

**CURRENT KNOWLEDGE ON PREVENTION AND CONTROL OF HUMAN
PAPILLOMAVIRUS INFECTION AND CERVICAL CANCER**

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ABSTRACT

Human papillomavirus (HPV) is the etiological agent of cervical cancer and has been associated to other anogenital and oropharyngeal tumors. Since screening procedures are not completely efficient in controlling such neoplasias, prophylactic measures are the most promising intervention to reduce burden caused by infection. This review discusses the available information regarding the two commercial prophylactic vaccines against HPV. Despite great expectations and clinical results, we still lack sufficient evidence of its efficacy and its real impact on cancer prevention will not be observable for decades.

INTRODUCTION

Human Papillomavirus (HPV) are small DNA viruses which are now accepted as the etiological agents of cervical cancer. Up to 70% of sexually active women will become infected with HPV during their lifetime (Bosch & Sanjosé 2003).

More than a hundred different types of HPV have now been described and classified according to their malignant potential. High risk types (e.g. HPV 16 and 18) have been linked to high grade intraepithelial lesions (HSIL) and invasive carcinoma, whereas low risk types (e.g. HPV 6 and 11) have been associated to benign or low grade SIL (LSIL).

Their relevance in public health is related to the fact that they are the most prevalent sexually transmitted viruses. Besides the World Health Organization recognizes them as the only independent factor for cervical cancer establishment. It is important to notice that cervical cancer is the second cause of malignant neoplasia and

death in women worldwide, with nearly 500,000 new cases and 250,000 deaths each year (Baseman & Koutsky 2005).

Prevention and control measures have began even before researchers elucidate the etiological agent of cervical cancer and it is the only human malignancy in which public health prevention initiatives have consistently reduced incidence and mortality rates, mainly in developed countries.

Widespread programmatic or opportunistic screening with Papanicolaou cytology technique was firstly implemented in Finland in 1963, followed by the other European as well as South and North American countries during the 60's. The impact of such programmes reflected in cancer incidence contributing to a reduction of 75% of cervical cancer cases. Additional factors important to further historical declines are the gradual reduction in population fertility and improvements in the diet.

Reduction in cancer rates was also remarkable in countries like Brazil, where over 65% of decrease in cervical cancer records was obtained after 2000, due to extensive public campaigns (INCA 2008).

Nevertheless, in the beginning of the 90ies, cancer incidence rates estabilized, what led several researchers to look for additional procedures to improve cancer control and prevention.

Initially, molecular DNA testing by using hybridization or PCR assays were the most promising approaches to achieve cervical cancer incidence reduction. Several protocols were adopted in developed countries worldwide, but results are till now controversial. The point detection of an HPV infection in the female cervix is not sufficient to result in an intervention on clinical routine of treatment or follow-up.

This is due to the fact that nearly 90% of all HPV infections are transient and are cleared from immunocompetent female organisms within 6 to 24 months. Thus, impact on cancer reduction showed to be small, leading several physicians to doubt in using DNA detection (Syrjänen & Syrjänen 2000) (Figure 1).

These unexpected results led several groups studying HPV to focus on primary prevention: reduction of disease by reduction of risk factors by reducing promiscuity, augmenting safe sex and blocking the circulation of the etiological agent by developing a prophylactic vaccine.

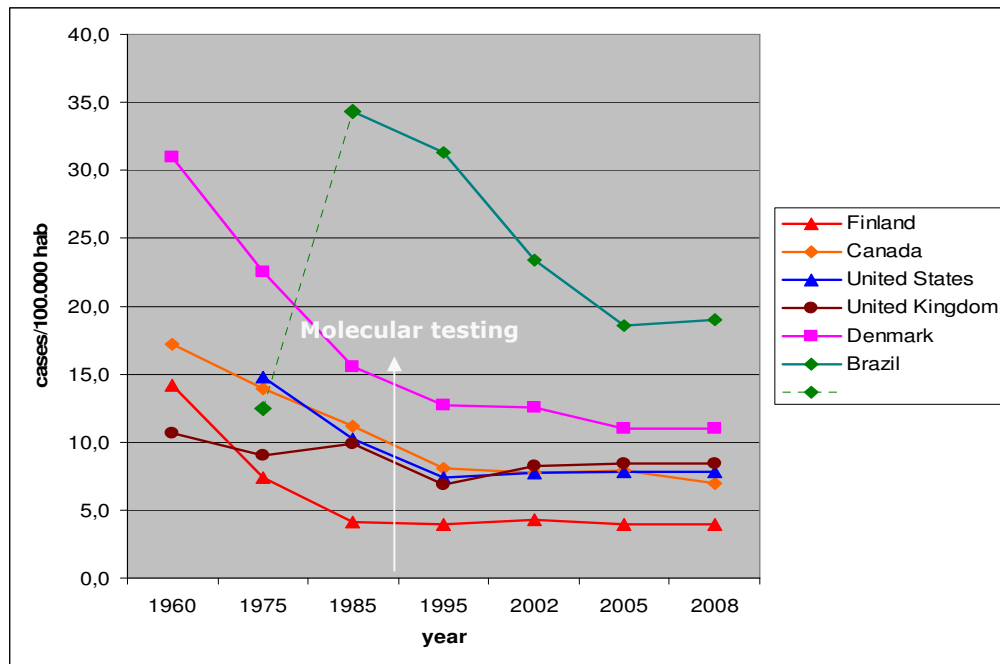


Figure 1. Incidence of cancer cases after implementing Papanicolaou test and molecular testing.

To develop an efficient vaccine, the knowledge of molecular events of immune response are necessary. Some studies pointed out that, despite the 90% of infection

clearance, only 50% of infected women developed antibodies response (Giuliano & Viscidi 2007).

Studies regarding antibodies effect of reinfection were conducted but results were conflicting: Ho et al. (2002) found significant protection to reinfection in antibody-responsive women but Viscidi et al. (2005) did not achieve the same results, discussing the role of prophylactic vaccines in conferring protection.

In fact, the available vaccines composed by Virus-Like Particles (VLP) are given intradermally, eliciting seric antibodies. The first trials showed that vaccination resulted in seroconversion of nearly 100% of the tested women. Antibody levels were obtained in concentrations 50 folder higher than the obtained in natural infection (Schiller et al. 2008).

By now, two recombinant vaccines are registered in Brazil: Gardasil, from Merck Inc., combining HPV 6, 11, 16 and 18 – prepared in a yeast system and Cervarix, from Glaxo Smith Kline – prepared in Baculovirus system including oncogenic HPV 16 and 18.

Both vaccines contain the most prevalent oncogenic HPV and are meant to prevent cancer. Gardasil contains also HPV 6 and 11 VLP and thus prevent benign condylomata acuminata.

Nevertheless, viral types selection has also been questioned since geographical variations among HPV distribution were described (Clifford et al. 2005). It is worthnoting that in India, HPV 18 is a low-circulation virus in the half of the cervical cancer cases and nearly 70% of mortality rates, appearing in 5th place among oncogenic circulating types and being preceded by HPV types 42, 56 and JC9710. Thus it seems

that specific formulations of the vaccines would be necessary to impact properly in different regions of the world.

Regarding the most relevant trials conducted in order to check efficacy, we observed that for Gardasil trial the attending to protocol group (ATP) achieved 100% of efficacy in preventing CIN 1. But when we analyzed the intention to treat group (ITT), we noticed that efficacy fall to 20% for CIN2/3 endpoints (Schiller et al. 2008). Kahn & Burk (2008) questioned that analysis of ATP group is distant from reality: First of all, because all women were already sexually active and to fulfill the protocol needed to remain negative for HPV infection during the seven months of the research, what made them naturally less promiscuous than the general population.

The authors suggested that we have to focus in the ITT group, that is our real world and then the vaccine seems to be poor as a cancer preventing tool. Kim & Goldie (2008) were optimistic suggesting that vaccine present interesting results but indicating that more extensive trials have to be concluded in order to reveal the exact impact in cancer control worldwide, what may take decades.

Haug (2008) comments that there has been pressure on policymakers worldwide to introduce the HPV vaccine in national or statewide immunization programs, with insufficient evidence of good results or answers, especially whether intervention will work or, in the worst case, do harm. The author then suggested that one way to provide decision support is to develop mathematical models of the natural history of the disease, introducing different intervention strategies and using cost-effective analysis to estimate the costs and health benefits.

Table 1. Outstanding questions and challenges of HPV vaccines.

Duration of immune-response and need of boosters
Safety and tolerability of the vaccines
Efficacy in reducing incidence of cervical cancer
Efficacy in reducing incidence of other anogenital cancers
Efficacy in reducing incidence of other HPV-related cancers (head and neck cancers)
Efficacy in men of different ages
Efficacy in immunocompromised individuals
Increase in prevalence of non-vaccine types after widespread vaccination
Impact on screening guidelines for cervical cancer
Impact on screening behaviours for cervical cancer
Impact on adolescents' sexual beliefs and behaviours
Social and familiar acceptance of the vaccines
Cost-effectiveness in women and men, in regions with or without organised cytological screening programmes

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