THE FUTURE OF HPV SCREENING IN PREVENTING CERVICAL CANCER

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Until now cervical screening in most countries is done by reading cervical smears for the presence of abnormal cells. This reading process is subjective and despite the success of cervical screening programmes with a call and recall system false positive and false negative smears still do occur. With the knowledge that High risk human papilloma virusses (HR HPV) are the ethiological agent of cervical cancer the question arises whether HPV testing can be used for cervical screening. HR HPV is necessary for the development, maintenance and progression of cervical precursor lesions (cervical intraepithelial neoplasia or CIN) to cervical cancer. HR HPV infect epithelia of skin and mucosal surfaces and are exclusively epitheliotropic. At present more than 120 HPV types have been identified and 40 of them are mucosal types.

On the basis of epidemiologic and phylogenetic relationship 15 have been classified as high risk or oncogenic HPV types and 3 are probably high risk or oncogenic HPV types. Of the HR HPV types HPV-16 and HPV-18 are responsible for 70% of cervical cancer. The main histotypes are squamous cell carcinoma (SCC) and adenocarcinoma (adenoCA). HPV-16 is found in about 50–55% of SCC, followed by HPV-18 in about 15–20%. Interestingly HPV-18 is more present in adenoCa than in SCC and together with HPV-16 they are found in 85–90% of adenoCa.

Because HPV types cannot be cultivated *in vitro*, HPV infections are detected by DNA-DNA or RNA-DNA hybridization techniques.

Since all HR HPV types can be detected with one diagnostic test 8 prospective clinical trials have been started to find out whether in cervical screening programmes HR HPV testing either alone or in conjunction with cytology was more effective in the detection of CIN2+ or CIN3+ than sole cytology. The HR HPV tests mainly used in these clinical studies are Hybrid Capture (HC2) or the GP5+/6+ PCR-EIA test. From these studies we learned that HR HPV has a higher sensitivity than cytology (± 90% for CIN2+ with a variance of 4.5% against cytology 65-70% with a variance of about 15%). Cytology has an average 8% higher specificity than the HR HPV test. The negative predicting value of the HR HPV test is 99% against 96% for cytology (1, 2).

The question arised whether the higher sensitivity of the HR HPV test for CIN2+ lesions indeed detected clinically relevant lesions or in other words that the lesions detected were lesions, which would regress spontaneously in due course.

In two recent studies in The Netherlands (POBASCAM) and Sweden (SWEDSCREEN) with a follow up of 5 and 4.5 years respectively it appears that this is not the case (3, 4). With a HR HPV test used in the first screening round up to 50–60% more CIN2+ lesions are found than with cytology. After 5 years significantly less lesions were found in the HPV arm than in the cytology arm. Since the total number of detected CIN2+/CIN3+ lesions over the two screenings round was equal the conclusion can be drawn that the earlier detected CIN2+/CIN3+ lesions in the HPV arm are non regressing clinically relevant lesions (3, 4). By using an HR HPV test the 5-year screening interval risk for a CIN2+ lesion is reduced with 70%. This means that the 5-year screening interval, as it exists in The Netherlands and Finland can be extended for at least 1 year, probably even for more years without increasing the 5-year interval risk. The results indicate that primary screening with a HR HPV test followed by cytological triage of HR HPV positive women even with an minimally extended screening interval of one year is far more effective than the existing screening by means of cytology. At the moment model analyses are conducted to determine the most optimal screening interval and algorithm. Moreover international guidelines have been developed which a clinically used HPV test has to comply with.

The present screening programs have an attendency rate between 65–75%. However, 50–55% of cervical cancers are found in women not attending the screening program. We have mailed these non-responder women self samplers for sampling cervical vaginal material. Thirty percent of the non-responder women sent back cervical vaginal material. Follow up of the HPV positive women revealed a 2.5 times higher number of CIN3+ lesions compared to the screening population. This means that self sampling in addition to the regular HPV adapted screening program has the potential to detect more CIN2+ lesions with an increased program sensitivity of approximately 85–90%.

Two commercial vaccines designed to prevent *de novo* HPV-16 and HPV-18 infection have been developed, one a bivalent L1 virus-like particle vaccine (5) and one a quadrivalent vaccine against HPV-6/11/16/18, which was used in the [FUTURE] II trial (6). These vaccines induce high titers of neutralizing antibodies, preventing infection of cervical epithelial cells by vaccine HPV types. These vaccines have high efficacy against HPV-16/18-related high-grade CIN and adenocarcinoma *in situ*, the intermediate endpoints of cervical cancer. They do not have a therapeutic effect on pre-existing HPV-16/18 infections nor CIN lesions caused by these types. In order to maximize the preventive effect of vaccination, in view of *public health*, women should be vaccinated before their sexarche and coverage should be high (preferably >90%). This can be achieved by incorporation of HPV vaccines in national immunization programmes offered to pre-pubertal women. Assuming a protective effect of at least 10 to 15 years this would have the highest impact on prevention of cervical cancers in younger women (<30 years of age), for whom cervical screening is less specific and less effective.

For older, sexually active women the decision to vaccinate is likely to remain an *individual* decision outside the *public health* domain, given the fact that part of these women is already infected with HPV-16 and/or -18.

Screening at older age will still remain important to protect vaccinated women against cervical cancer caused by non-HPV-16/18 high-risk HPV types and to ensure protection of non-vaccinated women. As argued in the near future, cervical screening with primary HPV testing is likely to replace cytological screening, since primary HPV testing has a substantially higher sensitivity for cervical cancer and high-grade precursor lesions than cytology (2). The result is a markedly decreased interval risk of high-grade lesions, permitting less frequent screening (4). This is particularly important because HPV-16/18 vaccination will lower the probability of high-grade lesions after a positive screening result both for cytological and HPV testing, arguing for a prolonged screening interval. Moreover, when high-grade cervical lesions become rare in case of vaccination, cytology will be more prone to loss of accuracy because it is highly subjective. This is another reason for advocating primary HPV testing. It might be envisioned that in the future women can screen themselves by self collection of cervico-vaginal material for HPV testing.

In short, we advocate a vaccine for pre-pubertal women and adapted cervical screening for older women.

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