Screening for cervical cancer: Should we test for infection with high-risk HPV?

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At present more than 70 types of human papillomavirus (HPV) have been recognized, of which 35 represent mucosal types. These mucosal HPV types can be subdivided into high-risk or oncogenic types and low-risk or non-oncogenic types.

Recent studies have shown that high-risk HPV is present in more than 99.7% of cervical carcinomas worldwide.[1] Moreover, prospective follow-up studies of women with cytomorphologically normal and abnormal cervical smears have shown that persistent infection with high-risk HPV can proceed to the manifestation of cervical intraepithelial neoplasia (CIN) (the precursor lesions for cervical cancer) and that a persistent infection is necessary for the development and progression of these CIN.[2–5]

The data collected thus far can be represented by the following causal framework (Fig. 1).

When a woman becomes sexually active, she may become infected with high-risk HPV. In about 80% of infected women, the infection is transient, a CIN lesion does not develop, and the virus clears in 6 to 8 months.[2,4,5] A neutralizing antibody response against high-risk HPV seems to protect these women from the development of CIN. In the other 20% of women infected with high-risk HPV, CIN do develop,[2] but in the vast majority of these (approximately 80% of those originally infected), the virus also clears and the lesion subsequently disappears.[4,5] The development of a cytotoxic T-cell response against HPV is probably essential in this process. However, in a small group of women (20% of those originally infected), the virus is not cleared, and the infection becomes persistent. This may lead to maintenance of the CIN or progression from CIN 1 (the mildest precursor lesion) to CIN 3 (the most advanced precursor lesion), and invasive cervical carcinoma ultimately manifests in a small subset of cases.

Infection with low-risk HPV types may also result in CIN 1 and some CIN 2.[6] However, these lesions never or only extremely rarely progress to CIN 3 and cervical carcinoma, as indicated by the fact that low-risk HPV types have never been found as single infections (without high-risk HPV types) in CIN 3 and cervical carcinomas.[6,7]

On the basis of data derived from an organized population-based screening program in the Netherlands, the interval between manifestation of the earliest precursor lesion (CIN 1) and development of cervical cancer is estimated at

about 12.7 years.[8] Because persistent infection with high-risk HPV is necessary for the development of CIN, the mean time between initial infection and manifestation of invasive cervical cancer is estimated at about 15 years. Assessment of the minimal interval between HPV infection and manifestation of cervical cancer is currently the subject of many studies. This long development period strongly suggests that, in addition to persistent infection with high-risk HPV and immunological factors (HPV-specific T cell response, antigen presentation), the development of overt malignancy requires changes in the cellular genome of the HPV-infected cells. It is well known that high-risk HPV types exert their oncogenic activity through the oncoproteins E6 and E7, which bind the tumour suppressor gene products p53 and Rb respectively. These interactions in proliferating cells lead to interference with control of the cell cycle and shortcomings in DNA repair, which result in genetic instability and increase the risk of specific oncogenetic alterations essential for progression to the malignant phenotype (e.g., activation of oncogenes, loss of oncosuppressor genes and activation of telomerase).

Epidemiological studies have shown that the risk of cervical cancer does not depend on the type of high-risk HPV with which a woman is infected.[4,9,10] Consequently, for clinical purposes related to cervical cancer, tests that detect infection with any high-risk HPV type are sufficient.[4] Tests suitable for mass screening are the hybrid capture II system and nonradioactive HPV consensus primer-mediated polymerase chain reaction (PCR) systems.

Given the causative role of high-risk HPV in the development of cervical cancer, HPV testing has a potential role in the following clinical settings:

- as a supplement for the triage of women with equivocal Papanicolaou (Pap) test results, such as ASCUS (atypical squamous cells of undetermined significance) or AGUS (atypical glandular cells of undetermined significance), given the high sensitivity of HPV testing for identifying underlying CIN 2 and CIN 3[11–14]
- for identifying, from among women whose Pap smears show mild to moderate dyskaryosis, those in whom CIN can be expected to progress, so that they can undergo colposcopy-directed biopsy[4]
- for detecting residual or recurrent CIN disease[15–18]
- as an adjunct for primary screening for cervical cancer.[19,20]

On page 503 of this issue Sellors and colleagues provide HPV prevalence data from a population-based survey of Ontario women.[21] Their results underline the validity of the framework described above. They found that the overall prevalence of high-risk HPV (without regard to the re-

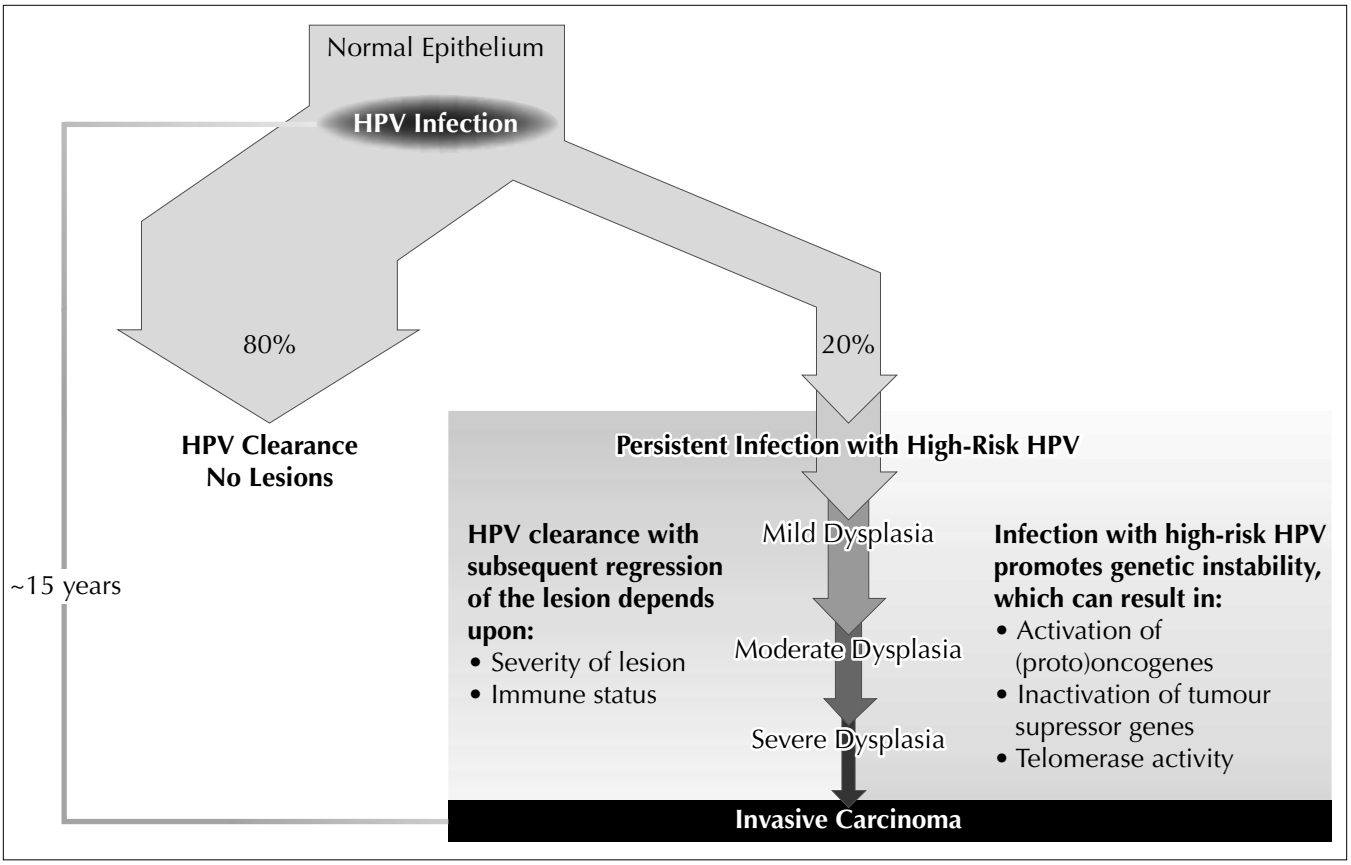

Fig. 1: Framework summarizing the relation between high-risk human papillomavirus (HPV) infection and the pathogenesis of cervical cancer. See text for detailed explanation.

sult of cytological testing) was highest among women 20 to 24 years of age and gradually decreased with age. These results confirm data from an earlier study of women with no abnormality on cytological testing.[22] The age dependence of HPV prevalence in pregnant women is similar to that of nonpregnant women.[23] Sellors and colleagues also found that several other factors — lifetime number of partners greater than 3, number of partners in the previous year greater than 1, current cigarette smoking, current use of oral contraceptives, marital status single and marital status divorced or separated — were associated with higher prevalence of HPV. Thus, acquisition of high-risk HPV appears to be associated with increased sexual activity with changing partners.[9,10,24]

An interesting aspect of this report[21] is the comparison between the results of an in-home consensus PCR assay using the MY09/MY11 primer system with those of a commercially available hybrid capture test, suitable for screening on a large scale. Remarkably, the PCR test, which in general is slightly more sensitive than the hybrid capture method, detected fewer cases of high-risk HPV than the hybrid capture method, except in older women (45–49 years of age). One possible explanation is that the hybrid capture test might detect some infections with low-risk HPV types that are not included in the test's probe mixtures and that apparently are more frequent in the smears of younger women. Indications for this phenomenon have also been obtained in a recent study on low-grade squamous intraepithelial lesions.[25] Alternatively, the performance of the PCR method may not have been optimal.

In older women (45–49 years of age) Sellors and colleagues[21] observed a significantly higher prevalence of HPV, including high-risk types, with PCR than with the hybrid capture method. In this group the additional positive results detected by PCR probably represented cases with low numbers of viral copies, which fell below the detection limit of the hybrid capture method. These additional positive cases might reflect re-emerging latent infections in older patients (who might be immunocompromised), as suggested by Sellors and colleagues, or de novo infections. Because long-lasting latent infections, even with low levels of high-risk HPV, are likely to result in CIN,[4] we favour the latter explanation.

The HPV prevalence data for Ontario reported by Sellors and colleagues[21] are similar to data obtained in Western Europe[22] and can be used to establish guidelines for screening for cervical cancer. The high prevalence of transient infection with high-risk HPV in women less than 30 years of age suggests that screening programs for cervical cancer should use tests for high-risk HPV only in women 30 years of age or older.[4,11] The sensitivity and the negative predictive value for CIN 2 and CIN 3 (high-grade squamous intraepithelial lesions) of a test for high-risk HPV are superior to those of a clinical Pap test, whereas the specificity and positive predictive value for these two tests are similar;[4] it therefore seems logical to replace the Pap test with a test for high-risk HPV in women 30 years of age or older. Although this approach seems justified by cost-effectiveness analyses,[26] there are some ethical concerns, given that a few CIN 3 may test negative for high-risk HPV. Clinicians may thus be reluctant to rely solely on HPV testing because of fear of allegations of malpractice. Therefore, despite the fact that CIN 3 that test negative for high-risk HPV probably represent cases in which the HPV has cleared and the lesion is regressing, clinicians may still prefer to combine a test for high-risk HPV with a clinical Pap test in primary screening for cervical cancer. Preliminary cost modelling studies have shown that, given the high sensitivity and negative predictive value of HPV testing for CIN 3 and cervical cancer, HPV testing in conjunction with cytological examination is apparently cost-effective.[26] The final proof for this conclusion is expected from a randomized trial currently being conducted in the Amsterdam area, in which the efficacy of high-risk HPV testing in conjunction with classical cytological examination is being compared with the efficacy of classical cytological examination alone in 44 000 women. Moreover, the combination of an HPV test and a Pap smear has the additional advantage of providing quality control for the cytological examination. Repeat reading of routinely screened HPV-positive smears originally reported as cytomorphologically normal yields abnormal cells in 5% to 7% of cases.[20] In this setting, the cost of an HPV test in addition to a cervical smear can be compensated by increasing the screening interval for women whose HPV test result is negative and whose Pap smear is cytomorphologically normal.[20]

A second paper by Sellors and colleagues,[27] appearing on page 513 of this issue, addresses the question of whether screening for cervical cancer by HPV testing on cervical scrapes taken by the physician can be replaced by HPV testing of urine, vulvar skin or vaginal material sampled by the woman herself. Only testing for high-risk HPV on self-sampled vaginal material gave results comparable to those of the cervical smear. The prevalence of high-risk HPV on the basis of self-sampled vaginal material is consistently about 5% to 10% lower than for cervical smears,[28] which would decrease the sensitivity in detecting CIN. Therefore, given current discussions about false-negative cervical smears, we do not believe that self-sampled vaginal material will replace cervical smears obtained by the clinician in future screening programs in developed countries. However, in the Netherlands, half of all cervical cancers are found in women who have never participated in an organized population-based screening program. Therefore, for women who decline to participate in such programs, vaginal self-sampling may be a good alternative and could largely reduce the risk of cervical cancer associated with not participating in a screening program.

In addition, this self-sampling method may open possibilities for screening in developing countries. In those countries it is difficult to initiate programs that require frequent rounds of screening over long periods of time.

Therefore, alternative approaches need to be considered. A potentially attractive option might be "once-in-a-lifetime" screening for high-risk HPV at 35 years of age, carried out on self-sampled material. Combined with a direct clinical intervention this method might result in a substantial reduction in cervical cancer in developing countries.

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Competing interests: Dr. Meijer is a consultant with Digene Corporation.

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