

Testing for high-risk HPV in cervical cancer screening programmes

by Dr Burkhard Ziebolz

While the value of the Pap smear in routine screening for cervical dysplasia is undisputed, it is now known that 99% of cases of cervical carcinoma are caused by infection with thirteen genotypes of the human papilloma virus (HPV). Identification of these high-risk genotypes is very valuable in the management of cervical carcinoma, both as a prognostic indicator and as a secondary screening test where results of a Pap smear are inconclusive. Results from the combination of the Pap smear and the HPV test can aid in determining the intervals for screening.

More than half a million women worldwide are diagnosed with cervical carcinoma every year, and more than 273,000 die from the disease. Even in countries with established Pap screening programmes, a significant number of women die from cervical cancer each year. According to the World Health Organisation, this disease is the second most common cause of cancer death in women (9% of female cancer deaths every year) [Figure 1]. More than 99% of cervical carcinoma cases worldwide are caused by the human papilloma viruses (HPV).

Pap screening programmes

The value of the Pap test in cervical carcinoma screening is undisputed. Routine cytological screening by this method has resulted in a reduction in the cervical carcinoma mortality rate of close to 60% in women aged 30 and older. It is normally recommended that cervical cancer screening should begin three years after vaginal intercourse is initiated and no later than the age of 21. The recommended frequency is annually for conventional cytology smears and every two years if liquid-based cytology is used. After three normal smears and no identified high risk factors the frequency of screening can be reduced [1].

However, Pap smears can prove technically unsatisfactory. The specimen may contain an inadequate number of clearly visible cells and a repeat smear is required as soon as the cervix has recovered from the minor trauma of the previous test. Up to two thirds of false negative Pap smears result from factors related to the collection procedure. In addition, in spite of optimal collection, specimen handling and screening procedures, the false negative (missed lesion) rate for a single smear is reported to be between 5 and 25%. However, since the development of cervical dysplasias to carcinomas typically takes a long period, if yearly screening is carried out the chance of a lesion being missed is low [2].

The role of HPV typing in screening programmes

There are more than 100 different genotypes of HPV, and more than 30 different HPV genotypes that can infect the human genital mucosa. Although the majority of HPV infections clear spontaneously, persistent infection with known single high-risk HPV

types is a significant risk factor for cervical cancer. Their role in other cancers, such as penile and anal cancer, is also increasingly recognised [3].

A large scale study of more than 20,000 women not surprisingly found that the risk of cervical carcinoma in the 45 month follow-up period after a Pap/HPV DNA test (the hybrid capture test was used for this study) was much higher in women who were positive for one or both tests compared with women who were negative for both tests. The decreased risk in the latter group was primarily due to the very high predictive value of a negative HPV test result [4]. The fact that combined negative tests predict the absence of cervical carcinoma with a certainty of about 99.21% has implications for future patient management, as shown in Table 1.

The PCR-based Amplicor HPV test identifies all 13 carcinogenic high-risk genotypes of HPV, and enables a very low viral load to be detected. The sample for the PCR test is obtained by the same method as the smear for the Pap test. The new PCR-based test offers considerable advantages for women identified as high-risk and women with unclear early-stage cytological dysplasia. It also facilitates decision-making regarding further treatment. If the woman has already had cervical intraepithelial neoplasia requiring treatment, the likelihood of her developing an invasive cervical carcinoma is consequently more than five times as high. Such aftercare examinations are a clear indication of when an HPV-PCR test is needed. A negative high-risk HPV result, for all practical purposes, rules out the risk of a relapse as it gives a negative predictive value of close to 100%. The HPV-PCR screening method thus provides valuable information not available from cytology alone. In many countries, clinical guidelines recommend that if results from both a Pap test and the HPV test are negative, the screening interval can be extended from 3 to 5 years before re-testing is necessary compared to a year for a negative Pap test result.

Positive Amplicor HPV test results can be further analysed with the Linear Array HPV genotyping test. This test detects the 37 HPV genotypes causing anogenital lesions, including the most common low-risk types as well as the high-risk types. This test complements existing HPV screening tests by identifying which HPV

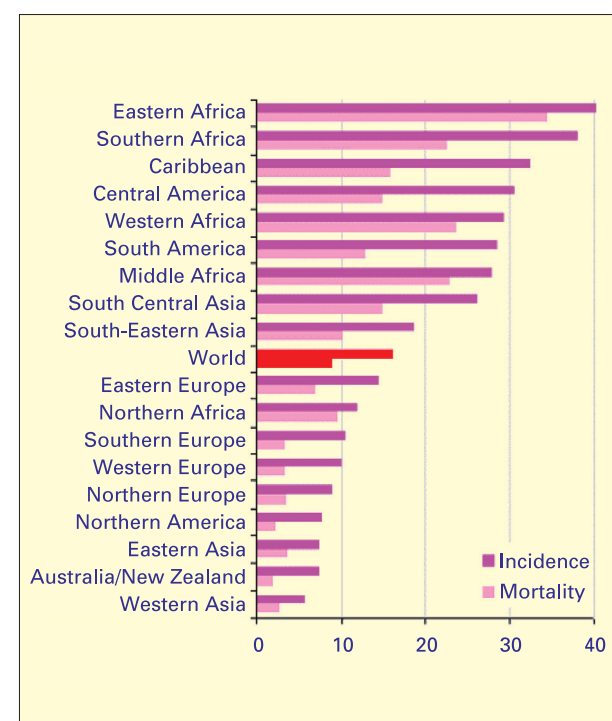


Figure 1. Age standardised incidence and mortality rates for cervical cancer in the different regions of the world (2002 estimates). Mortality rates vary seventeen fold. Cervical cancer is responsible for over 2.7 million years of life lost among women between the ages of 25 and 64 worldwide.

genotype is present in the patient sample. Only a persistent infection with the same high-risk HPV indicates a high risk of cervical cancer. Reported potential applications for HPV genotyping include monitoring clearance of specific HPV types; monitoring the persistence of high-risk infections; evaluating the effectiveness of excisional therapy, radiation treatment, and chemotherapy; pre- and post-vaccine evaluation; and facilitating epidemiological studies.

Treatment and prevention of HPV

In the absence of co-existent dysplasia, treatment is not recommended for subclinical HPV as no therapy has been identified to eradicate the infection. Prevention of HPV is a key factor in the prevention of cervical cancer, and the prevention measures are the same as those recommended for other sexually transmitted diseases. Specifically, meticulous condom use by all sexually active individuals who are not in long-term monogamous relationships is recommended.

Pap test result	HPV DNA test result	
	Positive	Negative
Negative for intraepithelial neoplasia (normal)	Pap and HPV DNA testing in 6 to 12 months	Pap and HPV DNA testing in 3 years
Atypical squamous cells of undetermined significance	Colposcopy	Repeat Pap in 12 months, possibly with repeat HPV test.
All other abnormalities including low-grade squamous intraepithelial lesion (LSIL), high-grade intraepithelial lesion (HSIL), atypical glandular cells (AGC) and atypical squamous cells where HSIL cannot be excluded.	LSIL: Close follow-up with HPV testing at 12 months or repeat cervical cytology at 6 and 12 months. Colposcopy if abnormalities persist or progress. HPV testing is preferred because it is as effective as cervical cytology but requires fewer visits and less need for colposcopy. HSIL: treat to prevent progression to invasive cancer. AGC: Treatment depends upon the underlying abnormality and may involve excision of a large portion of the endocervical canal or hysterectomy.	

Table 1. Management of patients based on the Pap test and HPV DNA testing.

References

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