information and having in hands more studies on the association between HPV infection and dyslipidemia, the benefits of HPV vaccines could surpass cancer prevention. This information can be relevant and support the increase of vaccination coverage.

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Conflict of interests

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