Natural history and epidemiology of HPV infection and cervical cancer

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Abstract

Cervical cancer is the most common cancer affecting women in developing countries. It has been estimated to have been responsible for almost 260,000 deaths annually, of which about 80% occurred in developing countries.

Persistent infection by certain oncogenic HPV types is firmly established as the necessary cause of most premalignant and malignant epithelial lesions of the cervix and of a variable fraction of neoplastic lesions of the vulva, vagina, anus, penis, and oropharynx.

There are more than 100 known HPV genotypes, at least 15 of which can cause cancer of the cervix and other sites. HPV 16 and 18, the two most common oncogenic types, cause approximately 70% of all cervical cancers worldwide. HPV, especially genotypes 6 and 11, can also cause genital warts. HPV is highly transmissible and it is now considered the most common sexually transmitted infection in most populations. Although most women infected with the virus become negative within 2 years, women with persistent high-risk HPV infections are at greatest risk for developing cervical cancer.

Since the identification of HPV as the necessary cause of cervical cancer, HPV-based technology has become the centre of novel primary and secondary cervical cancer prevention strategies by the introduction of HPV testing in screening and of HPV vaccines in preadolescent girls and young women. If implemented widely and wisely the deployment of these protocols has the potential to complete Papanicolaou’s goal of cervical cancer eradication by extending the benefits of prevention to the developing populations of the world.

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Introduction

One of the most important discoveries in the etiologic investigation of cancer over these last 25 years has been the demonstration that cervical cancer is caused by the persistent infection by certain genotypes of the Human Papilloma Virus (HPV). The scientific evidence accumulated from virological, molecular, clinical and epidemiological studies has demonstrated unequivocally that cervical cancer is in fact a sequel to a long term unresolved infection by certain genotypes of the HPV [1]. Thus, we can now affirm that cervical cancer is the final result of a viral infection and, as such, vaccination is a strategy to consider in the primary prevention of cancers and other diseases caused by HPVs.

The Human Papilloma Virus (HPV)

The human papilloma viruses (HPVs) are DNA double strand viruses and of small size (approximately 8000 pairs of bases) that have cohabited with the human specie over dozens of millennia suffering relatively few changes in their genetic composition. These nearly 100 different types of papillomavirus identified express a characteristic tropism. Some types are cutaneotropic (HPVs 1, 4, 5, 8, 41, 48, 60, 63 and 65) and are isolated frequently in cutaneous and plantar warts, in cutaneous lesions in the patients with verruciform epidermosisplasia, in cutaneous lesions in immuno-depressed patients after a transplant and in some epithelial tumours. Another group of HPVs are mucosotropic (HPVs 6, 11, 13, 44, 55, 16, 31, 33, 35, 52, 58, 67, 18, 39, 45, 59, 68, 70, 26, 51, 69, 30, 53, 56, 66, 32, 42, 34, 64, 73, 54) and they are identified in benign and malignant lesions of the anogenital tract in both sexes. Occasionally, these viral types are isolated in tissues and lesions of the oral cavity, oropharynx, larynx and oesophagus. Finally, another group of HPVs is isolated indifferently in cutaneous or mucous tissues and lesions (HPVs 2, 3, 7, 10, 27, 28, 29, 40, 43, 57, 61, 62 and 72) and its association with malignant lesions is less established.

The best known clinical expression of the viral infection is condylomas or genital warts, associated in approximately 90% of the cases by infections by HPVs 6 and 11 and, more rarely,
with HPVs 42 and 16. These viral types can be transmitted from the mother to the newborn at the time of childbirth and cause laryngeal papillomatosis, a strange complication but of recidivist prognosis and difficult to treat.

The neoplastic cervical (CIN), vulvar (VIN), vaginal (VaIN), penile (PIN) and anal (AIN) lesions are associated occasionally with “benign” or “low risk” HPVs such as HPV 6 and HPV 11, but more frequently with the typically “high risk” carcinogenic or oncogenic HPVs like HPV 16, 18, 45 and 31. More than 35 types of HPV have been isolated in neoplastic lesions of the anogenital tract.

### Natural History of Infections by HPV

Infection by HPV is basically a sexually transmitted disease. As such, both men and women are involved in the epidemiological chain of infection and are able at the same time to be asymptomatic carriers, transmitters and also victims of the infection by HPV [2]. In this sense, the risk factors associated with the infection by HPV are clearly related with the individual’s sexual behaviour. The most important are: early age at the start of the first sexual relationships, high number of sexual partners throughout life, sexual contacts with high risk individuals (in men, frequent contact with women that practice prostitution and in women, frequent contacts with men with multiple sexual partners). Male circumcision and the strict and systematic use of condoms are factors that can reduce, although without totally preventing, the risk of transmission of HPV between sexual partners [3–5].

High prevalence groups can be identified socially in the population of women who practice prostitution and in persons infected by the Human Immunodeficiency Virus (HIV). HPV transmission takes place, mainly, by sexual contact and the organs most susceptible to infection with potential of starting a neoplastic transformation are the cervix (transformation zone) and the pectineal line of the anal canal. HPV infections are frequently in sheet and HPV DNA can be detected in the cervix, vagina, and vulva in the woman, the glans, prepuce and skin of the penis and scrotum in the man, and in the anal canal and perianal area in women and men.

At the ages of greatest sexual activity, the prevalence of subclinical HPV infections (presence of viral DNA with normal morphology or minimal changes) can be up to 40% in the female population, with an annual infection rate of 10–15%. In the age groups beyond 30 years, the prevalence decreases to 5–10%. The half life of infections by HPV has been estimated at 8–10 months for the high risk types and of approximately half that for low risk viral types. The infections by HPV 16 are those that present the most prolonged longevities with average persistence values of 16 months in some studies [6]. The resolution of the infection seems to offer a certain degree of protection with respect to re-infections for the same type of HPV, with a certain degree of cross immunity between viral types being described (in few studies).

It is important to emphasize that at young ages and at the most sexually active ages in spite of very frequent infection by HPV, the great majority of infected women (more than 90%) resolve the infection spontaneously and the infection persists in

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**Fig. 1.** Estimated percentage of cases of cervical cancer attributed to the most frequent HPV types in all the regions of the world combined. Estimated from: (A) the combined analysis of the IARC with 3,085 cases [adapted from [17]], and (B) a meta-analysis including more than 14,500 cases [adapted from [18]].
only a small fraction of women [7]. It is this small group of women, chronic carriers of high risk HPVs, who have a high risk of progression and development of neoplastic lesions of the anogenital tract [8].

The well-known determinants of progression are the viral type, the persistence of the infection upon repeated examinations and, probably, the viral load per cellular unit, as well as the integration of the viral DNA into the cellular DNA. Infection by HIV constitutes a risk factor for infection as well as for neoplastic progression, in particular during the immunosuppression periods. Additional established progression factors include prolonged use of oral contraceptives, high parity and tobacco smoking [9,10]. Possible factors include diet, in particular diets poor in fruits and vegetables, and co-infection by other sexually transmitted agents such as Chlamydia trachomatis and Herpes Simplex Virus type 2 [11–13].

HPV and Cervical Cancer

The epidemiological and clinical studies that have incorporated molecular biology techniques of high sensitivity in appropriate biological specimens, detect oncogenic or high risk HPVs in practically 100% of the cervical cancers. Formally it has resulted in questioning the existence of cervical cancers unassociated with HPV. Equally, viral DNA is detected in the majority (70 – 90%) of the precursor lesions or intraepithelial lesions of high degree (CIN II-III) and, in a smaller fraction (20 – 50%), in the low grade lesions (CIN I). Finally, in the category of cytological lesions of uncertain nature (ASCUS and AGUS) the detection of HPV is close to 50%.

The most frequent viral types in cases of invasive carcinoma are reflected in Fig. 1. Among the cases, the cumulative prevalence of 4 types (HPVs 16, 18, 45 and 31) would explain 80% of the cases approximately. This information is of interest for defining the type-specific antigen composition of HPV vaccines for the prevention of cervical cancer.

Case-control studies of invasive cervical carcinoma yield relative risks (multiplying factor of the probability of developing disease on being exposed over the probability of developing disease on not being exposed) of between 50 and 100 for the DNA detection of HPV in general and risks (“odds ratios”) of between 100 and 500 for the HPVs 16 and 18. In some studies these figures reach values of between 500 and 1000. In Fig. 2 the estimations of the odds ratios are presented for the 15 most frequent viral types in invasive cervical carcinoma.

The estimation of the risk for the 15 most frequent types reinforces the concept that in screening programs, the assessment of type-specific positivity for a cocktail of all of them is sufficiently discriminative of the risk (high/low) and potential for progression to lesions, being therefore useful for the appropriate population control. These results do not suggest the requirement of differentiated specific clinical protocols for women with infections of the HPV 16 type or any other of the high risk viral types that are rather infrequent [14].

The fractions of cervical cancer attributable to HPV (proportion of cases in a population in which HPV is considered as a causal agent) calculated starting from these studies, are very high, between 95 and 99%. The associations observed between the infection by HPV and cervical cancer are among the highest ever identified in human cancerology, with a growing consensus existing in qualifying HPV as the “necessary cause” (absence of disease in absence of infection) although insufficient (presence of infection without presence of disease), due to the great number of infections of cervical cancer that are resolved spontaneously [1,15–17].

Prospective studies demonstrate that persistent cervical infection by high-risk HPVs precedes the appearance of the CIN and is required for the development, maintenance and progression of these lesions. Epidemiological studies in multiple populations show consistently that the bulk of the infections by HPV always precedes the bulk of the neoplasias by one or two decades.

New Options in the Prevention and Early Detection of Cervical Cancer

The description of the viral origin of cervical cancer and the refinement of techniques of clinical diagnosis has opened new and interesting options to improve screening programs. One of the first evaluated proposals has been the use of HPV DNA detection assays in the triage of women with cervical abnormalities. In this approach, HPV DNA detection is used as a prognostic marker in cases of ambiguous cytology results (ASCUS, CIN1, mild discariosis...) The conclusions of these studies that include among other a large controlled randomized trial, indicate that the viral detection in cases of ASCUS predicts the co-existence of high-grade lesions with greater sensitivity and better cost-benefit ratio than the repetition of the cytology or even than the immediate
colposcopy with or without directed biopsy. These conclusions are being evaluated by the medical societies for adaptation and adoption into routine clinical protocols.

In women older than 30–35 years, viral detection is being evaluated as the primary screening test associated with cytology in countries with established screening programs, or as primary test in populations where the cytological screening programs are lacking, in which case the cytology or the biopsy are considered as secondary screening tests and confirmation of the lesion. In all the cases, it has been demonstrated that the sensitivity of the viral detection is greater than that of the specialized cytology to detect prevalent lesions. The Food and Drug Administration, FDA recognized in 2003 the value of the cytology associated with the HPV test in women older than 30 years for the population from the United States.

The development of prophylactic vaccines, either therapeutic or combined is a new option for the prevention of infections by HPV and maybe for the treatment of established infections. Some research lines exists that are evaluating new molecules for the treatment of the infections by HPV and associated lesions, but the evidence is still limited. Some new immunomodulators have shown effectiveness in the treatment of condylomas and preparations are in the development phase adapted to the treatment of infections on mucous surfaces.

On the other hand, two prophylactic vaccines, Cervarix and Gardasil, are already in a very advanced phase of implementation at the world level, and both vaccines have demonstrated not only safety and immunogenicity but also efficacy for the prevention of cervical neoplastic lesions as well as vaginal, vulval and genital warts for Gardasil.

Conflict of interest statement
XC has received research grants from GlaxoSmithKline, Merck Sharp & Dohme and Sanofi Pasteur MSD, served on Speakers’ Bureaus for GlaxoSmithKline and Sanofi Pasteur MSD, and Steering Committees for GlaxoSmithKline and Sanofi Pasteur MSD.

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