Distinguished Expert Series

Current direction in the prevention of cervical cancer

J. Monsonego

Executive Secretary and Founder, EUROGIN, Paris (France)

Summary

Cervical screening seems to benefit a minor part of the world female population, and yet women who benefit from it still prove its weaknesses. The fact that these genital lesions are the consequence of a chronic genital infection with HPV opens new and extraordinary opportunities for prevention through vaccination. The highest efficacy is demonstrated in young women naive to the virus types associated with the vaccines. The effectiveness of HPV vaccines are limited by two factors: all genital cancers and precancerous lesions are not induced exclusively by HPV types 16 and 18, and the optimal benefit is demonstrated in adolescents and young women before they have encountered these viruses. Vaccination and screening act complementarily and synergistically, and constitute to date the new standards of disease prevention.

Key words: Cervical intraepithelial neoplasia; Cervical cancer; Genital warts; HPV vaccines; Human papillomavirus.

In spite of the considerable success registered by the early detection procedures for cervical cancer prevention, the "smear" has not fulfilled all hopes one could expect in reducing cancer incidence on a large scale. Cervical screening seems to benefit a minor part of the world female population, and yet a large proportion of women who benefit from it still prove its weaknesses [1].

Lower genital tract infections by human papillomaviruses (HPV) are very frequent, and the most virulent types, 16 and 18, are responsible for two-thirds of cervical cancer cases worldwide. Genital warts (condyloma acuminata) induced by HPV 6 and 11 affects nearly 2-4% of males and females younger than 25 years, and the clinical management is generally long and difficult [2]. The burden and weight of papillomavirus-associated diseases are significant. The psychological and emotional impact is also an important issue.

The fact that these genital lesions are the consequence of a chronic genital infection with HPV opens new and extraordinary opportunities for prevention through vaccination. HPV vaccines are the first vaccines presented as an anticancer immunization. Indeed, these prophylactic vaccines that protect against precancerous and cancerous lesions associated with HPV will save lives, reduce costly treatment interventions, and have an individual and collective benefit that should not be neglected.

Clinical studies of vaccines against papillomavirus based on the use of pseudo viral-like particles (VLPs), constituted by the major protein L1 of the virus capsid without any viral genetic material (immunogenic while not infectious and non-transforming) demonstrated their remarkable efficacy in preventing cervical precancers and cancers, as proven with Gardasil and Cervarix. Their level of clinical efficacy is unprecedented in the history of vaccination: close to 100% [3-7].

The highest efficacy is demonstrated in young women naive to the virus types associated with the vaccines. Additional preliminary results indicate that vaccination is also efficacious in protecting women who were infected in the past but naturally eliminated the virus. The vaccine has no therapeutic effect on existing lesions or on the course of viral infections already carried by healthy individuals [3, 4, 8, 9]. The impact of vaccination is also relevant in vaginal and vulvar lesions [4], which although somewhat less frequent than cervical lesions, however cannot benefit from early detection programs and treatment, can be scattered and relapsing, and hence traumatizing. Data supporting additional cross-protection vaccine efficacy have been reported in the 2007 Eurogin conference and are expected to be published in shortly [5, 8, 11].

In practice the effectiveness of HPV vaccines are limited by two factors: all genital cancers and precancerous lesions are not induced exclusively by HPV types 16 and 18, and the optimal benefit is demonstrated in adolescents and young women before they have encountered these viruses [1].

In fact, delaying the period of vaccination could imply losing its maximal valuable protective effects. Nevertheless, in clinical practice it is necessary to interpret trial results with a critical view. For instance, it is unlikely that a person has been exposed to all types of viruses included in the vaccines. Therefore a protective effect can always be achieved against the types that have not been encountered; in clinical trials 80% of girls and young sexually active women under 26 years were HPV and serology negative for HPV vaccine types. Furthermore, the benefit of vaccinating subjects

Revised manuscript accepted for publication October 10, 2007

already exposed to virus types of the vaccine seems to increase over time as compared to the subjects receiving a placebo [12]. Finally, among young women aged 15 to 25 years, the clearance rate of previous infections is high, and the frequency of infections by types 16 and 18 is low in the general population.

The question of vaccination before or after sexual debut is controversial, and depends on the concept of individual or collective benefits and arguments of effectiveness over efficacy.

The reported adverse effects of vaccination are generally minor. National and international plans for monitoring and evaluating risks linked to HPV vaccination are already in place, and will allow the benefits of vaccination by age group to be measured within a few years.

Practical questions will need to be addressed, such as the emergence of other viral types, the need to vaccinate boys, the duration of vaccine protection, the extent of cross protection against other HPV types, and access to vaccines in poor countries.

If vaccination would be left to individual choice and initiative, the coverage would be low and the benefit in reducing the frequency of this cancer would be barely perceived. We need to keep in mind that, in the context of public health, it may take several years to observe the benefits of preventing cervical cancer cases following a large number of vaccinated individuals, while the impact of individual vaccination in reducing precancerous lesions will be significant within a cohort in a relatively short time period following vaccination, as has been observed in clinical studies over two to four years.

Thus, there is a need for a vaccination policy, which is likely to differ in poor countries where the magnitude of disease represents a larger toll of disease and mortality, and in wealthy countries where screening programs have significantly reduced the frequency and mortality of this cancer.

The adoption of systematic or routine vaccination of girls aged 9-15 years, with a catch-up of cohorts of young women aged 16-26 years, corresponds to the indication of the product as defined in the marketing authorization by the European Medicines Agency (EMEA).

The success of vaccination as a public health intervention will depend on its acceptability and the degree of engagement of health professionals. A vast educational program for the general population, for patients and for health professionals is needed. As vaccines will not protect from all possible HPV types associated with cervical cancer, the screening programs should be maintained at current intervals and conditions. Vaccination and screening act complementarily and synergistically, and constitute to date the new standards of disease prevention.

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Address reprint requests to:
J. MONSONEGO, M.D.
Executive Secretary and Founder
EUROGIN
174 Rue de Cancelles
75017 Paris (France)