Cervical cancer

Could HPV testing become the sole primary cervical screening test?

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It has been argued that infection with one of the high risk types of the human papillomavirus (HPV) is a necessary event in the aetiology of cervical cancer.[1] Certainly, the population attributable risk is well over 90%. For this reason, there is great interest in the use of HPV testing in screening to prevent cervical cancer.[2] However, the vast majority of women infected by a high risk HPV will not develop cervical cancer. Most HPV infections are transient[3–5] and it is clear that even when the infection has been persistent for several years it may still regress without leading to cancer. It is largely unknown what determines viral persistence and what then determines progression to cancer. Immune factors,[6–8] smoking,[9] and oral contraceptives[10] are all implicated as cofactors, but their precise role in the long natural history of cervical carcinogenesis has yet to be determined.

Recently, Woodman *et al*[11] reported on a longitudinal study of 1075 teenage women, who were cytologically normal and HPV negative at recruitment. They estimated that 44% of such women would test positive for HPV and 28% would have an abnormal smear during 3 years of follow up with screening about every 6 months. High grade cervical intraepithelial neoplasia (CIN) was detected in 28 of those with an abnormal smear. Of these 28 women, 23 tested positive for HPV. The risk of high grade disease seemed to be greatest 6–18 months after first detection of HPV. Based on these findings, Woodman *et al* question the effectiveness of HPV testing in cervical screening. In particular, they remark on "the limited inferences that can be drawn from the characterisation of a woman's HPV status at a single point in time, and the short lead time gained by its detection". However they failed to note that the use of HPV testing in primary screening is proposed only for women aged over 30 years,[2] whereas their study was in teenagers.

The accompanying editorial by Miller goes further.[12] Citing studies that have shown that HPV testing is more sensitive at detecting biopsy confirmed high grade cervical lesions than is cytology, Miller states that "This finding is almost certainly due to the detection of non-progressive disease" and "the low sensitivity of the corresponding cervical smear is largely spurious." In our view, there is no logical basis for these claims. There is ample evidence that cervical cancer can develop within a few years of a negative smear test. Indeed, in an audit of cervical cancer in the United Kingdom, we found that 22% of 176 fully invasive cervical cancers in women aged under 65 years had had a negative smear within 3 years of diagnosis.[13] Further, Wallin *et al*[14] found HPV present in 30% of normal archival smears taken up to 26 years (median 5.6 years) before the diagnosis of invasive cervical cancer in 188 women compared with only 3% of archival control smears suggesting that HPV testing might have prevented additional cancers.

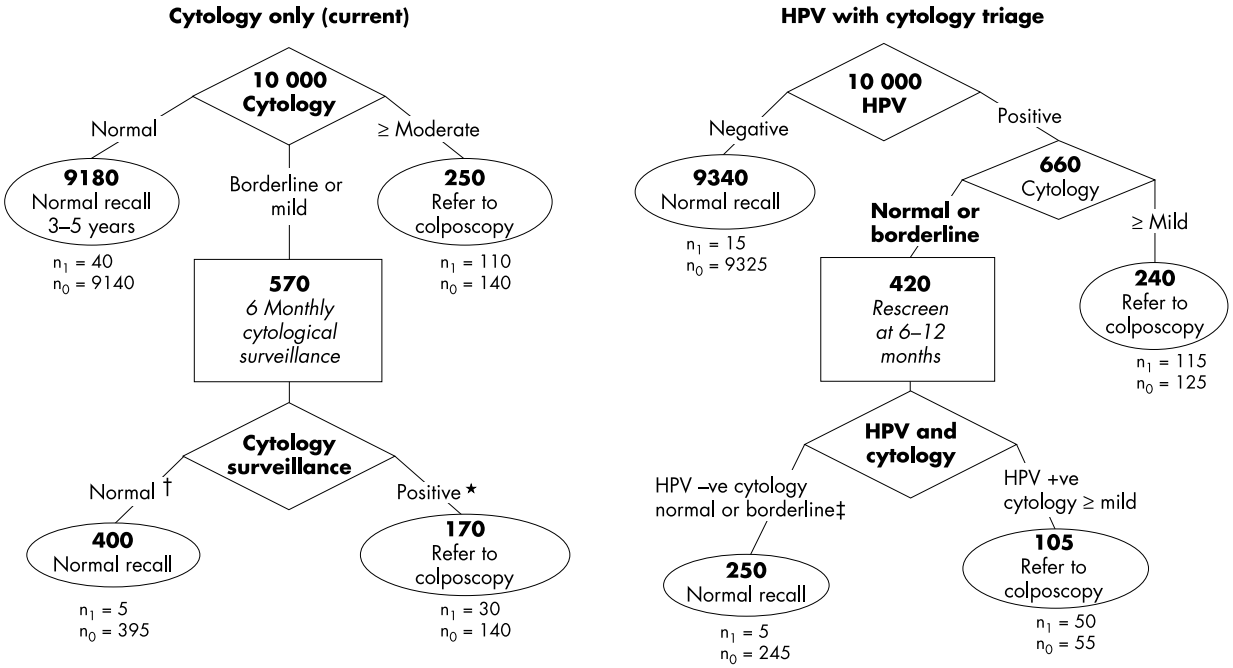
Several research groups have screened women with both a high quality HPV test and conventional cervical smears, fully investigating all women who have a non-negative result on either test. In all such studies, HPV testing detected a higher proportion of the histologically confirmed high grade disease than did cytology (table 1). For ethical reasons, most researchers feel obligated to treat all cases of high grade disease because of the high rate of progression to invasive cancer when untreated.[22] Nobbenhuis *et al*[23] kept women under close colposcopic surveillance—only treating those in whom the disease was colposcopically judged to be CIN 3 covering at least three quadrants of the cervix. Contrary to Miller's suggestion, they found that clinical progression was strongly associated with HPV status. In those who initially had mild to moderate dyskaryosis on cytology and a colposcopic lesion that covered at most two quadrants, 119 tested positive for HPV and 96 tested negative. Of the 119 who were initially HPV positive, six developed CIN 3 covering three or more quadrants and a further 31 had CIN 3 on histology after a median follow up of 33 months. By comparison, only one of the 96 women who were initially HPV negative developed CIN 3 and the lesion did not cover three quadrants. Nevertheless, the young peak in CIN 3 incidence and the fact that cumulative rates of CIN 3 are several times higher than those of invasive cancer, suggests that most CIN 3 in young women spontaneously regresses.

There are few indicators that enable us to predict which high grade lesions are most likely to progress to cancer. Classification of CIN is based on the depth of the abnormality and is at best an imperfect measure of the progressive potential

Table 1 Results of studies directly comparing HPV testing (by hybrid capture HC II) to cytology

		Sensitivity		Specificity		
Author	n	Cytology ≥LSIL	HPV	Cytology <LSIL	HPV	Comments
Blumenthal *et al*[15]	2199	44	80	91	61	Zimbabwe
Cuzick *et al*[16]	2988*	79	95	99	95	Age ≥35
Schiffman *et al*[17]	8636†	75	88	96	89	Conventional cytology
Hutchinson *et al*[18]‡		84		96		LBC
Ratnam *et al*[19]	2098	40	90	77	51	69% HC I, 31% HC II
Kuhn *et al*[20]	2944§	78	88	94¶	80¶	South Africa
Clavel *et al*[21]	2281	68	100	95	86	Conventional cytology
	5651	88	100	93	87	LBC

Sensitivities and specificities are with respect to biopsy confirmed cases of CIN 2 or worse. In most studies women were referred to colposcopy if either screening test was positive. *HC II on stratified sample of 1703; †HC II on stratified sample of 1119; ‡cytology results published separately from HPV results (all women received both conventional and liquid based cytology); §HC II on stratified sample of 424; ¶specificity differs from published value, because original paper excludes women with LSIL on histology from calculation. LSIL, low grade squamous intraepithelial neoplasia; LBC, liquid based cytology.



n_1 = Number with high grade disease (whether or not detected); n_0 = number without high grade disease.
★3 Borderlines or 1 borderline and 1 mild, or anything worse requires referral; † require 2 (or 3) consecutive negative smears for normal recall;
‡ borderline cytology could be rescreened in 6–12 months with referral of persistent borderline changes in the absence of HPV.

	Cytology only	HPV with cytology
Colposcopy referrals	420	345
High grade CIN detected	140	165

Figure 1 Flow charts comparing screening by cytology alone with screening based on HPV testing with cytology for those who are HPV positive. (Note that liquid based cytology could be done without the need to collect a second sample.) The numbers are based on a hypothetical population aged between 30 and 64. Data from the screening programme in England are used for cytology results. Estimates of the sensitivity and specificity of HPV testing with different cytology results are based on table 1. There is considerable uncertainty regarding the exact proportions in this figure.

of the lesion. The surface area of the lesion is also likely to be important, but this has never been shown conclusively. New molecular markers of progressive potential are needed. One such marker is HPV integration, but this is a late stage marker and cannot be used alone because it is not present in all cancers,[24 25] and because integration may happen too late to provide adequate lead time for screening. Eventually molecular markers should lead to an improved classification of CIN lesions. Host factors such as age and immune status are also likely to play a part.

There is a wealth of research showing that HPV testing can be used to identify cases of high grade disease—and indeed cancer precursor lesions—that are missed by routine cervical smears. The study of the natural history of HPV infection in very young women, although interesting from a purely scientific perspective and to those involved in vaccine development, is of little relevance to the possible use of HPV testing in cervical screening for women over the age of 30. Infection with HPV in younger women is simply too common and the risk of developing cervical cancer under the age of 30 is too low to make population based HPV testing attractive in this age group. Although it has not been proved that HPV testing in older women could reduce the incidence of cervical cancer, there is evidence to support this possibility. Even in older women, the relatively high rates of HPV infection will require the use of cytology as a triage test in those who are HPV positive. Those who are also positive on cytology would be referred for colposcopy, although those who are positive for HPV but negative on cytology would be tested again 12 months later and those with persistent infection would be referred for colposcopy. Screening in this way (fig 1) might not only lead to a reduction in the rate of cervical cancer, but might also make it possible to safely extend the screening interval. Despite the claims of Woodman *et al* and Miller, findings about the natural history of HPV infection in teenagers have no bearing on such an approach to screening.

With improvements in automated cytology, a combination of HPV testing and fully automated cytology could even be used in younger women, provided an affordable automated reliable test was available. Primary screening could be done in three steps: all women would have automated cytology and those above a certain threshold would be checked manually and referred for colposcopy if positive, the rest would be tested for HPV DNA and manual cytological screening would be used only for those who are HPV positive. Such an approach would greatly reduce the scope for human error as only a small percentage of women would require any manual screening. The lack of specificity of HPV testing in young women does not rule out its use in such circumstances.

Miller is correct in noting that the ability of HPV testing to detect disease missed by cytology does not necessarily mean that the use of HPV testing would further reduce the incidence of cervical cancer. It is theoretically possible that all such disease would either regress or be detected in the next screening round before progressing to cancer. We have called before for a very large randomised trial comparing HPV testing with cytology in women over the age of 35 with

ancer incidence as the end point.[2] The need for such a trial seems as great today as when we first proposed it. In the future, we may be able to test for markers of progression or oncogenic potential, but the lack of such markers does not alter our belief that HPV testing should be properly evaluated. Indeed, a well designed study would facilitate the retrospective testing of molecular markers on stored samples.

One day cervical cancer may be controlled by vaccination, but until that time screening provides the best protection against the disease. Cytology is saving thousands of lives in the developed world, but it is far from perfect and even with screening, the population lifetime risk of cervical cancer in Western Europe and North America is around 1%. The need for quality assurance and regular screening has meant that cervical screening has not been successfully implemented in any developing country, and current prospects for this are dim. There is clearly a need for a better screening test. Finding that test does require a better understanding of the natural history of the development of cervical cancer. To achieve this goal, we need to study the factors that influence late stages of carcinogenesis in older women—that is, very long term persistence and progression of CIN 3 to invasive cancer—rather than the history of newly acquired HPV infection in young women.

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The Medical Screening Society

There has been strong support for the Medical Screening Society announced in last issue of the Journal. Over 150 people from 32 countries have accepted the invitation to become founding members. The Society will be launched at a conference "Adult medical screening: new opportunities and challenges", sponsored jointly by the Journal, the British Medical Association, and BUPA Wellness, will take place on 29 November 2002 at the Royal College of Physicians in London. The programme is expected to cover a range of adult screening topics, including cardiovascular screening as well as screening for breast, stomach, lung, prostate, and colorectal cancer. Confirmed speakers for the meeting include Peter Boyle, Nick Day, Barnett Kramer, Lennarth Nystrom, and Alan Scott. All the subjects are topical, with a focus on new results and current research.

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