

## For debate

## HPV testing in cervical screening

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There is little doubt that well organised cytology based screening programmes, which achieve high compliance and good quality control are effective in saving lives. This has been well documented in Scandinavia and Scotland, and the recent downward mortality trend in England and Wales<sup>1</sup> indicates that the changes to the programme which occurred around 1988 also produced positive results.

However, a programme based on solely conventional cytology has important limitations. In places where screening was properly implemented initially in the 1960s, mortality has dropped by 50–70% but is now stable, suggesting that the limits of effectiveness have been reached. A recent audit of the UK programme<sup>2</sup> found that 47% of the fully invasive cancers (that is, ignoring microinvasive disease) in women under the age of 70 years occurred in individuals with an apparently adequate screening history. A further 11% had abnormalities reported on cytology, but were not diagnosed with cancer until at least 6 months (and often several years) later.

An ideal screening test should be performed infrequently and be capable of detecting precursor or early easily treatable lesions with great accuracy. A once in a lifetime sigmoidoscopy around age 60 to detect and remove colorectal adenomas may be the best embodiment of this principle.<sup>3</sup> The sensitivity of cytology is limited by sampling problems, in which the abnormal cells do not get placed on the smear, and interpretation problems, where the few abnormal cells that do appear may be missed when examining the 100 000 or so normal cells that also are sampled.

In many studies where other tests have also been employed to refer women with negative smears for colposcopy, sensitivities for cytology of only 50–80% for high grade cervical intraepithelial neoplasia (CIN) have been reported.<sup>4–6</sup> Also cytological screening is ineffective for adenocarcinoma, which is rapidly accounting for a larger fraction of cancers. The tediousness of the job of the cytoscreener must also be acknowledged, and regularity with which scandals appear in the popular press highlight all of these weaknesses.

Cytology not only has problems with sensitivity but also with specificity. Screening is drowning in the “dysplasia swamp” of borderline and mildly dyskaryotic smears, where the yield of high grade pathology is low and the cost of referral and follow up is enormous. The UK programme is currently estimated to cost about £130m a year (J Patnick, personal communication) and annual estimates of \$6 billion have been made for cervical screening in the United States.<sup>7</sup>

Improvements in cytology via thin layer preparations and automated screening are likely to improve performance, to some extent, but this will be at considerable expense and I believe that a new approach, more closely related to the process of cervical carcinogenesis, is likely to be the best way forward. Detection of the human papillomavirus (HPV) offers such an approach. It is found in well over 90% of all cancers<sup>8</sup> and has well established oncogenic potential.<sup>9</sup> Tests have been developed which can detect the virus in a cervical scrape and which are automatable and provide a quantitative output.

It is important to recognise that HPV can only be detected reliably by DNA based tests. Morphological changes on cytology or histology (koilocytosis) are not specific or sensitive for oncogenic HPVs and more often detect HPV 6 and other low risk types which produce benign lesions, and do not have oncogenic potential. Even among DNA tests, the performance differs widely. Early tests based on filter in situ methods were neither sufficiently sensitive nor specific enough to be useful as screening tests. The use of polymerase chain reaction (PCR) based tests has improved sensitivity, but unless carefully controlled, these tests are not sufficiently specific to be used in a screening context.

Persistence is a key attribute of infections related to high grade disease. This can only be directly verified by repeated testing, but fortunately there are correlates available which make it possible to improve the predictive value of a single test. The most important of these is age. Transient infections are much more common in younger women, and restricting HPV testing to women over age 30 (at least for primary screening) substantially reduces the false positive rate. Viral load is also important. PCR based tests are able to detect very low levels of virus, which are often transient and not of clinical significance, and quantitative assays with thresholds for positivity of about 10<sup>5</sup> HPV copies in a smear give much better specificity with little loss of sensitivity for high grade CIN. HPV type is also important although less well understood. Fortunately the commonest type (HPV 16) is most often associated with high grade disease.

Types 18, 31, 33, and 58 also give good predictive value, but other types are less specific and the gain in sensitivity may not be worth the increase in false positives, unless found repeatedly or other (cytological) abnormalities are also present.

Definitive studies have yet to be completed, but a number have shown very promising results.<sup>4–6</sup> Preliminary communications from studies using the commercially available hybrid

capture microtitre assay are reporting even higher sensitivities and specificities. Overall, these studies suggest that adding HPV testing to primary screening could increase the yield of high grade CIN by 50–100%, with a positive predictive value similar to that for moderate dyskaryosis. This may both reduce the incidence of cancer and allow the screening interval to be increased to 5 yearly or longer, especially in women over age 50 who have never had an abnormal smear.

Performing HPV testing as part of primary screening also offers the possibility of rapid and more accurate evaluation of women with borderline or mildly abnormal smears. In Britain approximately 6% of all smears show borderline or mildly dyskaryotic changes. Only about 10–25% of these women will have high grade underlying CIN lesions, a slightly higher proportion will have low grade lesions, and the remainder will have no detectable CIN at colposcopy. Current British guidelines recommend cytological follow up at 6–12 month intervals unless progression or persistence (two mild or three borderline smears) occurs. Return to routine 3–5 yearly screening is recommended after two consecutive normal smears at least 6 months apart. This approach leads to a large number of extra smears at short intervals which are both costly and cause anxiety. There are also an increasing number of reports of invasive cancer occurring in women who had a minor abnormality many years previously followed by a number of (presumably false) negative smears.<sup>10 11</sup> The alternative approach of performing colposcopies on all these women is even more expensive and results in overtreatment and the unnecessary anxiety of a hospital visit in the majority of cases. Testing for HPV DNA on material taken at the time of the index smear offers the possibility of better management for these women.

Additionally, HPV testing offers scope for better follow up of women who have been treated for CIN. Currently, these women receive annual smears for at least 5 years and often for the rest of their life. Several reports suggest that the persistence of HPV positivity after treatment is an accurate method of

assessing treatment failures and could be used to safely return negative women to positive screening after a single follow up.<sup>12 13</sup> This could be yet another way in which HPV testing improves the management of women with cervical abnormalities.

In summary, available evidence indicates great potential for HPV testing within the cervical screening programme. It offers the possibility of greater sensitivity, reduced follow up of low grade cytological abnormalities and treated lesions, increased screening intervals, and overall cost reductions. Large scale evaluation projects are urgently needed to verify and refine these indications.

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