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CLINICAL ARTICLE

Potential impact of introducing a nonavalent HPV vaccination ☆

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Synopsis: It appeared that the introduction of the nonavalent HPV vaccination would improve protection against infections and related genital dysplasia.

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Abstract

Objective

To test the theoretical utility of incorporating nonavalent vaccination against HPV into a clinical setting.

Methods

The present retrospective study included data from consecutive patients who underwent HPV-DNA testing between January 1, 1998, and December 31, 2015. Changes in the prevalence of different HPV types were assessed during three periods (T1, 1998–2003; T2, 2004–2009; and T3, 2010–2015) using XY analysis.

Results: The study included a total of 13 665 patients. Overall, 1361, 5130, 7174 patients were included in the T1, T2, and T3 periods, respectively. The quadrivalent vaccine would have potentially protected against HPV in 71.5% (973/1361), 46.5% (2385/5130), and 26.5% (1901/7174) of patients in T1, T2, and T3, respectively (P<0.001 for trend). The nonavalent vaccine could have protected against HPV in 92.5% (1259/1361), 72.3% 3709/5130), and 58.1% (4168/7174) of patients in T1, T2, and T3, respectively (P<0.001 for trend). The proportion of patients with genital dysplasia grade 2+ who did not have infections with HPV genotypes covered by the quadrivalent or nonavalent vaccines increased across the three periods (P<0.001 for trend). For all study periods, the protection provided by the nonavalent vaccine

would have been superior to the quadrivalent vaccine (χ^2 test P<0.001).

Conclusion: The introduction of a nonavalent vaccine could improve protection against HPV infections and HPV-related genital dysplasia.

1 INTRODUCTION

HPV is a DNA virus associated with precancerous conditions of the lower genital tract. Approximately 27 000 cases of HPV-related cancers occur each year in the USA [1, 2]. More than 100 HPV types are known, and more than 40 types can be spread through sexual contact. In particular, it is estimated that HPV16 and HPV18 are the most common HPV types involved in the genesis of genital cancers, being involved in more than 70% of cervical cancer [1, 2].

HPV vaccines can prevent the most common types of infections. In 2006, the US Food and Drug Administration (FDA) approved the use of a quadrivalent vaccine (4vHPV-V) against four types of HPV (6, 11, 16, 18) [3,4]. A systematic review focusing on the impact of the 4vHPV-V, suggested that a decline in HPV16 and HPV18 prevalence (approximately 75%–80%) occurred in countries with high vaccine uptake (such as Australia and Denmark) [5,6]. Similarly, reductions of approximately 45% and 85% for low-grade cytological cervical abnormalities and high-grade cervical lesions, respectively, have been reported [7]. However, the potential effects of HPV vaccination are not yet utilized [8,9]. In fact, HPV-related disease remains a significant cause of concerns in low- and high-income countries.

Recently, the FDA licensed a nonavalent vaccine against HPV (9vHPV-V). The 9vHPV-V adds protection against five additional high-risk HPV types (31, 33, 45, 52, 58), in addition to the four HPV types covered by the 4vHPV-V. Growing evidence

supports the safety profile of the new vaccine [10–16]. Ideally, the widespread implementation of the 9vHPV-V will dramatically reduce the prevalence of HPV-related conditions [17–19].

Data regarding trends in the prevalence of HPV types are still scant current evidence is based on non-recently published data. Here, we sought to investigate trends in prevalence of HPV types to test the potential utility of HPV vaccinations in women. A secondary aim was to identify emerging HPV types not covered by the new 9vHPV-V to improve awareness on potentially important HPV types.

2 MATERIALS AND METHODS

In the present retrospective study, records from consecutive women who underwent HPV-DNA test between January 1, 1998, and December 31, 2015, at the Gynecologic Oncology Unit of the National Cancer Institute of Milan, Italy. Data from women who underwent HPV-DNA testing owing to the presence of suspected/diagnosed HPV-related genital infections were included in a dedicated database. Exclusion criteria were: (1) aged younger than 18 years; (2) withdrawal of consent; (3) the presence of invasive genital cancer at diagnosis. All patients included gave written informed consent for the use of personal information for health research when undergoing HPV-DNA testing. In line with Italian law, the study did not need require institutional review board approval, only notification.

The primary endpoint was a comparison of the potential utility of the 4vHPV-V and 9vHPV-V by evaluating the prevalence of the different HPV types over the study period. A secondary endpoint measure was to identify new emerging HPV types. The

analysis would be only theoretical because vaccination against HPV was introduced in Italy in 1992 for girls aged 12 years.

Over the whole study period, no specific guidelines supporting different screening methods were in place and treating physician opted to perform HPV testing using their own discretion. Demographic details, HPV type data, and treatment data for genital precancerous and cancerous conditions were retrospectively reviewed. All patients underwent colposcopy evaluations in the outpatient clinic. A dedicated team of gynecologic oncologists performed all gynecological and colposcopic examinations. High-grade genital dysplasia (2+) was defined by the presence of moderate/severe cervical dysplasia (cervical intraepithelial neoplasia grade 2+), moderate/severe vaginal dysplasia, high-grade vaginal intraepithelial neoplasia (histologic vaginal high-grade squamous intraepithelial lesion), and moderate/severe vulvar dysplasia (high-grade vulvar intraepithelial neoplasia or usual type vulvar intraepithelial neoplasia).

HPV testing was performed using the Clinical Array Technology HPV 2 assay (CLART; Genomica, Madrid, Spain), which combines highly specific and sensitive PCR with low-density array technology. Details regarding HPV testing have been reported elsewhere [17].

To assess changes in the prevalence of HPV types over time, the study duration was stratified into three periods, denoted as T1 (1998–2003); T2 (2004–2009); and T3 (2010–2015). These periods were chosen arbitrarily to simplify data reporting. Data were summarized using basic descriptive statistics and the χ^2 test was used to

compare the prevalence of HPV serotypes between the three time periods. Trends were calculated using XY analysis to investigate changes in serotypes over the study periods. All *P* values were two-sided and $P<0.05$ was considered statistically significant. Statistical analyses were performed using GraphPad Prism version 6.0 (GraphPad Software, San Diego, CA, USA) and SPSS version 20.0 (IBM, Armonk, NY, USA).

3 RESULTS

Over the whole study period, 13 665 patients participated in screening. The mean±SD age was 43.3±19.6 years. Overall, 1361 (10.0%), 5130 (37.5%), and 7174 (52.5%) patients underwent testing in T1, T2, and T3, respectively. In the entire cohort, 2883 (21.1%) patients were affected by HPV-related genital dysplasia grade 2+. Considering the whole population, infections with types HPV16 and/or HPV18 were the two most common involved in genital infections and were diagnosed in 2664 (19.5%) patients. Other HPV types covered by the 9vHPV-V were commonly detected; HPV31, 33, 45, 52, and 58 were observed in 943 (6.9%), 328 (2.4%), 208 (1.5%), 426 (3.1%), and 601 (4.4%) patients, respectively. Considering HPV-type prevalence over the years, the prevalence of HPV16/18 decreased dramatically ($P<0.001$ for trend), whereas the prevalence of all other HPV types slightly increased ($P<0.001$ for trend).

It was observed that the 4vHPV-V could have potentially protect against HPV infection in 71.5% (973/1361), 46.5% (2385/5130), and 26.5% (1901/7174) of patients tested in T1, T2 and T3, respectively ($P<0.001$ for trend; Figure 1). Further, administration of the 9vHPV-V could have protect against HPV infections in 92.5%

(1259/1361), 72.3% (3709/5130), and 58.1% (4168/7174) of patients tested in T1, T2 and T3, respectively (*P*<0.001 for trend).

HPV-related genital dysplasia grade 2+ was diagnosed in 2883 (21.1%) patients; of these patients, 200 (6.9%), 1007 (34.9%), and 1676 (58.2%) were diagnosed in T1, T2, and T3, respectively. Among the patients with genital dysplasia grade 2+, HPV16/18 were observed in 467 (16.2%) patients. The proportion of HPV16/18 infections in patients with genital dysplasia grade 2+ decreased dramatically across the study periods. In particular, it occurred in 70/200 (35.0%), 204/1007 (20.3%), and 193/1676 (11.5%) patients in T1, T2, and T3, respectively (*P*<0.001 for trend).

The proportion of patients with genital dysplasia grade 2+, who had infections with HPV types not related covered by the 4vHPV-V (13.0% [26/200] in T1, 21.0% [211/1007] in T2, and 34.0% [570/1676] in T3) and the 9vHPV-V (3.0% [6/200] in T1, 12.0% [121/1007] in T2, and 19.0% [318/1676] in T3) increased over time (*P*<0.001 for trend; Figure 2). For all study periods, the 9vHPV-V appeared to be potentially superior to the 4vHPV-V in protecting against HPV infection ($\chi 2$ test *P*<0.001; Figure 3). If considering HPV types not covered by the 9vHPV-V, the most common HPV infection among the entire cohort was HPV53 (956 [7.0%]), followed by HPV51 (536 [3.9%]), and HPV66 (521 [3.8%]). Other HPV types had a limited prevalence (<2.5%). Figure 4 displays the prevalence of dysplasia related to HPV16/18 and to other high-risk HPV infection other than HPV16-18.

4 DISCUSSION

The present study investigated trends in HPV-type prevalence and reported several noteworthy findings. First, it was observed that, albeit HPV16/18 represent the most common HPV types detected both in the whole population and in patients with genital dysplasia 2+, a significant decrease in the prevalence of both HPV16/18 occurred over the study period, with a concomitant critical increase in the prevalence of the other high-risk HPV types. Second, as expected the 9vHPV-V demonstrated potentially higher coverage to high-risk HPV types than the 4vHPV-V. Third, although it was not possible to test any cross-protection, the proportion of HPV types not covered by the 4vHPV-V and 9vHPV-V was observed to increase over the study duration. Fourth, HPV53, 51, and 66, represented three new emerging HPV types that, thus, deserve further attention.

Accumulating evidence focusing on the clinical efficacy of the implementation of the 4vHPV-V, in countries with high vaccine uptake, report very high coverage against both the low- and high-grade cervical lesions [15, 18, 19]. In keeping with the rate reported in the Seattle study [18], it was observed in the present study that the 4vHPV-V protected approximately 65% of patients. Growing data support the safety profile of the new 9vHPV-V although evidence on its efficacy is still lacking owing to the recent introduction of this new vaccination program [19–21]. Therefore, in the absence of a high level of evidence supporting the implementation of the 9vHPV-V, the present retrospective study, testing the potential effects of the 9vHPV-V, could be useful in assessing its potential benefits. Moreover, cross protection is a well-known feature in HPV vaccination programs; it has been reported that vaccine efficacy against genital dysplasia grade 2+ associated with the composite of 12 non-vaccine

HPV types (HPV31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) ranged between 34.2% and 56.2% [10]. Interestingly, the combined results of the Costa Rica Vaccine Trial [19] and the PATRICIA trial [20] suggested that the efficacy of the 4vHPV-V against incident HPV31, 33, and 45 was approximately 37%, 38%, and 60% after one, two, and three doses, respectively, suggesting that the coverage guaranteed by both the 4vHPV-V and 9vHPV-V would be higher than expected in the present study [19, 20]. The main limitations of the present investigation included the inherent biases related to its speculative nature. Moreover, it was not possible to identify patients who had received the 4vHPV-V, thereby limiting the generalization of the results. Conversely, the large sample size included represent the main strength of the present study. Moreover, the present study had the merit of reporting data regarding HPV-type prevalence and data regarding new emerging HPV types.

In conclusion, the present study investigated trends in HPV-type prevalence, and compared the potential clinical utility of the 4vHPV-V and 9vHPV-V. Although it was not possible to test cross protection, the 9vHPV-V could be effective in protecting against most genital dysplasia. Further prospective studies are warranted to support these data and to investigate the clinical utility of vaccination programs.

Author contributions

GB and ULRM contributed to the conception of the study, data analysis, and writing the manuscript. FT, CL, MS, VC, CS, DR, AD, FM, CB, and SP contributed to data collection and revising the manuscript. JC contributed to data collection and writing the manuscript. SF, DL, and FR contributed to data interpretation and revising the manuscript.

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Conflicts of interest

The authors have no conflicts of interest.

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Figure 1 Trends in type-specific HPV prevalence among the entire study population. Abbreviations: T1, 1998–2003; T2, 2004–2009; T3, 2010–2015.

Figure 2 Trends in type-specific HPV prevalence among patients with genital dysplasia grade 2+. Abbreviations: T1, 1998–2003; T2, 2004–2009; T3, 2010–2015.

Figure 3 Trends in potential HPV-specific vaccine coverage. Abbreviations: T1, 1998–2003; T2, 2004–2009; T3, 2010–2015; 4v, quadrivalent vaccine; 9v, nonavalent vaccine.

Figure 4 Prevalence of genital dysplasia grade 2+ in women with infections of HPV 16/18 or other high-risk HPV types.