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# Cervical cancer screening in Europe: what next?

S. Franceschi [a,*], R. Herrero [b], C. La Vecchia [c]

[a] *Unit of Field and Intervention Studies, International Agency for Research on Cancer, 150, Cours Albert Thomas, F-69372 Lyon cédex 08, France*
[b] *Costa Rica Cancer Institute, PO 301-6151, San José, Costa Rica*
[c] *Istituto di Ricerche Famacologiche 'Mario Negri', Via Eritrea, 62, 20157 Milan and Istituto di Statistica Medica e Biometria, Università degli Studi di Milano, Via Venezian 1, I-20133 Milan, Italy*

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**Abstract**

This paper reviews how knowledge of human papilloma virus (HPV) and its association with cervical cancer has evolved over the years and discusses the potential usefulness of HPV testing as a replacement and or adjunct to current screening practices. © 2000 Elsevier Science Ltd. All rights reserved.

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This issue provides detailed information on the efforts 15 member states of the European Union (EU) have devoted to cervical cancer screening programmes over a more than 30-year period. The picture is far from homogeneous. Despite different degrees of achievement in reaching high coverage among target women, however, EU countries did share common values and projects. It is, however, worth bearing in mind that in parallel with the spread of cervical cancer screening programmes in Europe, the last 30 years or so have seen a major breakthrough in the elucidation of cervical cancer aetiology.

In the 1970s, as the first organised nationwide screening programmes were being implemented in the Nordic countries and The Netherlands, the aetiological studies of cervical cancer were still dominated by generic indicators of socioeconomic status and sexual activity, e.g. number of sexual partners, age at first intercourse, and the then surprising 'male factor' (i.e. partner's number of partners) [1]. The strongest candidate for an infectious cause was herpes genitalis (herpes simplex virus (HSV)-2), but other sexually transmitted infections (e.g. Trichomonas vaginalis) and even 'direct coital factors' (e.g. semen DNA) were still under consideration. At the same time, the first possibilities of detecting human papilloma virus (HPV) by cytology, histology and colposcopy were emerging as the link between koilocytosis in cervical smears and HPV was established [2]. History of genital warts (as a proxy of HPV-carriage) was shown to be associated with a 6-fold increased risk of cervical intraepithelial neoplasia compared with history of genital herpes, trichomoniasis, or gonorrhoea [3].

It was only in the 1980s, while England and Wales were opting for a national cervical screening programme analogous to those in the Nordic countries [4], that the relationship to HPV started to be elucidated. The first isolations of novel virus types (HPV 16 and 18) directly from cervical cancer dates back to 1983 [5]. Then came several dozens of case–control studies from all over the world that reported strong associations between HPV and cervical neoplasms [6]. Relative risks (RR) often greater than 100 were found [7] that could not be explained by chance, bias or confounding [8].

In the 1990s, as the European Guidelines for Cervical Cancer Screening were issued (1993) and organised screening programmes were gaining ground in Southern European countries too, polymerase chain reaction (PCR)-based tests were able to detect HPV DNA in 99.7% of cervical cancer specimens from 22 countries worldwide [9,10]. Approximately 90 types of HPV have been identified so far and the list of oncogenic (i.e. high-risk) HPV types is still growing (for example, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68) [9,11]. Is such strong evidence on the causal role of HPV

* Corresponding author. Tel.: +33-4-72-73-84-02; fax: +33-4-72-73-85-75.
*E-mail address:* franceschi@iarc.fr (S. Franceschi).


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going to leave strategies for cervical cancer prevention unchanged?

The demonstration that it is caused by a sexually transmitted virus may add cervical cancer to the list of severe diseases (where AIDS tops the list) where 'safe sex' educational campaigns have a role to play. Unfortunately, however, there is no clear evidence as yet that condoms or diaphragms protect against HPV infection [12].

With respect to screening approaches, radical improvements have taken place in the methods for detecting HPV, and this is continuing [13]. Detection of HPV on a large-scale is currently best performed by one of the two consensus PCR systems — MY09/11 or GP5+/6+, or by the Hybrid Capture (HC)-II system. The latter is commercially available and it targets 13 high-risk HPV types. A bulk of data suggests that the present HPV tests are more sensitive (approximately 90%) [14], than Papanicolaou (Pap) smear tests, thus reducing false-negative findings. Conversely, false-positive ones remain a drawback, since HPV tests are unable to distinguish transient from persistent (and, thus, more dangerous) infections. Another advantage of HPV testing lies in its high sensitivity for adenocarcinomas of the cervix, which are 5 to 10-fold less frequent than squamous-cell carcinomas, but have shown upward incidence trends in several European countries [15]. False-negative Pap smears are more common in women with adenocarcinomas than in those with squamous-cell ones [13].

There are three major potential roles for HPV testing. The first is improving the management of atypical squamous cells of undetermined significance (ASCUS) and low-grade squamous intraepithelial lesions (LSIL), groups which include up to 15% of smears in European screening programmes [16]. A large clinical trial is being conducted in the United States to investigate the usefulness of HPV testing with HC-II in the triage of low-grade cytological abnormalities and ASCUS. In a recent report from that study, high-risk HPV types were detected in 83% (95% confidence interval (CI): 79–86%) of specimens from 642 women referred for LSIL [17]. Because of such a high percentage, there seemed to be limited potential of this assay to guide decisions about the clinical management of women with LSIL. Some European groups, however, found lower percentages of HPV-positivity in LSIL (e.g. 39%) [18], probably on account of some difference in cytological diagnoses. Furthermore, HC-II may have a role in women with ASCUS, of whom only half showed high-risk HPV types [19].

A role of HPV testing in post-treatment surveillance of SIL is possible too, but the real issue is whether viral detection has the potential to improve the sensitivity of primary cervical cancer screening while maintaining adequate specificity. No final answer is as yet available but, according to the present overview, randomised trials of primary HPV screening are already enrolling thousands of women in Sweden, Finland and The Netherlands. The fact that HPV infections are very common among young women limits its potential use in primary screening of women under 35 years of age. Recent reports of increased detection of HPV in women over age 55 years in some populations [20,21] indicate the need to properly assess the sensitivity and specificity of HPV testing in different areas [14]. Finally, quantitative PCR assays which can estimate the amount of HPV DNA in cervical smears may improve our ability to distinguish between infections which have a high or low risk of progressing into cervical cancer [22].

HPV testing, however, is only one of the 'evolutionary' steps cervical cancer screening methods are going through. Others include liquid-based cytology, a technology that provides an evenly dispersed single layer of cervical cellular material and that has been shown in several studies to improve the sensitivity of Pap smears, with the additional advantage of allowing HPV testing from the same specimen for the triage of borderline lesions [23]. In addition, several computer-based cytology reading systems are being developed, which take advantage of high-resolution imaging systems, pattern recognition algorithms, and steadily improving computational systems (e.g. pc-based systems) [24]. Some far from new (at least in Europe) low-technology options (e.g. visual inspection of the cervix using acetic acid, VIA) look far more promising than anyone expected, with a reported sensitivity greater than 70% [25]. Methods such as VIA have limited specificity, but could have an important role in areas where no other screening method is available. Finally, self-collected vaginal samples may become an option in order to increase screening in settings where cytology can not be performed or, in Europe, among women unwilling to go to hospitals or clinics.

Thus, the Pap smear that we have known for more than 50 years [26] may have to be supplemented with or substituted by other tests. However, the great efforts most European countries have made (or are in the process of making) to achieve high coverage and to de-intensify tests among screened women will still pay. Screening programmes would actually become more effective (and cost-effective) if improved technologies such as HPV testing would allow for fewer 'screening failures' and thus fewer tests in a woman's life. Despite the fact that present alternatives, such as HPV testing and automation-assisted cytology, may seem expensive, technical advances will allow prices to fall. In the long-term, the ideal screening method is one that can be performed as infrequently as possible and employs the best available test(s) [13].

Still greater changes in the management of cervical tumours would be seen if the present knowledge on HPV could be translated into an effective vaccination

strategy. Prophylactic vaccines, based on virus-like particles (VLPs), are ready to enter phase III clinical trials, which means that a vaccine against a single or a few types of HPV could be available within the next few years [27]. More effective and less expensive HPV vaccines (e.g. recombinant live vector vaccines, protein and peptide vaccines, 'naked' DNA vaccines, or even edible vaccines) may be available in 10–20 years [27].

However, primary (vaccination) and secondary (screening) preventive strategies will have to be used together for quite some time. In order to test the efficacy of any prophylactic HPV vaccine in a reasonable period of time, phase III trials will have to rely on intermediate endpoints, i.e. SIL. Thus, an effective screening program is going to be a prerequisite for the evaluation of HPV vaccines. More important, even making the optimistic assumption that a mass programme of prophylactic vaccination is initiated in 2010 targeted at girls aged 12 years, projections show that vaccination would not begin to have an impact upon cervical cancer incidence rates until 2040 [28].

Another promising class of HPV vaccines, the therapeutic ones, may have a more immediate impact on the incidence of cervical cancer. The transforming proteins, E6 and E7, are synthesised in HPV-infected cells during the initial stage of infection, but they are necessary to maintain the malignant phenotype of cervical carcinoma. They are, therefore, potential targets for immunotherapy, alone (i.e. therapeutic vaccines) or in combination with capsid antigens L1 and L2 (i.e. chimaeric vaccines, having prophylactic as well as therapeutic potentials) [29]. While most early-phase therapeutic trials have focused on cervical cancer patients, pre-malignant cervical lesions may be more attractive targets for immunotherapy than cancer. In fact, they are more common and the vaccines have a greater chance for success, since the patients are more likely to be immunocompetent and the virally-infected cells are less likely to have defects in antigen processing [29].

In the light of so many exciting developments in the prevention of cervical cancer, it is essential that this 'success story' can reach all women. The gap between well-served and underserved populations is maximal between developed and developing countries [30], but it is not negligible in the EU either, as is well documented in this issue. Finland, with a more than 30-year old national screening programme and perhaps the most cost-effective one, shows a cervical cancer incidence rate (3.6/100.00 world standardised) nearly 5-fold lower than Austria (17.7/100 000 in Tyrol) [31]. In addition, Europe is not EU countries only. Incidence rates exceeding 15/100 000 can be found in the Czech Republic, Poland, Slovakia and Yugoslavia [31], not to mention former USSR countries, for which little information is available. In the pre-screening era cervical cancer was indeed very common in Europe too: in 1960, incidence rates in countries like Germany (Hamburg) and Denmark were similar to those found in the same period in Africa [32].

It is now tempting, on account of the steady decline of cervical cancer incidence in Europe, to relegate cervical cancer among the 'not so important' cancer sites, without considering the extent to which large-scale screenings have shaped the present statistics on cervical cancer. In Britain, for instance, the 300 000 or so cervical intraepithelial neoplasia (CIN) 3 detected and treated over the last 15 years have already reduced the number of future cancers by more than 100 000, corresponding to a saving of at least 50 000 lives over the next 30 or 40 years [33]. In many European countries, incidence rates of cervical cancer among young women have been increasing (e.g. England and Wales, Finland, Eastern Europe), or have not declined in the last few decades [30], probably on account of changes in sexual behaviour among women who were born in the 1950s. In addition, an increase in the relatively rare adenocarcinoma of the cervix has been reported in several developed countries [15]. Without screening programmes, these adverse cohort effects would have produced, and may produce in the future, substantial upward trends in incidence and mortality from cervical cancer in several European countries.

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