

Rapid Communication

Prevention strategies of cervical cancer in the HPV vaccine era

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Rationale

Pap testing

Organized and opportunistic screening programs for cervical cancer have been very successful in many developed countries with reductions in squamous cell cervical cancer incidence of the order of 70%. In these countries, age specific incidence rates tend to plateau in the age groups in which screening is recommended. In countries where screening programs have not been developed, the incidence of cervical cancer continues to rise with age (Fig. 1). The incidence of cervical cancer in the decades to come might in fact increase in developing countries due to the aging of the population and the persistent absence of adequate screening programs. The success of these programs requires repeated testing over a woman's lifetime and a population based network for early detection and treatment of cervical cancer precursors, with a public health cost that supersedes any other successful preventive program developed to date.

In countries with screening, the target of preventive efforts has shifted from cervical cancer detection to the diagnosis and treatment of cancer precursor lesions. However, the morphologic basis of the screening test cannot be substantially improved, inherently diminishing the accuracy for precursor lesion diagnosis. In these countries, a false negative Pap test occurs in 30% of all cervical cancers diagnosed and another 10% is attributable to errors in following up abnormal cytology reports. The goal of most programs is to reach the very low, but

achievable incidence rate of 2–3/100,000 women, a rate observed for example in the Finnish screening program.

Despite this limitation, a significant reduction in cervical cancer has been achieved with cytology-based technology and screening strategies to date. Improving the cost-effectiveness of the screening system has resulted in several national screening guideline committees recommending one or more of three changes: a) an increased screening interval for women who have repeatedly screened normal; b) new methods of processing cellular samples such as liquid based cytology; and c) various methods of testing for high risk Human Papillomavirus (HPV), the known etiologic agent of cervical cancer. It is too early in adoption of these strategies to determine whether they are truly an improvement in public health costs and disease detection.

In spite of screening efforts, women in developed countries continue to develop cervical cancer. The incidence rates in Western Europe continue to show a bimodal age distribution of those around 30 years of age and another equally prominent group around 60 years (Fig. 2). Mortality to cervical cancer increases steadily with age and represents about half of the incidence. It has been estimated that in Western Europe, some 30,000 new cases per year are diagnosed and about 15,000 deaths still occur.

The behaviours of women, besides the limitations of the test itself, also contribute to the continued incidence of cervical cancer. In the US, half of all women who develop cervical cancer have never had a Pap test; and another 10% did not present for screening within the five years preceding their diagnosis of cervical cancer. Women do not present for screening for a variety of reasons including fear, embarrassment, anxiety, gender of the physician, immigrant status, older age, lower income and religious beliefs.

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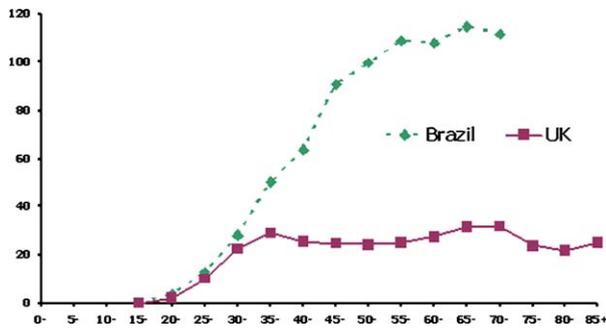


Fig. 1. Age-specific incidence of cervical cancer in two countries with and without centralized and widespread screening programs.

Human papillomavirus

HPV is established as the necessary cause of cervical cancer. HPV 16 is associated with about 60% of the cervical cancers, type 18 with about 10%, types 45 and 31 with 4% each, and types 33, 52 and 58 each contributing another 2% to cervical cancer globally [1,2]. HPV 16 and 18 also account for some 25% of the low grade cervical lesions (LSIL) and 50 to 60% of the high grade lesions (HSIL). HPV 6 and 11 are responsible for some 10% of low grade cervical lesions and about 90% of the genital warts.

There appears to be an anogenital HPV prevalence in girls and boys that starts at birth evidenced by the presence of antibodies or HPV DNA in the oral cavity or the external genital tract. High risk HPV types are detected in childhood, with an underlying prevalence of 3–10% before 11 years of age. With the exception of the rare cases of Recurrent Respiratory Papillomatosis (RRP) or the cases of genital warts in children, the clinical outcome of detecting viral DNA in infants is at present undetermined. Beyond puberty, the prevalence of high risk HPV types peaks at 30–50% for young women in their second and third decades of life. The prevalence of high risk HPV declines to 15% for women 26–30 years of age, to 10% for women 31–35 and to an underlying population prevalence of 5–15% during the fourth, fifth and sixth decades of life. Thereafter, the prevalence increases to peaks up to 30% for women older than 50 years completing the U shaped age specific HPV prevalence curve, observed in most but not all countries, with a cumulative lifetime prevalence rate of about 80%.

Data for boys are mostly limited to low risk HPV/genital wart occurrences at less than 1 per 1000 among young boys, The rate of HPV increases for males 20–25 years of age reaching a peak of 5/1000 at 25 and then slowly decreasing back to less than 1/1000 at the seventh decade of life [2].

The incidence of high risk HPV parallels the prevalence statistics reported. Women under 25 years of age have the highest acquisition of high risk HPV at 4.5% per year, with a drop to 1% per year for women 35–55 years, and an upswing in women older than 55 years to 2% per year. At the same time, the risk of not clearing a high risk HPV infection increases with age. In women younger than 25 years, 20% of the high risk HPV infections persist, but in women older than 55 years, at least 50% of high risk HPV infections persist. The interpreta-

tion of results from cohort studies is however complicated by the different intervals used to assess viral persistency across studies.

Current evidence based medicine

HPV screening

HPV testing has been extensively evaluated and major international reviews have concluded that it a) is more efficient than repeated cytology in the triage of ambiguous cytological lesions; b) is at least as efficient as cytology as a primary screening test; and c) is more efficient than cytology as a test of follow up for recurrence after treatment for pre-invasive lesions [1,2].

At present, there is only one FDA approved HPV testing system which uses a cocktail of the 13 HPV types that are prevalent in cervical cancer and HSIL. In the future, clinicians might benefit from knowing the number and the identification of the specific types present in order to follow for persistent infections and/or to test for cure after therapy.

HPV vaccines

The L1 Virus Like Particle (VLP) for specific HPV types is a highly efficacious vaccine antigen in humans. Clinical trials of multivalent L1 VLP vaccines intended to be disseminated in public health programs show safety, immunogenicity and high efficacy [3–5]. The L1 VLP vaccines are unlikely to be effective as a treatment of women currently positive for a persistent HPV infection of the same type. These vaccines are not therapeutic.

At present there are two vaccines in the latest stages of Phase III results and under licensure application procedures: A bivalent that includes antigens of HPV 16 and 18 [5,6] and a quadrivalent that includes HPV 16, 18, 6 and 11 [7]. Types 16 and 18 cause 70% of cervical cancers and 6 and 11 cause about 90% of genital warts.

In terms of immunogenicity, safety and efficacy for women, both vaccines perform well [5–7]. Immunogenicity is universal

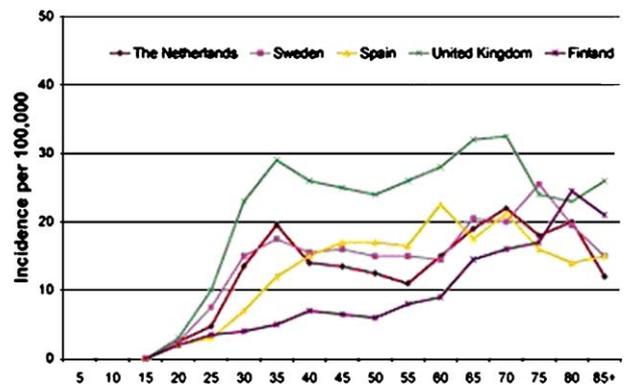


Fig. 2. Age-specific incidence rates of cervical cancer in five European countries. (With permission from: Bosch FX, de Sanjosé S. Chapter 1: Human Papillomavirus and Cervical Cancer-Burden and Assessment of Causality. *J Natl Cancer Inst Monogr* 2003,31:3–14).

with antibody titers higher than the titers observed following natural infection [8,9]. Protection against persistent infection and Cervical Intraepithelial Neoplasia (CIN) 2/3 up to 4 to 5 years of follow up has been reported at 100% for the HPV types included in the vaccines [6]. The quadrivalent vaccine phase III trial abstracts have reported 100% condyloma, vulvar intraepithelial (VIN) and vaginal intraepithelial neoplasia (VaIN) protection [7].

The bivalent HPV 16 and 18 vaccine has also shown high protection against incident infections due to HPV 45 (genetically related to HPV 18) and partial protection against HPV type 31 (genetically related to HPV 16) [5,6]. There are no reported data on cross-protection against other HPV types or against HPV type specific CIN. The quadrivalent vaccine has not yet reported results on cross-protection. The tolerability of both vaccines has been acceptable.

Several research issues are still outstanding and may have an influence on the vaccination protocols. These include, amongst other, the duration of protection after immunization, the requirements for additional boosting doses, the effectiveness in males and the long term safety. The HPV vaccines need to be evaluated in special populations such as the HIV infected women and in populations in Africa.

Recommendations

There is no age within populations that is completely protected from exposure to high risk HPV types. Of all the SIL reports made, approximately 2% occur in 10–14 year old girls, 3.7% in 15–19 year olds, 4% in 20–24 year olds, 2.5% in 25–29 year olds, about 1.6% in 30–40 year olds, and less than 1% in women older than 40 years. Given a varying prevalence of high risk HPV types during the entire lifetime of a woman, the age of vaccination depends on the duration of the vaccine protection and logistical implementation methods. Vaccination during childhood and/or adolescence will not be accompanied by cervical cytology screening until the woman reaches her early twenties, or the age at which national guidelines recommend initiation of cervical cancer screening. Women vaccinated during reproductive ages must continue with screening. HPV DNA testing, and interval of screening (e.g. every 2/3 or more years) are topics of cervical cancer screening under active investigation.

HPV vaccines are being proposed as an important added tool to the primary prevention of cervical cancer [3–8]. Although at present only two cancer causing HPV types are manufactured in each vaccine, there appears to be increased type coverage against other oncogenic types, which cost benefit analyses have not yet incorporated into their models. For high resource settings, the future of cervical cancer prevention may include a combination of HPV vaccination starting at young ages followed by a continued screening protocol. The latter will most probably be type-specific HPV testing based when new testing methods are validated and will be associated with longer screening intervals and fewer colposcopy referrals. The rationale for this combined strategy is an awareness of the viral etiology of cervical cancer by the medical professions and

the general public, as well as the expected reduction in cytology and histology test characteristics because of prevalent disease reduction in HPV 6/11/16/18/45/31 related lesions. HPV testing, clinically validated for many years, will be reported for type specific infections in an effort to monitor vaccine effectiveness.

HPV vaccination cannot be instituted at the cost of ignoring the current, successful, cervical cancer screening guidelines in countries with established screening programs [2]. Vaccination must be incorporated into the current national cervical cancer control guidelines of each country. Cytology, either conventional or liquid based, alone or in combination with HPV testing offer options for cervical cancer screening.

Research issues

Age of first vaccination will depend on a number of specific parameters under research including the duration of vaccine protection and the need and opportunities for and costs of boosting. Among women in the middle age groups, HPV vaccination trials are ongoing.

Follow up of vaccinated cohorts should include cost effectiveness evaluations. It is important to assess the value of HPV primary screening associated with triage by cytology following vaccine introduction. The importance of reducing screening intervals and colposcopy requirements is an issue of significant public health impact. Furthermore, it will be imperative to monitor closely how cytology performs as a screening test in such women because of the potential for the decreased rate of lesions to impact on the positive predictive value of this test. Close surveillance will also help determine if other performance characteristics of cytology will worsen if the changes in distribution of squamous abnormalities to inflammatory and reactive atypias tends to negatively affect sensitivity and specificity.

In countries without screening programs it is unlikely that widespread cytology based screening as the main primary prevention strategy will continue to be actively promoted and implemented in an efficient way. In these countries HPV vaccination is likely to be the most cost effective method of reducing cervical cancer burdens. Adolescent vaccination, low cost screening programs and eventually vaccination campaigns including young adults and middle age women are possibilities. The need for a booster dose is a research area of the greatest importance. Follow up of vaccinated women should continue to evaluate screening options.

The availability of multivalent vaccines including additional HPV types might reduce the requirements for subsequent screening in the vaccinated cohorts [7]. However, this future option should not delay the rapid introduction of the currently available vaccines [5–7]. The reasons are that a) extended valent vaccines might not be available for years; b) current adolescents at risk of exposure to HPV 16 and 18, the most commonly occurring types will not be protected; and c) the introduction of a vaccine targeted at adolescents will impose novel logistic requirements that need piloting and phased introduction. The introduction of the HPV 16/18 vaccines will be useful in offering immediate and nearly

complete protection to the current adolescent generation, setting a research framework for continued vaccine development and implementation.

Appendix A

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Disclosure:

None.

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