Screening for cervical cancer – future perspectives

Over the next years, the screening programme for cervical cancer will undergo significant changes. Up to now, precancerous lesions have been diagnosed with the help of cervical cytology (Pap smears or cell samples taken from the cervix). In the future, cell samples will still be taken from the cervix, but the cells will be placed and preserved in a liquid- based medium to enable testing for the presence of infection with human papillomavirus.

Over 70 years of practice is about to change. Since the development in the early 1940s of Papanicolaou's staining procedure for assessing cell smears from the cervix under the light microscope (1), this method has been used to detect precursors to cervical cancer. We are now facing a paradigm shift in which cervical cytology is being supplemented with a molecular biological test for human papillomavirus (HPV). Cervical cytology is still a more specific test (2) and will continue to exist as triage of HPV-positive samples in the diagnosis of cervical cancer precursors.

Infection with human papillomavirus is anecessary causal factor for the development of cervical cancer. The virus is transmitted mainly by sexual intercourse (3). In most cases, the infection clears up on its own, but about 10 % of infected individuals develop a persistent HPV infection, and in approximately 1 % of these the infection progresses to cervical cancer if the precursor lesions are not removed. With respect to subsequent cancer development, there are both high-risk and low-risk HPV types. The most frequent low-risk types are HPV-6 and HPV-11, while the most frequent high-risk types are HPV-16 and HPV-18. The latter two are the cause of approximately 70 % of cases of cervical cancer (4). A further 11 high-risk types are known but less common. The HPV vaccine that was introduced in the Childhood Immunization Programme as an option for 12-year-old girls in 2009 (Gardasil, SPMSD), provides protection against HPV 6/11/16/18 (4). Vaccination is expected to bring about a future decline in the incidence of HPV infection caused by the types against which the vaccine provides protection, and a decrease in the incidence of precancerous lesions and cancer of the cervix.

HPV testing in primary screening

The Norwegian Cervical Cancer Screening Programme is voluntary for women aged 25–69 years, and the women receive a reminder to take a Pap smear every third year. When findings are equivocal or indicate low-grade cervical dysplasia, women are advised to take another Pap smear and an HPV test within 6 to 12 months. The HPV test is thus already in use in secondary screening.

The health authorities now recommend that the HPV test be used in primary screening instead of the morphological examination of cell smears (5). If the virus that causes cervical dysplasia is detected, women who are at risk of developing cervical cancer may be identified more quickly. Whereas a cell sample can be smeared onto a glass slide, the cell material for a HPV test must be transferred to a container with a suitable medium. In many laboratories, liquid-based cytology has been introduced, which means that the cell sample in a liquid container can be used for both a regular Pap smear and an HPV test. There are several HPV tests on the market that are designed to investigate the presence of HPV in the cervix. Some of these are RNA tests, while most are DNA tests. DNA tests are usually more sensitive but less specific than RNA tests and Pap smears for detecting precancerous lesions (2).

«Cervical cytology will be supplemented with a molecular biology test for human papillomavirus»

In the near future, HPV testing in primary screening will be introduced in several European countries (6). I In Norway there are plans to start introducing HPV testing as a primary screening method for women aged 34–69 in four counties in 2015, and possibly extending it to more counties from 2016 (7). Because of the high prevalence of HPV infection in younger age groups, women under the age of 34 will continue with conventional cell sampling as the primary screening method for the time being. The reason for this is that younger women have a higher prevalence of HPV than older women. This may be because younger women have greater sexual activity, with more frequent changes of sexual partners. The HPV testing method would thus detect too many women with a HPV infection that will disappear without causing persistent cervical cancer precursors.

The introduction of HPV testing in primary screening will result in a reduction in the number of Pap smears sent to the laboratory for analysis. This number is forecast to be approximately one quarter of the current sample number by the year 2024, and to fall further when the vaccinated women reach screening age, since the vaccinated girls are likely to have a negative HPV test, and a PAP smear will therefore not be necessary (8).

Pathology laboratories

This reduction in the number of PAP smears will lead to the phasing out of screening activities in pathology laboratories that analyse these samples. The smallest laboratories that analyse cell samples will no longer have a sample volume that is sufficient to maintain their expertise in analysing Pap smears. The current requirement is analysis of at least 15,000 samples annually per laboratory, so that cytotechnologists and doctors are exposed to a wide enough range of morphological findings (8). At the same time, the number of HPV tests will increase significantly, which will create a need for enhanced molecular biology expertise. Bioengineers currently analysing cell smears must in the future be retrained to perform HPV testing.

In cases with positive HPV tests, cell samples will also be examined by cytology. It is practical for the HPV test result and Pap smear to be evaluated jointly and stored in the same computer system. It is also an advantage to be able to compare the results of the Pap smear with the histopathological diagnosis. This is an important quality indicator and used in the laboratory for teaching and training purposes (9). When centralising cytology diagnostics, procedures for cooperation must be developed so that results can be compared even if they are stored in two different laboratories. Eventually, semi-automated screening procedures with digital scanning of smears will make this comparison easier, while there will be a further decline in the need for cytotechnologists (8).

Other consequences

Not only pathology laboratories are affected by these changes. HPV testing in primary screening is a more sensitive method of detecting high-grade cervical lesions than Pap smears, and it is expected that

more women with persistent HPV infection will be referred to a gynaecologist for colposcopy and biopsy after the introduction of this new method (7). An increase in referrals to a specialist for diagnosis and treatment may require more government-funded gynaecologists. This increase is likely to be temporary, until more of the vaccinated women reach screening age.

The Cervical Cancer Screening Programme has seen a decline in attendance rates. There are various reasons for this. Generally, a woman gets an appointment with her GP for a Pap smear. With transition to an HPV-based screening programme, a future scenario may be to offer a home-HPV test so that the woman herself can take a sample from her cervix and send it for analysis (10). For women, a transition from primary screening with cytology to HPV testing will mean that the test results will indicate whether or not she is infected with a virus that is considered to be a sexually transmitted infection. It is important to emphasise that HPV is widespread in the population; approximately 80 % of all sexually active women and men will have one or more HPV infections during their lifetime (11). Information to the public about HPV and cancer is a prerequisite for creating acceptance for the new screening method.

The introduction of a more sensitive screening method coupled with the vaccination programme is expected to lead to a further reduction in the incidence of cervical cancer (7).

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References

1. Papanicolaou GN, Traut HF. The diagnostic value of vaginal smears in carcinoma of the uterus. Am J Obstet Gynecol 1941; 42: 193–206.
2. Szarewski A, Ambroisine L, Cadman L et al. Comparison of predictors for high-grade cervical intraepithelial neoplasia in women with abnormal smears. Cancer Epidemiol Biomarkers Prev 2008; 17: 3033–42.
3. zur Hausen H. Papillomaviruses and cancer: from basic studies to clinical application. Nat Rev Cancer 2002; 2: 342–50.
4. Folkehelseinstituttet. Vaksine mot HPV. Publisert 12.3.2010. www.fhi.no/eway/default.aspx?pid=239&trg=List_6212&Main_6157=6263:0:25,6089&MainContent_6263=6464:0:25,6091&List_6212=6218:0:25,6097:1:0:0:0:0. (3.4.2014).
5. Nasjonalt råd for kvalitet og prioritering i helse- og omsorgssektoren. Endring av screeningteknologi i Masseundersøkelsen mot livmorhalskreft. www.kvalitetogprioritering.no/saker/endring-av-screeningteknologi-i-masseunders%C3%B8kelsen-mot-livmorhalskreft. (4.3.2014).
6. Ronco G, Giorgi-Rossi P, Carozzi F et al. Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial. Lancet Oncol 2010; 11: 249–57.
7. Helsedirektoratet. HPV-test i primærscreening mot livmorhalskreft. Publisert 7.11.2013. www.helsedirektoratet.no/helse-og-omsorgstjenester/kreft/screening/hpv-screening/styringsgruppe/Documents/Fremtidig%20organisering%20av%20cellepr%C3%B8ver%20i%20laboratorier.pdf (4.3.2014).
8. Helsedirektoratet. Fremtidig organisering av celleprøver i laboratorier.www.helsedirektoratet.no/helse-og-omsorgstjenester/kreft/screening/hpv-screening/styringsgruppe/Documents/Fremtidig%20organisering%20av%20celleprøver%20i%20laboratorier.pdf. (3.4.2014).
9. Kreftregisteret. Kvalitetsmanual, Masseundersøkelsen mot livmorhalskreft. www.kreftregisteret.no/no/Forebyggende/Masseundersokelsen-mot-livmorhalskreft/ (3.4.2014).
10. Kreftregisteret. 800 kvinner tilbys hjemmetest mot HPV. Publisert 22.5.2013. http://kreftregisteret.no/no/Generelt/Nyheter/800-kvinner-tilbys-hjemmetest-mot-HPV (3.4.2014).
11. Syrjänen K, Hakama M, Saarikoski S et al. Prevalence, incidence, and estimated life-time risk of cervical human papillomavirus infections in a non-selected Finnish female population. Sex Transm Dis 1990; 17: 15–9.

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