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Human papillomavirus genotype attribution for HPVs 6, 11, 16, 18, 31, 33, 45, 52 and 58 in female anogenital lesions

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Abstract ***Objective:*** Human papillomavirus (HPV) vaccines can potentially control cervical cancer and help to reduce other HPV-related cancers. We aimed to estimate the relative contribution (RC) of the nine types (HPVs 16/18/31/33/45/52/58/6/11) included in the recently approved 9-valent HPV vaccine in female anogenital cancers and precancerous lesions (cervix, vulva, vagina and anus).

Methods: Estimations were based on an international study designed and coordinated at the Catalan Institute of Oncology (Barcelona-Spain), including information on 10,575 invasive cervical cancer (ICC), 1709 vulvar, 408 vaginal and 329 female anal cancer cases and 587 Vulvar Intraepitelial Neoplasia grade 2/3 (VIN2/3), 189 Vaginal Intraepitelial Neoplasia grade 2/3 (VaIN2/3) and 29 Anal Intraepitelial Neoplasia grade 2/3 (AIN2/3) lesions.
Consecutive histologically confirmed paraffin-embedded cases were obtained from hospital pathology archives from 48 countries worldwide. HPV DNA-detection and typing was performed by SPF_{10}-DEIA-$LiPA_{25}$ system and RC was expressed as the proportion of type-specific cases among HPV positive samples. Multiple infections were added to single infections using a proportional weighting attribution.

Results: HPV DNA prevalence was 84.9%, 28.6%, 74.3% and 90.0% for ICC, vulvar, vaginal and anal cancers, respectively, and 86.7%, 95.8% and 100% for VIN2/3, VaIN2/3 and AIN2/3, respectively. RC of the combined nine HPV types was 89.5% (95% confidence interval (CI): 88.8–90.1)-ICC, 87.1% (83.8–89.9)-vulvar, 85.5% (81.0–89.2)-vaginal, 95.9%

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(93.0–97.9)-female anal cancer, 94.1% (91.7–96.0)-VIN2/3, 78.7% (71.7–84.2)-VaIN2/3 and 86.2% (68.3–96.1)-AIN2/3. HPV16 was the most frequent type in all lesions. Variations in the RC of HPVs 31/33/45/52/58 by cancer site were observed, ranging from 7.8% (5.0–11.4)-female anal cancer to 20.5% (16.1–25.4)-vaginal cancer.

Conclusions: The addition of HPVs 31/33/45/52/58 to HPV types included in current vaccines (HPV16/18) could prevent almost 90% of HPV positive female anogenital lesions worldwide. Taking into account that most HPV-related cancers are ICC ones, the 9-valent HPV vaccine could potentially avoid almost 88% of all female anogenital cancers.

1. Introduction

Infection with high risk (HR) human papillomavirus (HPV) is recognised as one of the major causes of infection-related cancers worldwide [1,2]. HPV infection is a well-established cause of invasive cervical cancer (ICC) and there is an increasing body of evidence strongly linking HPV DNA with other anogenital cancers (anus, vulva, vagina and penis) and head and neck cancers (particularly the oropharynx, base of tongue and tonsils) [3]. The vast majority of female HPV-related cancers are ICC cases (more than 85%). ICC is the fourth most common female malignancy worldwide, with an estimated 528,000 new cases and 266,000 new deaths in 2012, more than 95% attributable to HPV infection [4–7].

The other female anogenital cancers are less frequent than ICC, but cases HPV-related are also potentially preventable by vaccination. Approximately 88% of invasive anal cancer (IAnC) cases, 70% of invasive vaginal cancer (IVaC) cases and 43% of invasive vulvar cancer (IVuC) cases are attributable to HPV infection [1,2]. However, recent data suggest that the HPV contribution in IVuC could be substantially lower, close to 30% [8]. HPV DNA prevalence has also been estimated at 94% of anal intraepithelial neoplasia (AIN) grades 2/3, 91% of vaginal intraepithelial neoplasia (VaIN) grades 2/3 and 85% of vulvar intraepithelial neoplasia (VIN) grades 2/3 lesions [9].

After HPV16, data confirm HPVs 18/31/33/35/45/52/58 as the most frequently detected types in ICC [10,11]. By contrast, although HPV16 is uniformly the most frequently detected type in the rest of female anogenital cancers and precancerous lesions, data on HPV type distribution are generally scarce. Currently licenced HPV prophylactic vaccines (bivalent CervarixTM and quadrivalent Gardasil®), using virus like particles (VLP), have been recognised as a major advance and the most effective intervention to control for HPV and cervical cancer [12]. The US Food and Drug Administration has recently approved a recombinant 9-valent HPV vaccine for the prevention of cervical, vaginal, vulvar and anal cancer cases caused by HPVs 16/18/31/33/45/52/58 and for the prevention of genital warts caused by HPVs 6/11 [13]. The 9-valent HPV vaccine adds protection against five additional HPV types (HPVs 31/33/45/52/58) that caused up to 20% of ICC not covered by previous vaccines. The 9-valent HPV vaccine is as efficacious as quadrivalent HPV vaccine for the prevention of diseases caused by the four shared HPV types (HPVs 16/18/6/11). Several randomised clinical trials have assessed suitable safety, tolerability and immunogenicity profiles of the 9-valent HPV vaccine [14,15]. The 9-valent HPV vaccine would be a cost-effective alternative if it is proven to be highly effective and the additional cost per dose is not excessive compared to current HPV vaccines [16].

In order to evaluate its potential impact in the reduction of HPV-related disease burden and to help to formulate recommendations on HPV prevention, we aim to summarise existing HPV type distribution data for the specific nine types: HPVs 16/18/31/33/45/52/58/6/11, targeted by the 9-valent HPV vaccine across world regions.

2. Materials and methods

To estimate the relative contribution (RC) of the nine HPV types included in the recently approved 9-valent HPV vaccine in female anogenital cancer and precancerous lesions we used data from an international project on HPV-related cancers designed and coordinated by the Catalan Institute of Oncology (ICO) (Barcelona-Spain) in collaboration with DDL Diagnostic Laboratory (Rijswijk-Netherlands) [8,11,17,18].

2.1. Study design

The project is a retrospective cross-sectional study to estimate the HPV DNA prevalence and type distribution in women with ICC and other anogenital cancers. Case recruitment protocols were previously described [8,11,17,18]. Briefly, formalin-fixed paraffin-embedded (FFPE) specimens from consecutive cases were obtained from hospital pathology archives in 48 countries (Africa: Algeria, Mali, Mozambique, Nigeria, Senegal, Uganda; Americas: Argentina, Brazil, Chile, Colombia, Ecuador, Guatemala, Honduras, Mexico, Paraguay, Peru,

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