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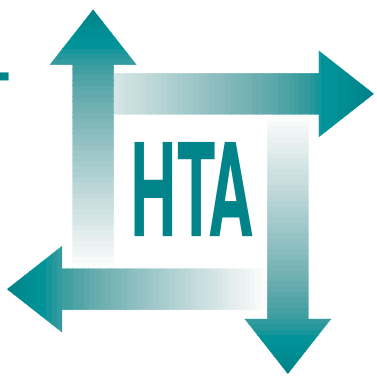
Review

A systematic review of the role of human papillomavirus testing within a cervical screening programme

J Cuzick
P Sasieni
P Davies
J Adams
C Normand
A Frater
M van Ballegooijen
E van den Akker

Health Technology Assessment
NHS R&D HTA Programme



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A systematic review of the role of human papillomavirus testing within a cervical screening programme

J Cuzick[1*]
P Sasieni[1]
P Davies[2]
J Adams[1]
C Normand[3]
A Frater[3]
M van Ballegooijen[4]
E van den Akker[4]

[1] Department of Mathematics, Statistics and Epidemiology, Imperial Cancer Research Fund, London, UK
[2] Molecular Diagnostics Ltd, London, UK
[3] Department of Public Health and Policy, Health Services Research Unit, London School of Hygiene and Tropical Medicine, UK
[4] Faculty of Medicine and Health Sciences, Erasmus Universiteit, Rotterdam, The Netherlands

[*] Corresponding author

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J Cuzick (funding from Digene Corporation to support an HPV screening study)
P Sasieni and J Adams (funding from the NHS Cervical Screening Programme)
P Davies (consultant for Digene Corporation)

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The overall aim of the NHS R&D Health Technology Assessment (HTA) programme is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and work in the NHS. Research is undertaken in those areas where the evidence will lead to the greatest benefits to patients, either through improved patient outcomes or the most efficient use of NHS resources.

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This report is one of a series covering acute care, diagnostics and imaging, methodology, pharmaceuticals, population screening, and primary and community care. It was identified as a priority by the Population Screening Panel and funded as project number 98/04/01.

The views expressed in this publication are those of the authors and not necessarily those of the Standing Group, the Commissioning Board, the Panel members or the Department of Health. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for the recommendations for policy contained herein. In particular, policy options in the area of screening will be considered by the National Screening Committee. This Committee, chaired by the Chief Medical Officer, will take into account the views expressed here, further available evidence and other relevant considerations.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The editors have tried to ensure the accuracy of this report but cannot accept responsibility for any errors or omissions. They would like to thank the referees for their constructive comments on the draft document.

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The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 1703 595 639 Email: hta@soton.ac.uk
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Contents

List of abbreviations

ASCUS	atypical squamous cells of unknown significance
CBr	cervical brush*
CIN	cervical intraepithelial neoplasia
CSc	cervical scrape*
CSw	cervical swab*
CSw(VP)	ViraPap cervical swab*
CVL	cervicovaginal lavage*
DB	dot blot*
DB(VP)	dot blot – ViraPap*
DB(VT)	dot blot – ViraType*
EIA	enzyme immunoassay*
EICC	early invasive cervical cancer*
ELISA	enzyme-linked immunosorbent assay*
EtBr	ethidium bromide*
FISH	filter *in situ* hybridisation
HC	hybrid capture
HC-I	hybrid capture – first generation
HC-I(HR)	HC-I assay using only the high-risk probe mixture*
HC-II	hybrid capture – second generation
HC-II(HR)	HC-II assay using only the high-risk probe mixture*
HLA	human leukocyte antigen*
HPV	human papillomavirus
HSIL	high-grade squamous intraepithelial lesion
hr	high risk*
IARC	International Agency for Research on Cancer
LCR	ligase chain reaction
LICC	late invasive cervical cancer*
LSIL	low-grade squamous intraepithelial lesion
NASBA	nucleic acid sequence-based amplification
NISH	non-isotopic *in situ* hybridisation
NPV	negative predictive value*
OR	odds ratio*
PC	PreservCyt liquid cytology medium
PCR	polymerase chain reaction
PPV	positive predictive value
RR	relative risk*
QALY	quality-adjusted life-year
RFLP	restriction fragment length polymorphism
RLU	relative light unit
RT-PCR	reverse transcript polymerase chain reaction
SB	Southern blot*
SD	standard deviation*
Sp	spatula*
T	tampon*
VSw	vaginal swab*

* Used only in tables

Executive summary

Background

It is timely to consider the role of human papillomavirus (HPV) testing within the cervical screening programme. A plateau of what can be achieved by conventional cytology is now being reached, and the fundamental importance of HPV in the aetiology of cervical cancer has been clearly demonstrated. There is much interest in the use of HPV testing to improve both the effectiveness and cost-effectiveness of cervical screening. It is thus opportune to review research into its potential implementation. Since the field is currently very active there is considerable flux in the state of knowledge, so that the current literature will quickly become obsolete.

Objectives

(1) To evaluate the available data concerning the role of HPV testing:
   (a) in primary screening, either alone or as an adjunct to cytology
   (b) to improve the management of women with low-grade cytological abnormalities
   (c) to improve the accuracy of follow-up after treatment of preinvasive or early invasive lesions.
(2) To review the methods available for HPV testing and determine their appropriateness for widespread implementation.
(3) To determine what future research is required to obtain more reliable answers about its use in screening.

Methods

Eight databases were searched, producing a total of about 2100 papers. Additional references were sought by scanning the citations of review articles and books devoted to HPV. Ongoing and unpublished studies were included.

Papers were divided into broad categories and initially screened by title and abstract using predefined criteria. Complete copies of papers not rejected were obtained, and data were abstracted. Abstractions were done by one author and checked by another. Tabular, graphical and textual material was used to synthesise the data.

Results

Testing methodology

A range of approaches have been used to detect HPV in smear material with widely differing results. The most thoroughly studied methods are now being superseded by newer methods which offer better sensitivity, specificity and reproducibility and are easier to perform. However, many of the most relevant studies are just beginning to reach the literature, and most of the large studies related to screening are still ongoing with at most only preliminary reports available. Currently, two consensus primer systems – the MY09/11 and the GP5+/6+ pairs – and the second-generation hybrid capture system (HC-II) would seem to be the methods of choice. These three methods all have high absolute sensitivity for detecting oncogenic viruses and have the potential for automation. Developments in the form of second-stage assays, may help improve specificity without substantially reducing sensitivity.

Natural history

HPV is a sexually transmitted disease with peak incidence in the age band 20–24 years which gradually declines up to about the age of 40–45 years, but then may begin to increase slowly again. Most infections are transient, with a median duration of at most 12 months, and pose no risk of cervical neoplasia: only the 10–20% that remain persistent are of concern. Evidence of infection, either by serology in stored blood samples or in fixed archival tissues, is found many years before serious disease is present, and indicates that infection precedes disease. Detection of HPV DNA in the absence of cytological abnormalities can also indicate presence of high-grade cervical intraepithelial neoplasia (CIN) which was missed by cytology. Women with minor cytological abnormalities who test negative for oncogenic HPV have a low risk of developing high-grade CIN within 3 years.

Prevalence

With modern tests, over 95% of all cervical cancers are HPV-positive, and 75–95% of high-grade CIN lesions are associated with a positive HPV test on exfoliated cells. In comparative studies, HPV testing has a greater sensitivity for CIN II/III than cytology. Greater variability in the HPV positivity rate of 'normal' populations is seen, ranging from 3 to 20%, or more in some studies, leading to concern about specificity. This variability reflects a number of factors, including age, extent of sexual exposure, previous disease, and type of assay used.

Potential roles in screening

The most appropriate group in which to initially consider the role of HPV testing as part of primary screening is in women aged 35 years or more, for whom false-positive rates are lowest. HPV testing may also have other roles within the screening programme. The most obvious is in improving the management of women with low-grade or borderline smears. In this context, HPV testing can help identify which women are in need of immediate referral for colposcopy. However, there is still uncertainty about the negative predictive value, and the safety associated with reduced surveillance in HPV-negative women. HPV testing has also been proposed for post-treatment surveillance of CIN, and early cancer, to monitor for complete excision. Early results look very promising, but more, better designed studies are needed here.

Modelling

A number of possibilities exist for introducing HPV testing at different ages and at different screening intervals. It could be used as the sole primary screening modality, as an adjunct to cytology, or in the triage of borderline and mild dyskaryosis. Published modelling studies are limited by the estimates of effectiveness, which are only now becoming available, and the cost of the test, which is still not known for high-volume applications. New modelling studies are presented based on the MISCAN micro-simulation programme, using costs based on the British programme, and disease models based on the natural history of HPV related cervical cancer. In the time available, only baseline calculations could be performed. These were sufficient to show that current knowledge is inadequate for assessing cost-effectiveness. The results of the modelling work show that for plausible values of prevalence, screening sensitivities and progression, HPV testing may be effective and cost-effective. For plausible assumptions about the model parameters, there are uses of HPV testing that would provide benefits at a lower cost than many existing healthcare programmes. However, the wide range of results that come from using high and low estimates for these parameters show that more data are needed to refine modelling using more accurate estimates of key parameters.

Economic issues

A range of economic issues related to introducing HPV screening were surveyed as well as the very sparse literature on psychosocial aspects. In neither case is the database adequate to draw firm conclusions.

Conclusions and recommendations

HPV testing is more sensitive than cytology for high-grade CIN, but has lower specificity, especially in young women. HPV testing cannot currently be recommended for widespread implementation. The evidence suggests it may be appropriate in certain limited situations such as the management of borderline smears or in older women when regular screening is problematic, so that high sensitivity is needed.

Full evaluation of HPV testing should provide information on the length of protection after a negative result, and consideration should be given to a very large trial with a reduction in cancer incidence as the end-point. Further studies and modelling simulations are needed to evaluate the range of potential roles and most cost-effective use of HPV testing, and how it should be implemented and integrated with other testing methodologies.

Chapter 1
Background

The policy context

The increasing and now overwhelming evidence of a causal link between certain types of human papillomavirus (HPV) and the development of cervical cancer has led to suggestions that a programme of testing for the virus should be developed as part of the strategy for preventing cervical cancer. In order to consider the role of HPV testing in cervical screening, it is important to first under-stand the objectives of health policy, and the extent to which a programme of testing would help meet these. It is also important to look at the current cervical screening programme and the relationship between HPV infection and cervical disease. These topics will be discussed in turn.

Health policy issues

Cancer screening programmes play an important role in the reduction of morbidity and premature mortality. If potentially invasive cancers can be detected and treated in the preinvasive stages, outcomes can be significantly improved. As with all health interventions, appropriate screening policy must consider the balance between benefits and costs. Better health and improved survival come at the cost of the provision of screening, follow-up and treatment, human costs of over-treatment, unnecessary follow-up tests and investigations, and worry to those individuals whose positive screening results represent no significant risk. In most screening programmes only a proportion of those who test positive have significant pathology, and only some of those will enjoy significant benefits of better health and longer life. It is therefore common for many people to suffer some cost to achieve the health gains for the few who benefit. However, it is not known which of the screen-positive individuals will and which will not benefit from follow-up tests and treatment.

In terms of reduced burden of disease, cervical cancer screening has been successful in lowering the incidence of invasive cancers and the resulting morbidity and mortality. Since the introduction of cervical cancer screening there has been controversy about the appropriate screening interval and the age ranges within which screening should be encouraged. As with all screening programmes the yield in terms of additional (treatable) cases falls as the screening interval is shortened, and as the programme is extended to cover people at lower risk. In the past a high proportion of women presenting with invasive cancers did not have the recommended screening history. Significant progress in reducing disease burden from cervical cancer has occurred as a result of improved coverage. However, this has resulted in an increase in the number of women who develop cervical cancer despite an apparently adequate screening history (Sasieni *et al.,* 1996), and such cases will only be prevented in the future if more sensitive tests are employed.

The objectives of health policy are to improve health and reduce premature mortality. This requires that health services be used in cost-effective ways so that they produce the maximum overall health gain. For the secondary prevention of cervical cancer a number of factors are important. In addition to population coverage, these include the sensitivity and specificity of the screening test, the screening interval, the effectiveness of follow-up in terms of identifying and treating treatable disease and the level of risk for those covered by the screening. Despite the success of the current programme in reducing disease burden, it is likely that some changes could be justified on the grounds of increased cost-effectiveness. In addition, the availability of new screening technologies provides particular reasons for considering more extensive changes. It is important to evaluate HPV testing in the context of alternative approaches to cytology testing which may affect cost and may affect sensitivity of screening.

This review assesses the potential value of testing for HPV as a method of reducing disease burden. Using modelling techniques the cost-effectiveness of HPV testing is assessed in the context of a range of options in terms of cytology screening. This allows a preliminary evaluation of the cost-effectiveness of HPV screening, but also identifies a number of areas where knowledge is currently inadequate to assess its potential role.

Current policy for cervical cancer screening

There is little doubt that well-organised cytology-based screening programmes for cervical cancer have been effective in reducing cancer incidence and preventing premature deaths, especially if they have good quality assurance. Potential reductions in disease of 60–90% are possible in the 3 years after screening (IARC, 1986; Sasieni *et al.,* 1996). The importance of good coverage and quality control is demonstrated by the accelerated decline in mortality in England and Wales following the changes implemented in 1988 (Sasieni *et al.,* 1995), addressing problems identified in the early 1980s (ICRF, 1984, 1986). However, a recent audit (Sasieni *et al.,* 1996) found that 47% of fully invasive cancers occurred in women with apparently adequate screening history, suggesting problems with the sensitivity of the test. Further progress in reducing the disease burden is therefore likely to come from a combination of measures to extend the coverage of screening, and by finding ways to more accurately identify women with precursor lesions.

The sensitivity of cytology is limited by sampling error, in which the abnormal cells do not get placed on the smear, and reading error, where a few abnormal cells are not identified among the multitude of normal cells that are also present in a well-taken cervical smear. Sensitivities for cytology of only 40–80% for high-grade cervical intraepithelial neoplasia (CIN II/III) have been reported (Reid *et al.,* 1991; Cox *et al.,* 1995; Cuzick *et al.,* 1995). Furthermore, cytological screening is poor at detecting glandular lesions or adenocarcinoma, which account for a growing number of cervical cancers (Kjaer and Brinton, 1993). Cytology also has problems with specificity, and the screening programme is overburdened by borderline and mildly dyskaryotic smears, which are costly to follow-up, cause anxiety to the women concerned, but have low predictive value for high-grade pathology (Shafi, 1994; Raffle *et al.,* 1995).

HPV and the aetiology, diagnosis and treatment of cervical cancer

The causal association between infection with certain HPV types and the development of cervical cancer is now beyond reasonable dispute. The epidemiological data supporting this assertion include reports that HPV DNA can routinely be recovered from over 95% of all cervical tumours (Schiffman *et al.,* 1993) and that women infected with oncogenic HPV types have relative risks of 40–180 for the development of high-grade cervical disease (IARC, 1995; Olsen *et al.,* 1995). Additionally, molecular studies have identified mechanisms by which high-risk HPV types contribute to carcinogenesis. The World Health Organization and the International Agency for Research on Cancer (IARC) have officially designated HPVs 16 and 18 as carcinogenic agents. Even higher relative risks (100–500) are reported for persistent HPV infection, which appears to be the key step in cervical carcinogenesis.

HPV testing could be useful in several ways. First, since HPV appears to be implicated in virtually all clinically significant disease, knowledge of HPV status could help to identify asymptomatic women who were false-negative for CIN II/III on cytology, and who are at greatly increased risk of developing cervical cancer. Second, the appropriate follow-up of low-grade cytological abnormality might be improved by knowledge of HPV status. Those infected with HPV are much more likely to have – or go on to develop – high-grade CIN. For HPV-negative women, more conservative follow-up might be indicated. Thirdly, in some categories of women, knowledge that they are not infected with HPV could justify less frequent screening, or for older women, no further screening. In the light of these potential advantages, some researchers have called for the introduction of HPV testing within cervical cancer screening programmes (Meijer *et al.,* 1997) although there are more cautious voices (Bonn and Bradley, 1998). In addition to the roles in detecting people at risk of clinically significant cervical disease, HPV testing may also have a role in post-treatment surveillance. Women who, following treatment, remain infected with the virus may not have had their lesions fully removed and require more frequent and comprehensive follow-up.

HPV testing could be implemented in a number of ways, such as: a stand-alone primary screening test; a primary screening test in conjunction with cytology; or only as a triage test for low-grade cytological abnormalities. Referral strategies might differ significantly if cytologically negative or minor disease associated with HPV infection is more likely to be CIN II/III. This review brings together the evidence that will help to inform decisions about which, if any, of these is likely to be cost-effective, and identifies gaps in our knowledge. There are issues about the ages at which testing might be appropriate, the interpretation of test results, testing methodologies, the importance of viral persistence and viral load as a surrogate for persistence, test sensitivity and specificity and acceptability to women. The value of HPV testing will depend on

the resolution of these issues, and careful consideration of the most appropriate context within which the testing might take place.

In carrying out this review the research team faced some particular difficulties. The literature on the use of HPV testing in a screening context is very limited, but rapidly evolving. However, there are several other related aspects for which there is much relevant published material. One problem is to select those parts of the wider literature that are relevant for screening. For example, it is important to understand the evolving technology of HPV testing, including interpretation of test results, and to use epidemiological based case–control and cohort studies to understand the natural history and prevalence of infection in different disease groups.

Another problem is the dearth of randomised controlled trials in cervical cancer screening, and a belief, to some extent justified by the effectiveness of current methods, that it is unethical to randomise patients to different screening protocols, and, in particular, to different management strategy for high-grade CIN lesions. This means that much of the evidence has to be taken from other types of study, with the need to look critically at the (diverse) study designs and methodologies. There is good evidence from population studies that there has been a decline in cervical cancer mortality, but it is more difficult from these studies to identify the particular role played by screening and treatment of pre-symptomatic disease.

There were other, technical problems carrying out this review. The terminology in use in cervical cancer is often confusing, with imperfect concordance between different classification systems (e.g. dyskaryosis, dysplasia, carcinoma *in situ*, CIN, SIL). It is also probable that clinicians use the same classifications in different ways. In addition, the variety of HPV assays have different sensitivities, specificities and cross-reactivities. Only recently has there been any agreement and consistency among the results of these assays.

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Chapter 2

Research questions addressed

In this review a range of questions have been addressed ranging from policy issues to the current state of HPV testing technology. In particular we have focused on the following issues:

(1) Does HPV testing have a role as part of the primary screening test for cervical neoplasia? In addressing this question we have considered a number of more detailed questions including:
   (a) Would the use of HPV testing increase the amount of high-grade CIN detected?
   (b) What are the false-positive rates of the available HPV tests? A false-positive test is defined as one with a positive result in a woman who does not have, and will not shortly develop, high-grade CIN.
   (c) Can HPV testing be used to safely lengthen the screening interval?
   (d) Can HPV testing be used to safely restrict the population undergoing screening (e.g. < 50 years of age)?
   (e) Would HPV testing be most effective if applied only to a particular subpopulation (e.g. only in women over 30 years old)?
   (f) Would increased detection of high-grade CIN by HPV testing result in a reduction in subsequent cancer? What proportion of the additional high-grade CIN lesions detected by HPV would progress to cancer before being detected by subsequent cytological tests?
   (g) Could women with inadequate cytology, but a negative HPV test, be safely recalled at the standard interval?

(2) Can HPV testing be used to improve the management of low-grade cytological abnormalities? Would use of HPV testing in this setting:
   (a) Reduce or increase anxiety?
   (b) Reduce the rate of invasive cancer?
   (c) Affect the number of unnecessary invasive procedures?
   (d) Shorten the time taken to resolve the disease status in women with low-grade abnormalities?

(3) Can HPV testing be used to improve the accuracy of follow-up after treatment for precancerous or cancerous lesions? Can women who have had a negative HPV test after treatment be safely returned to routine call and recall?

(4) Would HPV testing be cost-effective in any of the three settings considered: (a) primary screening; (b) management of low-grade cytological abnormalities; and (c) post-treatment surveillance? To address this question we have considered:
   (i) The likely cost of HPV testing.
   (ii) The effect of introducing HPV testing on the number of smears taken, the number of colposcopy referrals and the number of women treated, and on the number of cancers prevented and lives saved.

(5) How might HPV testing be implemented in practice?
   (a) What is the most effective technology for the detection of HPV?
   (b) How will HPV testing be influenced by other developing technologies such as (semi)automated cytology and liquid cytology?
   (c) Could HPV testing replace cytology as the primary screening test? If they are both to be used, how should one manage a woman who had a normal smear, but tested positive for HPV?
   (d) What quality assurance measures would be needed for laboratories undertaking HPV testing for the cervical screening programme?

(6) What future research is needed to provide more reliable answers to the questions posed?

These questions are answered in chapter 10.

Chapter 3

Methods used for the systematic literature review

Literature searches

We searched eight databases using a variety of key words producing a total of about 2100 papers. Details of the searches are given in appendix 1. Additional references were sought by scanning the citations of review articles and books devoted to HPVs.

Ongoing and unpublished studies are included based on personal knowledge of our research group, our consultants and from the epidemiological abstracts presented at the 16th and 17th International Papillomavirus Conferences.

In view of the short time span for the project the review was restricted to English language studies.

All 2100 publications were divided into the following broad categories based initially on their titles and abstracts (where available): **methodological**; **natural history**; **prevalence**; **modelling**; **economic**; **psychosocial**; **review**; **miscellaneous**; and **not relevant – excluded**.

'Methodological' papers (coded 'ME' in this report) are concerned with HPV assays. Typically they describe a new assay, evaluate an assay to establish its absolute sensitivity, or compare two or more assays on aliquots of the same clinical material. 'Natural history' papers (coded 'NH') all include sequential testing of women, and must have an HPV test at the beginning of the 'follow-up' period. They may be retrospective, testing for HPV on archival material. Natural history studies of HPV antibodies were also included. Papers that quantify the prevalence of HPV infection in one or more groups of women were included in the 'prevalence' category (coded 'PR'). Only HPV tests potentially relevant for screening were included in this section. 'Modelling' papers present a model used to describe the natural history of cervical cancer or to evaluate the effects of cervical screening. 'Economic' papers evaluate the economics of HPV testing in cervical screening. This category included papers that estimate the cost of cervical screening using either conventional cytology or HPV testing. 'Review' papers review or summarise the epidemiological evidence for a causal role of HPV in cervical cancer, the possible role of HPV testing in cervical screening, or the natural history of HPV infection without containing new data. The 'miscellaneous' category was mostly used as a holding category of papers that could not be accurately classified without obtaining a copy of the paper.

A paper could be included in more than one category. We obtained copies of all but a very few of those papers not excluded. The 'excluded – not relevant' list was reviewed by a second reader, and certain papers were reclassified. The miscellaneous papers were all reclassified on the basis of the full text of the articles. Most of the miscellaneous papers were in fact excluded. Several papers were reclassified after reading the full text.

Additional papers were subsequently excluded using the following category-specific inclusion–exclusion criteria.

Methodological

Papers describing or evaluating an HPV assay that could be used in a screening context were included. Papers evaluating assays on biopsy material were included if the technique could also be applied to smear or lavage material. We were particularly interested in sensitivity, specificity, quantification of viral load, repeatability, quality assurance, and large-scale implementation/automation.

Specifically articles had to satisfy the following inclusion criteria:

(1) provide a direct comparison of two or more of the technologies being considered (as listed below)
(2) use of a sampling technique that is applicable to a cervical cancer screening programme
(3) a sample size ≥ 75.

Reasons for exclusion were:

(1) technology not appropriate for large-scale screening applications (inappropriate technologies were included if compared with

appropriate technologies to establish their relative sensitivities)
(2) there was no comparison of technologies, for example prevalence studies using a single technique for the identification of HPV were needed (except where the paper was the initial report of a relevant technology)
(3) there was no direct comparison of technologies such as when the different technologies were applied to two or more distinct study populations
(4) technology detects only a single HPV type such as type-specific polymerase chain reaction (PCR) for HPV 16
(5) sample size too small for accurate comparison ($n < 75$)
(6) data incomprehensible, missing or highly suspicious relative to other articles in the field.

Natural history

These papers report on longitudinal studies. They must include an HPV DNA- or antigen-based assay at the beginning of follow-up. Studies retrospectively testing archival material (including nested case–control studies) were also considered. Morphological diagnosis of HPV (whether on cytology or histology) was not sufficient for inclusion. Papers may or may not include monitoring of CIN. Those papers looking at progression must include at least 6 months' follow-up; papers looking only at the transience of HPV infection must include at least 2 months' follow-up. Ideally, CIN status should be assessed from a biopsy at the end of the follow-up period. Several papers describing studies that met these criteria did not provide results relating to the sequential development of disease following HPV infection. For instance, one paper related CIN on visit j and $j - 1$ to HPV on visit j and $j - 1$. This supposedly relates persistent CIN to persistent HPV, but the two are concurrent whereas, in the natural history section, we are interested in CIN subsequent to HPV. Results on concurrent HPV infection and CIN have been included in the prevalence section. Papers that only reported on cohorts of women whose natural history of cervical disease following HPV infection is likely to be atypical (such as women who are immunosuppressed) were excluded.

All papers on HPV testing following treatment for CIN are included in the prevalence section even if they satisfy the criteria for the natural history section.

Prevalence

These papers give the prevalence of oncogenic HPVs in at least one group of women. Typically the groups were defined by cervical disease category, for instance: all women; those with a negative smear test; those with borderline changes or mild dyskaryosis on cytology; or those with biopsy confirmed high-grade CIN. Subgroups may be defined by age or race. Many of these papers report case–control studies, but we have also included cross-sectional studies and case only studies. To be included the studies must have used a reliable assay for HPV DNA on material that could be collected in a screening context (cervical smear, vaginal lavage or urine sample). The following assays are considered reliable: PCR and hybrid capture (HC-I and HC-II). The following are not considered reliable: filter *in situ* hybridisation (FISH), dot blot, ViraPap® and non-isotopic *in situ* hybridisation (NISH). Southern blotting of smear material is only reliable if used after PCR. Southern blotting of biopsy material is adequate, but such studies have been excluded from this section because the material tested must be suitable for screening healthy women. A few other studies were included at the discretion of the group and these are always marked with a footnote. For instance, one study using Southern blotting with a very low threshold is included. Additionally we have included studies that used PCR only on those negative for a less-sensitive test and in which women positive on either test are considered to be HPV-positive. Studies that **only** consider special groups of women of little interest to a population-based screening programme such as AIDS patients, adolescents or pregnant women were excluded.

Economic, modelling and psychosocial issues

Very few papers directly relevant to the economics of or psychosocial issues relating to HPV testing in cervical screening were located. For this reason we did not impose strict exclusion criteria. Articles on modelling were selected from MEDLINE using the key words 'model', 'screening' and 'cervical'. Articles dealing with data analysis were eliminated. Additional references were obtained from review articles.

Review

We did not systematically review articles included in the review category. Those published in or after 1994 were scanned for new references.

A list of the papers that were to be formally reviewed was circulated to the two consultants for comment and completeness.

Evaluation forms

Data entry forms were developed for reviewing methodological, natural history, prevalence, economic and modelling papers. A copy of each of the four forms is included in appendix 2. In developing the forms we tried to strike a balance between completeness and brevity. The idea was that the completed forms should eliminate the need to refer back to the paper. We decided to limit each form to two sides of A4. The forms include data extraction elements and structured text fields. Draft forms were each circulated around the whole group for comments and piloted on ten papers by two different researchers. Revised forms were created and printed using the word-processing 'mail merge' function so that details of the paper including authors, title and our unique identifier were printed on the top of each form.

Guidelines for completing the forms were discussed, and limited instructions were included on the forms.

Reading papers

Each paper not excluded after the initial readings was given a unique identifier. One research scientist was placed in charge of each section. He or she read and completed a form for all papers in that section and wrote the first draft of the results for that section. Methodological papers were read by one person only. Natural history papers were all read by two researchers independently – two copies of each form were completed. Prevalence papers were read by one person. A second researcher checked the majority of the completed forms scanning the original papers for data extracted. All papers on economics and modelling were read by two reviewers.

Assessment of study design/validity

Initially we intended to assess the validity of all studies included in the systematic review using relevant prespecified criteria. However, this was not possible given the variety of study designs included and the time constraints for completing the review. Although no formal assessment was made, we paid special note of

- blinded interpretation of assays (and use of panel review)
- quality control of assay and cytology
- study inclusion criteria
- length and completeness of patient follow-up
- selection of control groups (if relevant)
- size of study
- appropriate of data analysis

when reading the papers.

There was little scope for quantitative synthesis of the findings of the different types of studies (meta-analysis). However, simple aggregate and Forest plots were created for prevalence studies looking at disease states. Full evaluation of their comparability was not possible.

Chapter 4

Methodologies for the detection and typing of HPV

Introduction

This chapter compares and evaluates the various technologies that have been used for the detection of genital HPV infections. This review specifically examines their suitability for application to cervical cancer screening and, in this regard, it is necessary that the technologies must be capable of processing a large number of samples in a cost-effective fashion. Ideally they should be sensitive enough to ensure that carcinogenic HPVs are not missed and sufficiently specific in order to avoid the expense and anxiety engendered by the unnecessary follow-up of large numbers of women with little chance of having or developing cervical cancer or its precursors.

With regard to the level of sensitivity and specificity that would be appropriate for screening applications, it is important to note that while the association between infection with carcinogenic types of HPV and the development of cervical cancer is strong, the correlation between the detection of HPV and the coexistence of current cervical disease is somewhat weaker. It has been well established that a proportion of women will be HPV-positive but not have clinically relevant cervical lesions on colposcopy or histology. Whether these represent low-level infections that have no clinical manifestations, infections that will resolve spontaneously, or the small but significant proportion of infections that will progress to overt disease has not been established. As a consequence, this chapter examines three measures of sensitivity (and where possible specificity) in order to characterise the technologies as fully as possible. These are:

(1) analytical sensitivity as assessed by the detection of known quantities of HPV DNA
(2) relative sensitivity for the detection of the virus as assessed by comparing the numbers of positives detected by each technique on the same sample
(3) relative clinical sensitivity and specificity for the identification of women with current cervical disease.

Of these three, analytical sensitivity is the simplest to measure in that a dilution series of a known quantity of HPV plasmid DNA- or HPV containing cell line is assessed by each technique and the lowest quantity detected is interpreted as its minimum sensitivity. However, such a measure is unlikely to directly reflect the performance of the technique on clinical samples even if the plasmid DNA or cell line has been diluted with human DNA or human cells, as there may be contaminants in clinical samples that effect the sensitivity of the technology in the circumstances in which it is used in practice.

Relative sensitivities for the detection of HPV in clinical samples as assessed by positivity rates is a more accurate measure of clinical performance provided that an analysis of discrepant samples is undertaken. However, few of the studies included in this review have undertaken a formal discrepant analysis, and it is therefore difficult to distinguish higher sensitivity from a tendency to produce false-positive results.

Perhaps the measure of test performance that is the most relevant to a screening application is the ability to identify women with concurrent cervical disease or, looked at from another perspective, to identify women who do not have cervical disease. This aspect of test performance is not necessarily directly correlated with an ability to detect the virus, and it has yet to be established if the most sensitive test for the detection of the virus is actually desired in the context of a screening programme where specificity and positive predictive value for disease are both very important.

Overview of the technologies

In order to make this report accessible to a wider audience, a summary of the technical basis of the methodologies reviewed is provided below.

Southern blotting

This technique was named after the scientist who developed it, and it has revolutionised molecular biology, forming a foundation for all of the other techniques described below. For this assay, DNA is extracted from the cells being analysed and is digested with restriction enzymes which cut the

DNA into characteristic fragments depending upon its sequence of nucleotides. The DNA is then size fractionated by electrophoresis through an agarose gel, denatured to render it single-stranded, and transferred to a solid support, usually a nylon or nitrocellulose membrane or filter. The filter is probed for specific DNA sequences using a complementary single-stranded DNA or RNA molecule (the probe) that has been labelled with a radioactive or colorimetric molecule. Under appropriate conditions, this probe will only bind (hybridise) to its complementary target DNA sequence so that once the filter has been washed to remove unhybridised molecules the target sequence can be detected by virtue of the label on the hybridised probe.

Dot blot

The dot blot assay is a simplification of the Southern blot procedure in which the extracted DNA is neither restriction enzyme digested nor size fractionated by electrophoresis. Instead, the DNA is denatured, applied directly to a solid support, and then probed in exactly the same way as the Southern blot using a labelled single-stranded DNA or RNA probe that is complementary to the target sequence to be identified.

Filter *in situ* hybridisation

FISH represents a further simplification of the Southern blotting over that offered by the dot blot procedure with the additional removal of the step to extract DNA from the cellular material being investigated. In this technique, the cells are applied directly to a solid support which is then treated to denature the DNA in advance of probing with a labelled DNA or RNA probe.

In situ hybridisation

This technique is not to be confused with FISH. *in situ* hybridisation assays are performed directly on histological material that has been fixed to a glass microscope slide. The cells are treated to increase their permeability, and the DNA in the nucleus is denatured with an alkaline solution or heat. Complementary labelled hybridisation probes, analogous to those used in Southern blotting, are used to detect the target DNA sequences within the cells on the slide. This technique preserves cellular morphology and therefore has the added advantage of demonstrating the cellular location of the target sequences, or in the case of HPV, which cells are infected with the virus.

Hybrid capture

With the HC assay, we move from solid phase hybridisation techniques to solution hybridisation, although the principle of using complementary probes to detect the target sequences remains exactly the same. In this assay, cellular DNA is extracted, denatured in an alkaline solution, and then hybridised with complementary RNA probe(s) to produce DNA–RNA hybrid molecules. All of this takes place in the liquid phase, and the hybrid DNA/RNA molecules are then removed from solution or 'captured' by antibodies that coat the walls of the reaction vessel. These antibodies specifically recognise the three-dimensional structure of the hybrid DNA–RNA molecules, and will not capture double-stranded DNA or single-stranded molecules, which are subsequently removed during the wash step. The presence of the target molecules is detected by the addition of anti-hybrid antibodies labelled with alkaline phosphatase which bind to the immobilised target hybrid molecules. The alkaline phosphatase is then reacted with a dioxetane substrate to produce light which is measured in a luminometer. Results are then expressed as relative light units (RLUs), which are a measure of the light produced by the individual sample reaction divided by the mean level of light generated by three 1.0 pg/ml positive calibrators. As such, a reading of 1.0 RLU is equivalent to 1.0 pg/ml.

Polymerase chain reaction

The PCR is patterned on the *in vivo* replication of DNA. The first step, denaturation, requires the separation of the double-stranded DNA molecule into two single strands, which is accomplished *in vitro* by heating the sample to > 95°C. At this temperature, the hydrogen bonds between the complementary bases break, and the strands separate. The next step is annealing, which involves cooling the reaction to 40–60°C, at which temperature short synthetic single-stranded DNA molecules in the reaction mixture can find and hybridise with their complementary sequences on the target strand. These synthetic DNA molecules then act as primers for the last step in the reaction, extension, which is the formation of two new double-stranded DNA molecules using each of the original target DNA strands as templates.

By repeating this cycle of denaturation, annealing and extension, each new double-stranded DNA molecule will serve as a template for the next cycle of the reaction, and the number of molecules will increase in an exponential fashion. PCR can theoretically produce 10^6 copies from a single double-stranded DNA molecule after only 30 cycles of amplification, a process that would take about 90 minutes in the laboratory.

Of relevance to screening applications where the detection of a broad spectrum of HPV types is likely to be required, two basic consensus PCR protocols have been developed: degenerate primers and mismatch acceptance primers. The first is typified by the MY09/11 primer system, which uses degenerate bases to account for heterogeneity between various HPV types. As such, a mixture of 25 primers is used to detect a wide range of HPV types, which include 6, 11, 16, 18, 26, 31, 32, 33, 35, 39, 40, 42, 44, 45, 51–59, 62, 66, 67, 68, 70, 73, P155, P291, W13B, CP6108 and CP8061, together with further as yet unidentified types.

The second consensus protocol is typified by the GP5+/6+ primer system, which uses only two primers, one forward and one reverse, that are designed to be complementary to a region of high homology between the various HPV types, allowing for amplification of HPV types 6, 11, 13, 16, 18, 30, 31, 32, 33, 34, 35, 39, 40, 43, 45, 51, 52, 54, 55, 56, 58, 59 and 66. Clearly, given the range of genital HPV types to be detected, it is impossible to design a primer pair that is highly complementary to all, and the GP5+/6+ primers achieve broad-spectrum amplification by using a low annealing temperature which allows for mismatch acceptance at non-complementary bases.

Other techniques

A number of other techniques for the detection and typing of HPV have been reported which include the ligase chain reaction (LCR), nucleic acid sequence-based amplification (NASBA) and *in situ* PCR. At present, there are too few data to assess the application of these technologies for the detection of HPV in any meaningful way, and they have been excluded from this review.

Preliminary assessment of the technologies

In considering the practical requirements of a screening programme, it is evident that the diagnostic technologies employed must be capable of meeting the following criteria:

(1) readily available
(2) highly sensitive and specific for the detection of a broad spectrum of cancer-associated genital HPV types
(3) capable of using minimally invasive sample types (cervical scrape or brush samples)
(4) possessing a high level of intra- and interlaboratory reproducibility
(5) suitable for high-volume test execution (such as 96-well microtitre plate or higher-density format)
(6) the potential for full or semi-automated execution of the tests
(7) the potential for automated reading/evaluation of test results with electronic data transfer to a central computer database
(8) cost-effective execution within a large-volume screening programme.

Given these criteria, certain technologies can be readily excluded from further consideration on the basis of generally accepted sensitivity and specificity limitations or characteristics that would limit their ability to process the required sample volume. Due to time constraints and the large number of scientific articles published on these technologies, it has not been possible to systematically review all of the available technologies. We have therefore drawn upon the experience of the authors to prepare the following preliminary evaluation which narrows the range of technologies being reviewed systematically.

Southern blotting

This technique has been widely used for the identification and typing of HPV. In expert hands, it is sensitive, specific and robust. However, obtaining this performance requires a relatively large amount of input DNA (5–10 µg). This in turn requires a large tissue sample such as would be obtained from a biopsy, while sample types more appropriate for a screening programme, such as a cervical scrape or brush sample, would not provide sufficient DNA for optimal performance. Southern blotting is also labour-intensive, time-consuming and impossible to automate. As such, it is not suitable for screening applications.

Dot blot

This method is simpler and quicker to execute than Southern blotting, can be used to screen large numbers of samples and can be automated to some extent. However, the removal of the size fractionation step leaves all of the cellular DNA concentrated in a single dot. This can produce high background signals, which makes it difficult to distinguish weak positive signals and increases the potential for erroneous results. Two commercially available dot blot systems that have been widely reported in the research literature are the ViraPap and ViraType® kits (Life Technologies). In general, this technique has a lower sensitivity and specificity than Southern blotting, which, together with a requirement for a large amount of input DNA, renders it unsuitable for screening applications.

Filter *in situ* hybridisation

While this technique is simple to execute, it is neither sensitive nor specific, and it has now been abandoned for clinical applications.

In situ hybridisation

Older *in situ* hybridisation protocols were less sensitive than Southern blotting, could not be used to type HPV infections, were highly labour-intensive and not amenable to automation. As such, they were limited to specific research applications.

Recent modifications to this technology appear to have increased its sensitivity and specificity through the use of more efficient labels together with improved hybridisation protocols. Preliminary reports indicate that *in situ* hybridisation techniques can now be used to detect and type HPV in standard cervical smears, and automated systems are under development which could allow the processing of large numbers of samples. Given verification of these preliminary reports, the practicalities of implementing HPV testing as an adjuvant to cervical cytology would make this technique an attractive option. Data comparing these new *in situ* hybridisation protocols with established technologies are not available at present, and they have not been included in this review.

Hybrid capture

For the detection of HPV, the first-generation HC test (HC-I) detected a reasonable spectrum of low-risk and high-risk HPV types (low risk – types 6, 11, 42, 43 and 44; high risk – types 16, 18, 31, 35, 45, 51, 52 and 56), but the test suffered from suboptimal sensitivity and specificity. It also required processing in individual tubes, limiting the number of samples that could be processed and making automation difficult.

This assay has now been superseded by the second-generation version (HC-II), which detects a broader spectrum of HPV types (low risk – types 6, 11, 42, 43, 44 and 59; high risk – types 16, 18, 31, 33, 35, 39, 45, 51, 56, 58 and 68) and possesses an analytical sensitivity that has been increased tenfold over its predecessor, which within a clinical context appears to approach that of PCR. The test has been formatted to detect either low-risk or high-risk HPV types, and once the original sample has been denatured, it is subsequently processed in a microtitre plate format that is suitable for automation with electronic transfer of data to a central computer database for reporting. With these modifications, the HC-II HPV system is suitable for use in large-scale screening programmes.

Polymerase chain reaction

At present there are no commercially produced PCR kits for the detection of HPV although many protocols have been published in the literature. While kits are reported to be under development, it is currently necessary for individual laboratories to adapt and validate published protocols that are available for use in their own facilities. Accepting this limitation, PCR can be processed in a microtitre plate format, and once the DNA has been extracted, the remainder of the process can be automated with the use of enzyme immunoassay-based systems for the detection and typing of the PCR products. This would also allow for electronic transfer of data to a central database for reporting. Several such PCR detection systems have been reported in the literature.

With regard to the MY09/11 primer set, it is important to note that the efficiency of amplification across HPV types is not uniform, for example there is poor amplification of HPV 35. Also, the complexity of the primer set can lead to lot-to-lot variability in its sensitivity for some types. The original primer set developed by Manos and colleagues (Manos *et al.,* 1989) was modified by the addition of a primer specific for HPV 51 (Hildesheim *et al.,* 1994) and, more recently, the PGMY09/11 primers have been developed. This simplified primer set consists of 5 upstream and 13 downstream primers that have been designed from the same region as the MY09/11 primers, but with greater sequence complementarity across a broad range of HPV types. Initial reports of this system indicate that it has increased sensitivity and uniformity of amplification over the complete range of types detected by the original system together with an improved detection of multiple infections. Further, an associated line blot assay has been developed for typing the PCR products which could be semi-automated for the processing for large numbers of samples.

Meanwhile, the GP5+/6+ primer system has also been demonstrated to lack uniform amplification across the various types with reduced amplification of HPV 53 and 61. It appears to have a lower sensitivity than the MY09/11 primers for the detection of multiple infections. An associated microplate enzyme immunoassay has been developed for the both detection of the PCR products and their classification as high- or low-risk types. This would allow for a high degree of automation and the processing of large numbers of samples, making the system suitable for screening applications. However, while results using the GP5+/6+ primers have been particularly good in the originating laboratory, other laboratories

have experienced difficulties in getting this primer set to work effectively. An additional practical consideration for the non-research use of these primers is that the patent rights are owned by Digene Corporation, and they may not be made available commercially.

Historically, a variety of techniques have been used to subsequently detect the products of the PCR reaction. These include Southern blot and dot blot, but in this context they are used only to detect the previously amplified material, not to detect the original DNA sequences. As such, the combined technique derives the majority of its sensitivity from the PCR amplification, with the Southern blot or dot blot adding a relatively small amount to sensitivity (approximately a factor of ten) but substantially increasing specificity if conducted appropriately. However, the use of these techniques even for the detection of PCR products would probably not be suitable for processing the volume of samples required by a screening programme.

Summary

In summary, the techniques noted above can be assigned to the following categories:

(1) Low sensitivity and/or specificity:
  (a) *in situ* hybridisation protocols
  (b) FISH
  (c) dot blot procedures
  (d) HC-I.
(2) Complex execution and/or low potential for automated execution or evaluation:
  (a) *in situ* hybridisation protocols
  (b) FISH
  (c) Southern blot procedures
  (d) HC-I.
(3) High sensitivity and specificity:
  (a) PCR
  (b) HC-II.
(4) Suitable for high-throughput applications and/or amenable to automation:
  (a) consensus PCR
  (b) HC-II.

Therefore, of the currently available technologies, the ones that could be applied to screening programmes are limited to the consensus PCR systems and HC-II. These two primary technologies constitute the main focus of this chapter, and the other techniques are included only to establish the relative performance of PCR and HC-II.

The field of medical diagnostics is progressing rapidly, and new techniques or advances on old techniques may soon present suitable alternatives to those noted above. It is therefore important to monitor the field and ensure that all suitable technologies are included in any clinical studies that may be undertaken.

Analytical sensitivities of the primary technologies

Many of the articles reviewed in this section include an evaluation of the sensitivity of the techniques for the detection of known quantities of HPV DNA (analytical sensitivity) either as a pure solution or mixed with human DNA. These studies demonstrate that both PCR systems have a lower limit of detection that is typically about 100 HPV genomes with a range across the studies (apart from one outlying study) of 1–500 HPV genomes. Full data are presented in *Table 1* (to aid legibility, the tables in this report are collected together at the end of each chapter), which demonstrates that there is very little difference in average analytical sensitivity between the two PCR systems, while differences in the range in detection probably results from variations in dilution and/or the PCR protocol between the different laboratories.

Data evaluating the analytical sensitivity of HC-II have not been published, but the manufacturer recommends a clinical positive/negative cut-off value of 1.0 pg of viral DNA per millilitre of their proprietary sample buffer, which equates to about 5000 HPV genomes per test. However, this is the value that has been set for optimal clinical performance and is not a minimum detection level for the test. As such, it is not comparable to the analytical sensitivity measurements noted above for PCR.

Assessments of sensitivity using purified DNA or cell lines carrying HPV, even if the reaction is supplemented with additional human cells or DNA, are unlikely to be representative of the performance of these techniques on clinical samples that will often be contaminated with a variety of biological materials which may affect the various technologies to different degrees.

Evaluation of the primary technologies for the detection of HPV DNA in clinical samples

This section compares the relative performance of the primary technologies for the detection of viral DNA in clinical samples. When considering the data presented in the text and in the tables, it is important to keep in mind the following two points:

(1) Unless otherwise indicated, articles included in this review do not include a formal analysis of discrepant samples (samples that are positive on one test but negative on the other) and the total number of positive samples has been calculated as the aggregate of the positives by each technique. For these articles, it has therefore not been possible to establish the 'true' sensitivity or specificity of the techniques because the status of the discrepant samples was not established. While this is likely to be less of a problem where the products from PCR reactions are identified by Southern blot or dot blot using specific probes, it needs to be considered as a possible confounding variable for discrepant samples where confirmation by a separate test has not been possible.

In many of the published papers, only the proportion of samples testing positive by each method studied is reported, but in addition to the raw numbers the tables in this chapter report the ratio of positivity rates for the two tests considered. Thus, if method one was positive on 20% of the samples and method 2 was positive on 10% of the samples the positivity ratio of method 2 relative to method 1 would be 50% (10%/20%).

Where additional data are available on the number of samples with each combination of results on the two tests, we also summarise this information by calculating 'relative sensitivities'. These are calculated for each test treating the other test as the gold standard. Thus the sensitivity of method 1 relative to method 2 is calculated as the proportion of samples positive with method 1 that are also positive using method 2:

$$\frac{(1+/2+)}{(1+/2+) + (1-/2+)}$$

Note that if one compares two different thresholds of the same test then the sensitivity of the less stringent test relative to the more stringent one is always 100% and the sensitivity of the more stringent test relative to the lest stringent one is equal to the positivity ratio of the two tests. If, however, the two tests both report 10% of samples as positive, the positivity ratio will be 1, and the 'relative sensitivity' will measure the extent to which the two tests agree.

(2) Of the articles reviewed, the majority compared techniques that differ in the range of HPV types detected. We have therefore included the types detected by each technique (where available) for the studies listed in *Tables 1–8*, and the relative sensitivities reported will reflect both different spectra of detection together with any differences in analytical sensitivity.

Tables 2, 3 and *4* provide data from the articles that compare the primary methods to Southern blot, dot blot, *in situ* hybridisation and HC-I.

PCR versus Southern blot, dot blot and *in situ* hybridisation

All studies noted in *Table 2* demonstrate a greater relative sensitivity for PCR over each of the other techniques. In articles ME34, ME70 and PR108, PCR (MY09/11) detects from 1.5 to 2.4 times more positive samples than Southern blotting, using a variety of sample types and populations. This advantage remained even when the analysis was restricted to HPV types detected by both methods. Articles ME9, ME31 and PR8 compare PCR (MY09/11) to dot blot procedures, with PCR detecting from 1.4 to 4.4 times as many positive samples. Article ME31 illustrates the influence that range of detection can have, with the higher relative sensitivity of PCR dropping from 83.6 to 70.6% upon the addition of probes for HPV 42, 43, 44, 45, 51, 52 and 56 to the dot blot system. A similar trend is exhibited when PCR is compared with *in situ* hybridisation in article ME36, with PCR detecting 23 fewer positive samples when the range of HPV types detected was restricted to only those detected by *in situ* hybridisation.

PCR versus HC-I

The studies summarised in *Table 3* demonstrate that comparisons of PCR to the HC-I assay generally reveal a higher HPV detection rates for PCR. Article ME17 clearly illustrates this trend and also demonstrates the effect of differing spectra of detection, comparing the performance of the techniques when using their respective full spectra of detection and when the analysis was restricted to types detected by both assays. The key articles are reviewed in detail below.

ME17 (Cope JU, Hildesheim A, Schiffman MH, et al. *Comparison of the hybrid capture tube test and PCR for detection of human papillomavirus DNA in cervical specimens.* J Clin Microbiol *1997;35(9):2262–5*

In this study, the authors compared PCR using the MY09/11 primer system with HC-I for the detection of HPV in 499 cervicovaginal lavage specimens from women with normal cytology and 97 cervicovaginal lavage specimens from women with varying degrees of squamous intraepithelial lesions. The study population possessed a mean age of 31 years with a range of 16–77 years. The

two technologies compared in this article detect different ranges of HPV types, with HC-I detecting types 6, 11, 16, 18, 31, 33, 35, 39, 42, 43, 44, 45, 51, 52, 56 and 58, and MY09/11 detecting types 6, 11, 16, 18, 31, 33, 35, 39, 40, 42, 45, 51, 52–59, 66, 68, Pap155, Pap238A, Pap291 and W13B. MY09/11 amplification products were first tested with a generic probe, and generic probe positives were subsequently tested with type-specific probes. However, generic probe positives that were negative for any of the type-specific probes were counted as negative in this analysis.

When the tests were compared on the basis of any type-specific positive result without accounting for different ranges of detection, MY09/11 detected 134 HPV-positive samples (22.5%) while HC-I identified 81 (13.6%), giving HC-I a relative positivity rate of 60%. When the analysis was restricted to 14 HPV types detected by both methods (types 6, 11, 16, 18, 31, 33, 35, 39, 42, 45, 51, 52, 56 and 58), MY09/11 detected 108 positive samples (18.1%), while HC-I identified 79 (13.3%), giving HC-I has a relative positivity rate of 73%. The relative sensitivities of the two techniques were 91.1% for PCR and 66.7% for HC-I. Overall, the two methods agreed 93% of the time on whether a specimen was positive or negative for one of the 14 types detected by both methods, and 97.2% of the time they agreed on whether specimens were positive for carcinogenic types.

ME61, ME73A, ME75, ME77 and PR110

These articles demonstrate similar trends, with PCR generally detecting from 1.1 to 4.7 times more positive samples the HC-I assay. The largest difference of 4.7 times was reported in ME73A, where the different ranges of detection were not taken into account. Article PR110 reports virtual equivalence of the two techniques, and when the analysis of PCR products was restricted to HPV types 16, 18, 31, 33 and 35, it identified two fewer positives than HC-I, which detected a broader range of types (16, 18, 31, 33, 35, 45, 51, 52 and 56).

HC-II versus HC-I

Due to the recent introduction of HC-II and the general movement away from the more traditional techniques for the detection of HPV, articles directly comparing HC-II to the secondary techniques are difficult to find. Exceptions are provided by articles ME16 and ME28, which evaluate HC-II in comparison to its predecessor HC-I, and data from these articles is presented in *Table 4*. Of these two articles, ME16A uses a population of 42 women, which was considered too small for a reliable analysis although the trends demonstrated in this article are similar to those of ME28, which is reviewed below.

ME28 (Ferris DG, Wright TC Jr, Litaker MS, et al. *Comparison of two tests for detecting carcinogenic HPV in women with Papanicolaou smear reports of ASCUS and LSIL.* J Fam Pract *1998;46(2):136–41)*

In this study, Ferris and colleagues compare the performance of HC-II with that of HC-I for the detection of carcinogenic HPV types in a population of 242 women referred to colposcopy with atypical squamous cells of unknown significance (ASCUS) or low-grade squamous intraepithelial lesion (LSIL) cytology. Samples for HC-I testing were taken with a Dacron® swab and transported in specimen transport medium (STM – Digene Corporation). Samples for HC-II testing were collected with a cytobrush and Ayre spatula or an Accellon® device, which were immersed in PreservCyt® solution (Cytyc) after the preparation of a standard Pap smear. HC-II tests were then conducted using cells remaining in the PreservCyt solution after preparation of the monolayer cytology specimens.

These two assays detect different ranges of HPV, even when using only the high-risk cocktail with HC-I detecting types 16, 18, 31, 33, 35, 45, 51, 52, 56 and HC-II detecting types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56 58, 59, 68. In this study, positive results were recorded when high-risk types were detected by either assay without accounting for the different ranges of detection. When the entire population of 242 women was examined as a single group, the HC-I test using a 10 pg/ml cut-off detected 108 positive samples (45%) while HC-II using a 0.2 pg/ml cut-off detected 175 (72%), giving HC-I a relative sensitivity of 61.7%. When the analysis was restricted to the 143 women referred to colposcopy for an ASCUS Pap smear, the HC-I test (10 pg/ml cut-off) detected 49 positive samples (34%) while HC-II detected 88 (61%), giving HC-I a relative sensitivity of 55.7%. In both cases noted above, the data demonstrate that the second-generation HC-II assay detected almost twice as many positives compared with the older HC-I assay.

ME65A

This article demonstrated a similar trend although the performance of the two assays was much more comparable. In this examination of 483 women with abnormal cytology, 290 were found to be HPV-positive by HC-II while only 275 were positive by HC-I, and there were no samples positive on

HC-I but negative on HC-II. The 15 discrepant samples were analysed by PCR with 14 confirmed as positive. This analysis gives HC-I a relative sensitivity of 95% compared with HC-II.

Summary

As noted previously, few of the articles considered in this chapter included a formal analysis of discrepant samples. However, making the assumption that none or only an insignificant proportion of the additional positives detected by the primary technologies were false positives, the trend in these studies uniformly supports the superior sensitivity of both PCR and HC-II over Southern blot, dot blot, *in situ* hybridisation or HC-I. These results confirm the authors' decision to exclude the secondary technologies from the systematic review on the basis that they have been superseded by PCR and HC-II.

Using HC-I as a common baseline, it is interesting that the increase in relative sensitivities for PCR (MY09/11 and GP5+/6+) and HC-II were remarkably similar across the various studies, providing an indication that their relative performance on clinical samples is substantially the same. This position is further supported by data presented in the two following sections.

Comparison of the primary technologies: PCR (MY09/11 and GP5+/6+) and HC-II for the detection of HPV in clinical samples

Having established that the primary technologies possess higher sensitivities than the secondary technologies, it remains to evaluate their performance relative to each other. Here again, our analysis has been hampered by a lack of articles providing a direct comparison of these technologies within the terms established for this review. The exceptions are ME64A, which compares the MY09/11 PCR system with HC-II, and ME66, which compares the two PCR systems, MY09/11 and GP5+/6+, with each other. Data from these articles are presented in *Table 5* and they are both been reviewed below.

ME64A (Peyton CL, Schiffman M, Lorincz AT,* et al. *Comparison of PCR- and hybrid capture-based human papillomavirus detection systems using multiple cervical specimen collection strategies.* J Clin Microbiol *1998;36:3248–54)

In this study, the authors compared PCR using the MY09/11 primer system with both HC-I and the HC-II for the detection of HPV in 208 women drawn from a prospective natural history study undertaken in Costa Rica. The median age of the women was 37 years, and cervical diagnoses were all within normal limits except for ten women with low-grade cytological abnormalities. Initial specimens were collected with a broom device (Cervex Brush®), and following preparation of a routine cervical smear, the residual cells were placed into a liquid cytology medium, PreservCyt. A second sample was then taken from the women, approximately half had the second sample taken with a Dacron swab placed into sample transport medium (STM, Digene Corporation), and the remainder had a second sample taken with a conical brush placed into STM. Residual cells in PreservCyt were tested with both PCR and HC-II, while swab and brush specimens were tested with HC-I and HC-II, respectively.

Looking only at the comparison of PCR with HC-II, it should be noted that the two technologies detect different ranges of HPV types. PCR samples were first analysed on ethidium bromide-stained gels, and gel-positive samples were then analysed with a dot blot procedure using probes specific for types 6, 11, 16, 18, 26, 31, 32, 33, 35, 39, 40, 42, 44, 45, 51–59, 62, 66, 67, 68, 70, 73, P155, P291, W13B, CP6108 and CP8061. Gel-positive, dot blot-negative samples were further analysed by restriction enzyme analysis and type-specific PCR analysis. HC testing used the high-risk probe cocktail only, with HC-I detecting types 16, 18, 31, 33, 35, 45, 51, 52, 56 and HC-II detecting types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68. Discrepant results were 'independently arbitrated', although details of this process were not provided.

When these two tests were compared on the basis of any positive result without the different ranges of detection being taken into account, PCR identified 51 HPV-positive samples (24.5%) while HC-II testing of PreservCyt specimens detected 27 (13.0%) when using the manufacturer's recommended 1.0 pg/ml cut-off. When the HC-II cut-off was lowered to 0.5 and 0.2 pg/ml, the test detected 33 positive samples (15.9%) and 46 positive samples (22.1%), respectively. Agreement between the methods for the detection of HPV DNA was moderate to good, with the 1.0, 0.5 and 0.2 pg/ml cut-offs producing κ values of 0.58, 0.58 and 0.7, respectively. However, the authors note that false-positive results were observed more often with HC-II on PreservCyt specimens at the 0.2 pg/ml cut-off, and this level is probably too low for routine clinical use.

These data demonstrate that HC-II testing of PreservCyt specimens using the 1.0 and 0.5 pg/ml cut-offs, has relative sensitivities of 71 and 87%, respectively, when compared with samples positive by PCR for a similar range of types with a moderately good agreement between the methods ($\kappa = 0.58$ for both cut-off levels). The authors concluded that when using the HC-II system on STM specimens, a cut-off of less than 1.0 pg/ml may be optimal, and suggested that the HPV DNA detection ability of HC-II at this cut-off approaches that of the MY09/11 system.

ME66 (Qu W, Jiang G, Cruz Y,* et al. *PCR detection of human papillomavirus: comparison between MY09/MY11 and GP5+/GP6+ primer systems.* J Clin Microbiol *1997;35(6):1304–10)
In this study, the authors compared the MY09/11 primer system with the GP5+/6+ system for the detection of HPV in 208 women drawn from two different HPV epidemiological studies. Cervicovaginal lavage specimens were collected and prepared by standard techniques for the PCR reactions. Samples were scored as positive on the basis of appropriately sized bands on ethidium bromide-stained agarose gels together with the result of subsequent Southern blotting of the PCR products using a generic probe. All positive samples were then typed by dot blot using a range of 39 oligonucleotide probes. MY09/11 products were typed for HPVs 2, 6, 11, 13, 16, 18, 26, 31–35, 39, 40, 42, 45, 51–59, 61, 62, 64, 66–70, 72, 73, AE2, PAP155, PAP291 and W13B while GP5+/6+ products were typed for 2, 6, 11, 13, 16, 18, 26, 31–35, 39, 40–45, 51–59, 61, 62, 64, 66–70, 72, 73, AE2, PAP155, PAP291 and W13B.

Overall agreement between the two systems for the detection of HPV DNA was good ($\kappa = 0.79$). Of the 102 samples found to be positive by either of the two methods, 81 samples were positive on both, 13 samples were positive by MY09/11 only for a total of 94/208, and eight were positive by GP5+/6+ only for a total of 89/208. Accepting that all 102 samples positive by either or both techniques were true positives, the relative sensitivities of the MY09/11 and the GP5+/6+ systems were 91.0 and 86.2%, respectively. However, of the 21 discrepant samples, it is interesting to note that 15 were not positive on type-specific hybridisation with the broad range of probes used in this study, indicating either that they were types not included in the panel or they were the products of non-specific amplification.

Looking at the individual typing results, a broader range of types was identified by the MY09/11 method, with types 26, 32, 34, 52, 53, 61, 67, 68 and PAP155 being detected by MY09/11 amplification but not by GP5+/6+. Further, HPV 58 was identified in ten samples by MY09/11 but in only three samples by GP5+/6+. In contrast, types 35, 55 and 59 were each detected once by GP5+/6+ but not at all by MY09/11. This differential amplification ability was further investigated using serial dilutions of plasmid DNA or type-specific PCR amplicons, which demonstrated that there was a 5000-fold reduction in the ability of the MY09/11 primers to amplify HPV 35 while the GP5+/6+ primers demonstrated a similar reduction in their ability to amplify HPV 53 and 61.

The authors also reported differences in the abilities of the two systems to detect multiple infections, with MY09/11 identifying 27/30 (90%) of such samples and GP5+/6+ identifying only 14/30 (47%). Of the 30 samples with multiple infections, only six had complete agreement by both methods for the HPV types detected, five had partial agreement, 18 were detected by MY09/11 alone and three were detected by GP5+/6+ alone.

Summary

In conclusion, article ME64 indicates that PCR using the MY09/11 primers and HC-II have broadly equivalent performance characteristics ($\kappa = 0.58$–0.70) for the detection of HPV DNA in clinical samples. Meanwhile, article ME66 demonstrates that the relative sensitivities of the two PCR systems, MY09/11 and GP5+/6+, is also highly comparable ($\kappa = 0.79$). However, there are differences in the performance of these two systems for the amplification of certain HPV types, most notably HPVs 35, 53 and 61, while the detection of multiple infections may also be of concern, with the GP5+/6+ system demonstrating a reduced detection ability compared with that of the MY09/11 system.

PCR (MY09/11 and GP5+/6+) and HC-II compared with the secondary technologies for the identification of cervical disease

In this section, we have attempted to give an impression of the relative abilities of the technologies being examined to detect cervical disease. This evaluation has been restricted by a lack of relevant articles and the fact that some studies report a correlation between HPV status and cervical cytology results without confirmation

of disease state by biopsy and histology. It is now commonly accepted that cervical cytology has an inherent false-negative rate of 20–30% together with a false-positive rate of 5–10% for the identification of cervical disease. As such, correlations between HPV positivity and cytological results alone are unlikely to evaluate accurately the HPV detection methodologies being examined. However, this may have less influence upon an evaluation of two technologies for the detection of HPV when both are compared with a common baseline (cytology), as any bias introduced would effect both equally.

PCR (MY09/11 and GP5+/6+) versus dot blot, *in situ* hybridisation and HC-I

Table 6 presents summary data for the comparison of the MY09/11 and GP5+/6+ PCR methods with the secondary technologies for the identification of existing disease. Of the data presented, the studies comparing PCR (MY09/11) to dot blot or *in situ* hybridisation found that PCR had a higher sensitivity and NPV, an equivalent PPV, but a lower specificity. Meanwhile, comparisons of PCR to the HC-I assay found similar trends, with the exception of article PR110, which examined the use of these technologies for the identification of histologically confirmed CIN II/III in women referred to colposcopy because of an abnormal smear. This article demonstrated that the sensitivity, specificity, PPV and NPV of PCR were 80, 72, 78 and 75%, respectively, which were all superior to HC-I, with 70, 59, 67 and 6%, respectively.

HC-II versus HC-I

Table 7 presents data from article ME28, which is the only published paper that evaluates HC-II using liquid cytology medium (PreservCyt) in comparison to its predecessor HC-I for the identification of histologically confirmed CIN II/III in women referred to colposcopy with a previous ASCUS or LSIL smear. The mean age of the study participants was not reported, although the range was 18–71 years. For the detection of CIN II/III in women with either an ASCUS or LSIL smear, the authors report the sensitivity, specificity, PPV and NPV of HC-II as 90.5, 29.4, 10.9 and 97.0%, respectively, compared with 61.9, 57.0, 12.0 and 94%, respectively, for HC-I. The equivalent statistics for women referred with ASCUS smears alone are 88.9, 40.3, 9.1 and 98.2%, respectively, for HC-II, and 55.6, 67.2, 10.2 and 95.7%, respectively, for HC-I. These data demonstrated a far higher sensitivity for the second-generation assay, which was accompanied by an equivalent PPV and NPV but a lower specificity.

Summary

The data presented above for the identification of clinical lesions are consistent with the data demonstrating the higher relative sensitivity of PCR and HC-II for the detection of HPV DNA in clinical samples, supporting the view that the higher relative sensitivities reflect the detection of true infections rather than false-positive results. These data indicate the primary technologies all possessed superior sensitivity, leading to a higher NPV when compared with dot blot, *in situ* hybridisation or HC-I. In terms of screening, the ability to identify women who do not have disease and can therefore be excluded from further investigations is important with respect to the cost-effective utilisation of a test, especially in this triage of borderline or low-grade cytological abnormalities.

Clearly, all of these measures are influenced to varying extents by the prevalence of infection in the population examined, and many of the studies noted above examined student populations or had a substantial component of younger women participating in the trials. It has been well established that the prevalence of HPV in women under the age of 30 years is much higher than that in women over the age of 30 years. This fact alone will influence the specificity and PPV of the technologies being examined and tend to favour those with lower sensitivity. This is illustrated by the data presented in *Table 6*, where the studies demonstrating the highest specificity and PPV for PCR were the ones with the older study populations.

Comparison of the primary technologies: PCR (MY09/11 and GP5+/6+) and HC-II for the identification of cervical disease

For the direct examination of the primary technologies, it would be ideal to compare their respective performances on the same screening population. However, published articles evaluating the primary technologies for the identification of cervical lesions on such a population have not been found in the searches undertaken for this review. We have therefore relied upon preliminary data from a number of studies presented the 17th International Papillomavirus Conference held in Charleston, North Carolina, in January 1999. In addition, we have drawn upon published articles evaluating the performance of each technology individually, together with studies using HPV for the triage of women with low-grade cytological

abnormalities. Data from these studies are presented in *Table 8*.

Of the presentations at the 17th Papillomavirus Conference, the report by Cuzick and colleagues (ME19A) is directly relevant as it examined the use of HC-I, HC-II and PCR (MY09/11–Digene Sharp enzyme imunoassay) for the identification of high-grade cervical lesions in a routine cervical cancer screening population. The population was composed of 3002 women aged from 34 to 64 years, with a mean age of 46 years, who were attending for routine cervical cancer screening in the UK. Cervical smears were taken using an Aylesbury spatula and prepared in the conventional manner, with the remaining material used for PCR analysis. A second cervical sample was then taken using either a Dacron swab for analysis by HC-I or a cervical brush sampler for analysis by HC-II.

This study demonstrated that the HC-II test had the best sensitivity and specificity of the three techniques analysed for the identification of high-grade disease, particularly when using higher cut-off levels. In this regard, the best performance for HC-II was obtained when using a positive/negative cut-off value of 4.0 pg/ml which gave a sensitivity and specificity of 88.9% and 67.1%, respectively. Comparative statistics for HC-I were 63.2% and 56.8%, respectively while PCR using the Digene Sharp assay gave 75.6% and 34.9%, respectively. Meanwhile, the sensitivity of cytology for the identification of high-grade disease was 62% for moderate or severe dyskaryosis, and 76% for any dyskaryosis. In this study, it is worth noting that the authors state that they have experienced problems with sensitivity and specificity of the PCR/Digene Sharp assay and these results are probably not representative of the performance of the PCR generally when using other means to identify the amplification products.

Another paper presented at the conference by Meijee and colleagues (ME53A) reported data from a study of 2224 women drawn from a routine screening population who were examined by cytology and HPV testing using the GP5+/6+ PCR method. These data demonstrate that HPV testing with the GP5+/6+ PCR method detected 100% of all CIN II/III and cervical carcinomas with a specificity of 52.0%, results that are comparable with those reported for HC-II in the study by Cuzick and colleagues.

Five other reports from the 17th International Papillomavirus Conference have produced similar results using HC-II for the identification of high-grade disease (histologically confirmed CIN II or worse) in screening populations when compared with cytology. These data are consistent with the results of Cuzick and colleagues, and uniformly demonstrate that HC-II has a superior sensitivity to conventional cervical cytology for the identification of high-grade cervical disease.

Given the lack of published studies assessing the sensitivity and specificity of the primary techniques for the identification of cervical lesions in screening populations, we have also drawn upon studies using these techniques for the identification of women with underlying cervical lesions who were referred to colposcopy on the basis of abnormal cytology. While this cannot be directly compared with a screening population, the results are remarkably consistent across the studies and in line with the screening data reported at the 17th International Papillomavirus Conference. Details of these studies are also provided in *Table 8*.

Summary

While the data presented in this section are either preliminary or taken from studies on non-screening populations, they are given weight by their consistency across the studies and by the fact that the trends established are in keeping with those from other sections of this chapter. For the identification of women with high-grade cervical disease, the three primary technologies all possess superior performance to the secondary technologies Southern blot, dot blot, *in situ* hybridisation and HC-I.

Further, the relative performance of the three primary technologies appears to be broadly similar in terms of sensitivity and specificity for the identification of women with coexisting cervical lesions. In this regard, it is also worth noting that they performed as well as or better than cervical cytology, particularly with regard to sensitivity.

However, these comments must be qualified because of the lack of data formally comparing the three primary technologies for the identification of clinically relevant cervical lesions in a routine screening population. Studies of this nature are therefore required in order to distinguish which would provide the optimal performance for screening applications.

Chapter summary

In this chapter, we have reviewed the research literature on the various technologies that are currently available for the detection and typing

of HPV and assessed their applicability to cervical cancer screening. In doing this, the authors have used their own experience to exclude technologies commonly accepted to have insufficient performance characteristics or complexities of execution that would render them unsuitable for the task. This narrowed the field to the three primary technologies – the MY09/11 consensus PCR method, the GP5+/6+ consensus PCR method, and the HC-II method – which were reviewed systematically. This analysis has demonstrated the following:

(1) the three primary technologies were confirmed to have superior sensitivity and negative predictive value compared with other methods currently available for the identification of HPV related cervical lesions
(2) all three technologies appeared to have similar performance characteristics in terms of their sensitivity, specificity, PPV and NPV for the identification of cervical lesions although a formal comparison in a screening population needs to be undertaken.

Further comments

In addition to the foregoing, the authors feel that it is necessary to comment on the practicalities of using these technologies within a cervical cancer screening programme. In this regard, it is important to note that the only technology that is currently available as a commercial 'off the shelf' kit is the Digene HC-II assay, while execution of either PCR system would require the establishment and validation of an in-house procedure based on published protocols. Further complications are introduced because the PCR process needs to be conducted in a facility designed to prevent the contamination of samples with previously amplified PCR products. These issues have been fully reviewed elsewhere, and while they can be easily overcome in specialist laboratories, they need to be accounted for when considering the implementation of PCR on a large scale. Meanwhile, HC-II is not subject to these concerns because it does not depend upon amplification of the target material to achieve its sensitivity.

Finally, technologies for the detection of HPV are developing at a rapid pace. Should a large-scale trial be undertaken to assess the efficacy of HPV testing for cervical cancer screening, it would be important to re-evaluate upcoming methods at the time the trial is undertaken to ensure that the latest technologies are evaluated.

TABLE 1 *Analytical sensitivities of the primary technologies*

Study No.	Study details	Sample	Sample HPV types examined	Sample No.	Method	Primers	Source	HPV types detected	Detection method	Sensitivity	Specificity	Comments
ME12	Cavuslu *et al.* (1996)	SeHa	16	Serial dilution	PCR	MY09/11	Manos (1989)		EtBr-stained gel	250 HPV genomes	NA	
ME25	Evander *et al.* (1992)	SeHa	16	Serial dilution	PCR	MY09/11	Manos (1989)		EtBr-stained gel	100 HPV 16 genomes	NA	
ME31	Gravitt *et al.* (1991)	Plasmid	NA	Serial dilution	PCR	MY09/11	Manos (1989)	NA	NA	19 HPV genomes	NA	
ME36	Herrington *et al.* (1995)	SeHa	16	Serial dilution	PCR	MY09/11		16	DB	1–10 HPV 16 genomes (SeHa) in a background of > 100,000 cells	NA	
ME45	Karlsen *et al.* (1996)	SeHa	16	Serial dilution	PCR	MY09/11		16	SB?	6300 HPV genomes in a background of 100, 000 human cells	NA	
PR8	Bauer *et al.* (1991)	Plasmid	16	Serial dilution	PCR	MY09/11		16	DB	< 500 copies of HPV 16 in a background of 20,000 human cells	NA	
		HeLa	18	Serial dilution	PCR	MY09/11		18	DB	10 HeLa cells (100–500 HPV 18 genomes)	NA	
ME39	Jacobs *et al.* (1995)	Plasmids or cervical scrape cells	6, 11, 16, 18, 31, 33, 34, 35, 39, 40, 42, 43, 44, 45, 51, 52, 54, 56, 58	NA	PCR	GP5+/6+	de Roda Hussman (1995)	6, 11, 16, 18, 31, 33, 34, 35, 39, 40, 42, 43, 44, 45, 51, 52, 54, 56, 58	SB ^{32}P oligo probe (HR and LR cocktails)	100 pg of PCR product	100%	Sensitivity expressed in terms of picograms of PCR product not picograms of input HPV DNA
ME40	Jacobs *et al.* (1996)	Plasmids or cervical scrape	6, 11, 16, 18, 31, 33, 34, 35, 39, 40, 42, 43, 44, 45, 51, 52, 54, 56, 58	Serial dilution	PCR	GP5+/6+	de Roda Hussman (1995)	16, 18	EIA	20 HPV 16 and 18 genomes in a background of 100 ng of human placental DNA	100%	
								16, 18	EtBr	> 200 HPV 16 and 18 genomes in a background of 100 ng of human placental DNA		
								16, 18	SB	20 HPV 16 and 18 genomes in a background of 100 ng of human placental DNA		
ME41	Jacobs *et al.* (1997)	Plasmids or cervical scrape	6, 11, 16, 18, 31, 33, 34, 35, 39, 40, 42, 43, 44, 45, 51, 52, 54, 56, 58	Serial dilution	PCR	GP5+/B6+	de Roda Hussman (1995)	6, 11, 16, 18, 31, 33, 34, 35, 39, 40, 42, 43, 44, 45, 51, 52, 54, 56, 58	EIA	0.5–10 fg of each HPV in 100 ng of human placental DNA (10–200 HPV genomes)	100%	

DB, dot blot; EIA, enzyme immunoassay; EtBr, ethidium bromide; SB, Southern blot. Cell types: HeLa, cells containing 10–50 copies of HPV 18 per cell; SeHa, cells containing 1–2 copies of HPV 16 per cell

TABLE 2 *PCR compared with SB, dot blot and* in situ *hybridisation (ISH) for the detection of HPV in clinical samples*

Study No.	Study details	Population	Sample type	Method and HPV types analysed				No.	No. of positives		Relative positive rate, M2+/M1+ (%)	Comparative data				Relative sensitivity (%)		Comments
				Method 1	Types analysed	Method 2	Types analysed		M1+	M2+		1+/2+	1+/2–	1–/2+	1–/2–	M1:M2	M2:M1	
ME34	Guerrero *et al.* (1992)	Cases (carcinoma)	CSc, CSw, CBr	PCR MY09/11	Generic probe and type-specific probes for 6, 11, 16, 18, 31, 33, 35	SB	Low stringency and high stringency for types 6, 11, 16, 18, 31, 33, 35	263	185	77	41.6	70	115	7	71	90.9	37.8	
		Controls	CSc, CSw, CBr	PCR MY09/11	Generic probe and type-specific probes for 6, 11, 16, 18, 31, 33, 35	SB	Low stringency and high stringency for types 6, 11, 16, 18, 31, 33, 35	247	21	14	66.7	3	18	11	215	21.4	14.3	
ME70	Schiffman *et al.* (1991)	Cases (atypical/CIN) and controls	CVL	PCR MY09/11	Generic probe and type-specific probes for 6, 11, 16, 18, 31, 33, 45	SB	Generic probe and type-specific probes for 6/11, 16, 18, 31, 33, 42–45, 51, 52, 56	120	56	36	64.3	36	20	0	64	100.0	64.3	
PR108	Sherman *et al.* (1994)	Cytology screening	CVL	PCR MY09/11	Not specified	SB	Not specified	200	106	96	90.6							Analysis does not account for different ranges of detection
ME9	Borg *et al.* (1995)	Sexually transmitted disease	CSc	PCR MY09/11	EtBr-stained gel, generic probe, 6/11, 16, 18, 33	DB(VT)	6/11, 16/18, 31/33/35	293	69	37	53.6	35	34	2	222	94.6	50.7	Analysis does not account for different ranges of detection
ME31	Gravitt *et al.* (1991)	Out-patients	CSw(VP)	PCR MY09/11	DB 6/11, 16, 18, 31, 33, 35, 39, 40, 42, 45, 51, 52–59, 66, 68, Pap155, Pap238A, Pap291, W13B	DB(VP)	6/11, 16/18, 31/33/35	362	118	55	46.6	46	72	9	235	83.6	39.0	
				PCR MY09/11	DB 6/11, 16, 18, 31, 33, 35, 39, 40, 42, 45, 51, 52–59, 66, 68, Pap155, Pap238A, Pap291, W13B	DB(VP)	6, 11, 16, 18, 31, 33, 35, 42–45, 51, 52, 56	362	118	85	72.0	60	58	25	219	70.6	50.8	Analysis does not account for different ranges of detection

CBr, cervical brush; CSc, cervical scrape; CSw(VP), ViraPap cervical swab; CSw, cervical swab; CVL, cervicovaginal lavage; DB(VP), dot blot – ViraPap; DB(VT), dot blot – ViraType ; PPV, positive predictive value

continued

TABLE 2 contd *PCR compared with SB, dot blot and* in situ *hybridisation (ISH) for the detection of HPV in clinical samples*

Study No.	Study details	Population	Sample type	Method and HPV types analysed				No.	No. of positives		Relative positive rate, M2+/M1+ (%)	Comparative data				Relative sensitivity (%)		Comments
				Method 1	Types analysed	Method 2	Types analysed		M1+	M2+		1+/2+	1+/2–	1–/2+	1–/2–	M1:M2	M2:M1	
PR8	Bauer *et al.* (1991)	Routine gynae-cological care	CSw(VP)	PCR MY09/11	DB for generic probe, 6/11, 16, 18, 31, 33, 35, 39, 45, 51, 52, W13A, Pap88, Pap155, Pap251	DB (VP/VT)	6, 11, 16, 18, 31, 33, 35	454	154	35	22.7							Analysis does not account for different ranges of detection. Negative data include insufficient specimens
ME36	Herrington *et al.* (1995)	Colposcopy referral	CSc	PCR MY09/11	DB generic probe	ISH	16, 18, 31, 33	167	83	41	49.4							Analysis does not account for different ranges of detection
				PCR MY09/11	16, 18, 31, 33	ISH	16, 18, 31, 33	167	60	41	68.3							Data estimated from PPV and sensitivity figures
ME53	Margall *et al.* (1993)	Colposcopy referral	CSc	PCR	EtBr 16, 18	ISH	16, 18	95	50	17	34.0							

CBr, cervical brush; CSc, cervical scrape; CSw(VP), ViraPap cervical swab; CSw, cervical swab; CVL, cervicovaginal lavage; DB(VP), dot blot – ViraPap; DB(VT), dot blot – ViraType ; PPV, positive predictive value

TABLE 3 *PCR compared with HC-I for the detection of HPV in clinical samples*

Study No.	Study details	Population	Sample type	Method and HPV types analysed				No.	No. of positives		Relative positive rate, M2+/M1+ (%)	Comparative data				Relative sensitivity (%)		Comments
				Method 1	Types analysed	Method 2	Types analysed		M1+	M2+		1+/2+	1+/2–	1–/2+	1–/2–	M1:M2	M2:M1	
ME17	Cope *et al.* (1997)	Screening	CVL	PCR MY09/11	SB 6/11, 16, 18, 31, 33, 35, 39, 40, 42, 45, 51, 52–59, 66, 68, Pap155, Pap238A, Pap291, W13B	HC-I	6/11, 16, 18, 31, 33, 35, 39, 42–45, 51, 52, 56, 58	596	134	81	60.4							Does not account for different ranges of detection but generic probe positives are counted as negative in the analysis
				PCR MY09/11	SB 6/11, 16, 18, 31, 33, 35, 39, 42, 45, 51, 52, 56, 58	HC-I	6, 11, 16, 18, 31, 33, 35, 39, 42, 45, 51, 52, 56, 58	596	108	79	73.1	72	36	7	481	91.1	66.7	Analysis restricted to types detected by both assays
ME75	Smits *et al.* (1995)	Out-patient	CSw(VP)	PCR MY09/11	EtBr + hybridisation for 6, 16, 18, 31, 33, 45, 51	HC-I	6, 11, 16, 18, 31, 33, 35, 42–45, 51, 52, 56	206	96	80	83.3	72	24	8	102	90.0	75.0	Analysis does not account for different ranges of detection
ME77	Sun *et al.* (1995)	Colposcopy referral	CSw(VP)	PCR MY09/11	EtBr + restriction enzyme digest	HC-I	6, 11, 16, 18, 31, 33, 35, 42–45, 51, 52, 56	520	357	317	88.8							Analysis does not account for different ranges of detection
ME73A	Shah *et al.* (1997)	HIV programme and controls	CVL	PCR MY09/11	SB 2, 6, 11, 13, 16, 18, 26, 31–35, 39, 40, 42, 45, 51–59, 61, 62, 64, 66, 70, 72, 73, AE2, Pap155, Pap291, W13B	HC-I	6, 11, 16, 18, 31, 33, 35, 39, 42, 45, 51, 52, 56, 58	222	123	26	21.1							Analysis does not account for different ranges of detection

continued

TABLE 3 contd *PCR compared with HC-I for the detection of HPV in clinical samples*

Study No.	Study details	Population	Sample type	Method and HPV types analysed				No.	No. of positives		Relative positive rate, M2+/M1+ (%)	Comparative data				Relative sensitivity (%)		Comments
				Method 1	Types analysed	Method 2	Types analysed		M1+	M2+		1+/2+	1+/2–	1–/2+	1–/2–	M1:M2	M2:M1	
PR110	Sigurdsson *et al.* (1997)	Colposcopy referral	CSw(VP)	PCR MY09/11	Gel EtBr and DB for 6, 11, 16, 18, 31, 33, 35	HC-I	6, 11, 16, 18, 31, 33, 35, 42–45, 51, 52, 56	358	329	209	63.5							
					Gel EtBr and DB for 16, 18, 31, 33, 35	HC-I	16, 18, 31, 33, 35, 45, 51, 52, 56	358	201	203	101.0							
ME61	Nindl *et al.* (1997)	Colposcopy referral	CSw	PCR GP5+/6+	SB 6, 11, 16, 18, 31, 33, 35, 39, 40, 42–45, 51, 52, 56, 58, 59, 66, 68	HC-I	6, 11, 16, 18, 31, 33, 35, 42, 43, 45, 51, 52, 56	253	121	84	69.4							Analysis does not account for different ranges of

TABLE 4 *HC-II Compared with HC-I for the detection of HPV in clinical samples*

Study No.	Study details	Population	Sample type	Method and HPV types analysed				No.	No. of positives		Relative positive rate, M2+/M1+ (%)	Comparative data				Relative sensitivity (%)		Comments
				Method 1	Types analysed	Method 2	Types analysed		M1+	M2+		1+/2+	1+/2–	1–/2+	1–/2–	M1:M2	M2:M1	
ME16A	Clavel *et al.* (1997)	Colposcopy referral	CSc	HC-II(HR)	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68	HC-I(HR)	16, 18, 31, 33, 35, 45, 51, 52, 56	42	32	23	71.9							Analysis does not account for different ranges of detection
ME28	Ferris *et al.* (1998)	ASCUS/LSIL colposcopy referral	CSw(VP) HC-I CBr(PC) HC-II	HC-II(HR) 0.2 pg/ml	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68	HC-I(HR) 10 pg/ml	16, 18, 31, 33, 35, 45, 51, 52, 56	242	175	108	61.7							Analysis does not account for broader range of HC-II (+39, 58, 59, 68)
		ASCUS colposcopy referral	CSw(VP) HC-I CBr(PC) HC-II	HC-II(HR) 0.2 pg/ml	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68	HC-I(HR) 10 pg/ml	16, 18, 31, 33, 35, 45, 51, 52, 56	143	88	49	55.7							Analysis does not account for broader range of HC-II (+39, 58, 59, 68)
ME65A	Poljak *et al.* (1999)	Abnormal cytology	CBr	HC-II(HR)	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68	HC-I(HR)	16, 18, 31, 33, 35, 45, 51, 52, 56	483	290	275	94.8	275	15	0	193	100.0	94.8	Analysis does not account for different ranges of detection. Discrepant analysis by PCR with 14/15 positive

HC-I(HR), HC-I assay using only the high-risk probe mixture; HC-II(HR), HC-II assay using only the high-risk probe mixture; PC, PreservCyt liquid cytology medium

TABLE 5 *Comparison of PCR and HC-II for the detection of HPV in clinical samples*

Study No.	Study details	Population	Sample type	Method and HPV types analysed				No.	No. of positives		Relative positive rate, M2+/M1+ (%)	Comparative data				κ	Relative sensitivity (%)		Comments
				Method 1	Types analysed	Method 2	Types analysed		M1+	M2+		1+/2+	1+/2–	1–/2+	1–/2–		M1:M2	M2:M1	
ME66	Qu *et al.* (1997)	NA	CVL	PCR MY09/11	SB 2, 6, 11, 13, 16, 18, 26, 31–35, 39, 40, 42, 45, 51–59, 61, 62, 64, 66, 70, 72, 73, AE2, Pap155, Pap291, W13B	PCR GP5+/6+	SB 2, 6, 11, 13, 16, 18, 26, 31–35, 39, 40, 42–45, 51–59, 61, 62, 64, 66, 70, 72, 73, AE2, Pap155, Pap291, W13B	208	94	89	94.7	81	13	8	106	0.79	91.0	86.2	MY detected 27/30 (90%) samples with multiple HPV types while GP+ detected 14/30 (47%). Analytical sensitivity analysis indicated lower sensitivity for HPV35 by MY and HPV 53/61 by GP+
ME64A	Peyton *et al.* (1998)	Screening (Costa Rica cohort)	CBr(PC)	PCR MY09/11	Gel EtBr and DB for 6/11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 44, 45, 51–59, 66, 68, 73, Pap155, Pap291, W13B	HC-II(HR) 1.0 pg/ml on PC specimens	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68	208	51	27	52.9	23	28	4	153	0.51	85.2	45.1	Analysis does not account for different ranges of detection
				PCR MY09/11	Gel EtBr and DB for 6/11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 44, 45, 51–59, 66, 68, 73, Pap155, Pap291, W13B	HC-II(HR) 0.5 pg/ml on PC specimens	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68	208	51	33	64.7					0.53			Analysis does not account for different ranges of detection

continued

TABLE 5 contd *Comparison of PCR and HC-II for the detection of HPV in clinical samples*

Study No.	Study details	Population	Sample type	Method and HPV types analysed				No.	No. of positives		Relative positive rate, M2+/M1+ (%)	Comparative data				κ	Relative sensitivity (%)		Comments
				Method 1	Types analysed	Method 2	Types analysed		M1+	M2+		1+/2+	1+/2–	1–/2+	1–/2–		M1:M2	M2:M1	
ME64A *contd*				PCR MY09/11	Gel EtBr and DB for 6/11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 44, 45, 51–59, 66, 68, 73, Pap155, Pap291, W13B	HC-II(HR) 0.2 pg/ml on PC specimens	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68	208	51	46	90.2					0.48			Analysis does not account for different ranges of detection
				PCR MY09/11	Gel EtBr and DB for 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68	HC-II(HR) 1.0 pg/ml on PC specimens	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68	208	38	27	71.1					0.58			Analysis restricted to types detected by both assays
				PCR MY09/11	Gel EtBr and DB for 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68	HC-II(HR) 0.5 pg/ml on PC specimens	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68	208	38	33	86.8					0.58			Analysis restricted to types detected by both assays
				PCR MY09/11	Gel EtBr and DB for 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68	HC-II(HR) 0.2 pg/ml on PC specimens	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68	208	38	46	121.1					0.52			Analysis restricted to types detected by both assays

TABLE 6 *Comparison of PCR (MY09/11 and GP5+/6+) to Southern blot, dot blot and* in situ *hybridisation for the identification of clinical disease*

Study No.	Study details	Population	No.	Mean age (range) (years)	Clinical disease	Method 1						Method 2						Comments
						Method	Types analysed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Method	Types analysed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
PR8	Bauer *et al.* (1991)	Routine gynaeco-logical care	454	22.9	CIN I/II on cytology	PCR MY09/11	DB 6/11, 16, 18, 31, 33, 35, 39, 42, 45, 51, 52, 56, 58, W13A, Pap88, Pap155, Pap251	80	67	3	100	DB	6, 11, 16, 18, 31, 33, 35	20	92	3	99	Analysis does not account for different ranges of detection
ME36	Herrington *et al.* (1995)	Colposcopy referral	167	Not known	CIN II/III on histology	PCR MY09/11	Generic probe, 6/11, 16, 18, 31, 33	92	NA	43	NA	ISH	16, 18, 31.33	68	NA	66	NA	Analysis does not account for different ranges of detection
ME61	Nindl *et al.* (1997)	Colposcopy referral	253	32.9 (16–73)	CIN II/III on histology	PCR GP5+/6+	16, 18, 31, 33	81	71	58	88	HC-I	16, 18, 31, 33, 45, 51, 52, 56	61	89	73	82	Analysis does not account for different ranges of detection
ME75	Smits *et al.* (1995)	Out-patients	206	Not known	PAP III–V on cytology	PCR MY09/11	EtBr + SB 6, 16, 18, 31, 33, 45, 51	92	53	51	96	HC-I	6, 11, 16, 18, 31, 33, 35, 42–45, 51, 52, 56	75	74	50	90	Analysis does not account for different ranges of detection
ME77	Sun *et al.* (1995)	Colposcopy referral	520	Not known	High-grade CIN or cancer on histology	PCR MY09/11	EtBr + restriction enzyme digest	82	35	24	89	HC-I	6, 11, 16, 18, 31, 33, 35, 42–45, 51, 52, 56	79	44	26	89	Analysis does not account for different ranges of detection
PR110	Sigurdsson *et al.* (1997)	Colposcopy referral	358	33 (18–71)	CIN II/III or cancer on histology	PCR MY09/11	Gel EtBr and DB for 6, 11, 16, 18, 31, 33, 35	80	72	78	75	HC-I	6, 11, 16, 18, 31, 33, 35, 42–45, 51, 52, 56	70	59	67	62	Analysis does not account for different ranges of detection

NPV, negative predictive value

TABLE 7 *Comparison of HC-II with HC-I for the identification of clinical disease*

Study No.	Study details	Population	No.	Mean age (range) (years)	Clinical disease	Prevalence	Method 1						Method 2						Comments
							Method	Types analysed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Method	Types analysed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	
ME28	Ferris *et al.* (1998)	ASCUS/ LSIL colposcopy referral	242	18–71			HC-II	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68	90.5	29.4	10.9	97.0	HC-I	16, 18, 31, 33, 35, 45, 51, 52, 56	61.9	57.0	12.0	94.0	Analysis does not account for broader range of HC-II (+39, 58, 59, 68)
		ASCUS colposcopy referral	143	18–71			HC-II	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68	88.9	40.3	9.1	98.2	HC-I	16, 18, 31, 33, 35, 45, 51, 52, 56	55.6	67.2	10.2	95.7	Analysis does not account for broader range of HC-II (+39, 58, 59, 68)

TABLE 8 *Evaluation of PCR and HC-II for identification of clinical disease*

Study No.	Study details	Population	No.	Mean age (range) (years)	Clinical disease	Method	Types analysed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
ME19A	Cuzick *et al.* (1999)	Cervical cancer screening	3002	46 (34–64)	CIN II/III or worse on histology	PCR/Sharp	NA	75.6	34.9		
			1302			HC-I	16, 18, 31, 33, 35, 45, 51, 52, 56	63.2	56.8		
			1700			HC-II(HR) 1.0 pg/ml	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68	88.9	59.4		
			1700			HC-II(HR) 2.0 pg/ml	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68	88.9	66.8		
			1700			HC-II(HR) 4.0 pg/ml	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68	88.9	67.1		
ME53A	Meijer *et al.* (1999)	Cervical cancer screening	2224	NA	CIN II/III or worse on histology	PCR GP5+/6+	NA	100	52.0		
ME15A	Clavel *et al.* (1999)	Cervical cancer screening	1165	37 (15–72)	CIN II/III or worse on histology	HC-II(HR)	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68	100	86.6	11.4	100
ME35A	Hill *et al.* (1999)	Cervical cancer screening	2719	NA (35–65)	CIN II/III or worse on histology	HC-II(HR) 1.0 pg/ml	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68	86.0	82.0		
ME47A	Lorincz *et al.* (1999)	Cervical cancer screening	10,049	37 (NA)	CIN II/III or worse on histology	HC-II(HR) 1.0 pg/ml	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68	90.7	88.6	10.1	99.8
ME66A	Ratnam *et al.* (1999)	Cervical cancer screening	2098	NA (25–49)	CIN II/III or worse on histology	HC-II(HR)	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68	86.2	57.1	37.3	93.3
ME93A	Womack *et al.* (1999)	Cervical cancer screening	2206	NA (25–56)	CIN II/III or worse on histology	HC-II(HR)	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68	81.0	62.0	19.0	97.0
ME36	Herrington *et al.* (1995)	Colposcopy referral	167	NA	CIN II/III or worse on histology	PCR MY09/11	Generic probe, 6/11, 16, 18, 31, 33	92.0	NA	43.0	NA
ME61	Nindl *et al.* (1997)	Colposcopy referral	253	32.9 (16–73)	CIN II/III or worse on histology	PCR GP5+/6+	16, 18, 31, 33	81.0	71.0	58.0	88.0
ME77	Sun *et al.* (1995)	Colposcopy referral	520	NA	High grade CIN or cancer on histology	PCR MY09/11	EtBr and restriction enzyme digest	82.0	35.0	24.0	89.0
PR110	Sigurdsson *et al.* (1997)	Colposcopy referral	358	33 (18–71)	CIN II/III or worse on histology	PCR MY09/11	Gel EtBr and DB for 6, 11, 16, 18, 31, 33, 35	80.0	72.0	78.0	75.0

Chapter 5
Natural history

Introduction

This chapter reviews what is known about the natural history of HPV infection and cervical neoplasia. It is widely accepted that over 90% of invasive cervical cancer is caused by HPVs (Bosch *et al.,* 1995). Cervical HPV infections are largely sexually transmitted (Burk *et al.,* 1996; Dillner *et al.,* 1996). In may cases the infection is transient (Hildesheim *et al.,* 1994; Wheeler *et al.,* 1996) and the majority will not cause any lasting cervical pathology (Koutsky *et al.,* 1992). Occasionally HPV infection will lead to high-grade CIN, and approximately a third of such lesions progress to cancer if untreated (Ostor, 1993). The focus of the literature review in this chapter is the persistence of HPV infections and the incidence of high-grade CIN following HPV infection. Studies looking at HPV infection following treatment for CIN are included in chapter 6.

There are no prospective studies monitoring HPV infections, cervical neoplasia and invasive cervical cancer in women initially negative on an HPV (DNA or antibody) test. Apart from logistic difficulties following a very large cohort of healthy women for many years to observe new cases of cancer, it is ethically unacceptable not to treat precancerous disease that has a high potential for progression. Another difficulty conducting prospective studies is the definition and diagnosis of precancerous disease. Such disease can in theory be identified by any one of the techniques of cytology, colposcopy, or histology, but there is only partial correspondence between the disease states identified by each of these. Histology is generally regarded as the best indicator of disease status of the cervix, but good histology requires material obtained by loop excision of the transformation zone or multiple colposcopy-directed punch biopsies. This presents a dilemma for prospective studies, since even a single punch biopsy can induce disease regression (Koss *et al.,* 1963; Campion *et al.,* 1986), presumably by stimulating the immune system. Diagnosis of HPV infection too is not perfect. Older assays were not very sensitive and failed to identify a high proportion of infected women. Some newer assays are too sensitive and find evidence of HPV infection from just a few copies of viral DNA which may not be relevant for subsequent cervical disease. Even quantitative assays are subject to false-positive results due to contamination. Other assays do not distinguish between different HPV types, so samples containing DNA from a low-risk type such as HPV 6 may be classed together with others containing the oncogenic HPV 16.

Studies reviewed in this section satisfy the following inclusion criteria:

- material taken from each woman on at least two occasions separated by at least 1 month
- either HPV DNA or HPV antibodies assayed from material taken at the first visit.

Studies looking at the repeatability of HPV testing or the persistence of HPV infection must use the same HPV assay on material collected from at least two occasions. Studies looking at the natural history of cervical neoplasia following HPV infection must have some measure of disease status (cytology or histology) from the first visit. Ideally such studies will confirm cervical disease based on histology at the final visit. Studies investigating seroconversion following HPV infection must include serology on at least two occasions.

Studies in this section were further subdivided into five groups:

(1) prospective follow-up, of women tested for HPV, with cytology and histology in those with abnormal cytology
(2) retrospective assay of HPV from archival material in women with known disease status
(3) detection of HPV antibodies in women previously seronegative with and without cervical HPV DNA
(4) serial measurement of HPV over several weeks recording the frequency of positive tests immediately following a previous positive test
(5) serial measurement of HPV over several months recording persistence of HPV infection and incidence of new infection.

Results

A total of 41 articles and ten abstracts are included in this section. A further 29 papers initially placed within this section were later excluded, six of these were review articles or contained no new data, five only diagnosed HPV infection using morphological signs on cytology or histology, five had no assessment of HPV at all, five were reclassified as prevalence studies and eight were excluded for other reasons. The included abstracts are all from the 16th and 17th International Papillomavirus Conferences.

HPV infection as a precursor of CIN

Several published studies have monitored development or progression of CIN in women tested for HPVs. Only one of these, the study by Rozendaal *et al.* (1996, PR102) from The Netherlands, followed 'normal' women, the rest report on cohorts who had at least abnormal cytology at the outset.

Of the studies reviewed in this subsection, 11 followed women monitoring development of biopsy confirmed CIN II or worse, one did not confirm all cases of high-grade squamous intraepithelial lesions (HSILs) by histology, and four others monitored progressive and persistent histology without specifying the grade of histology. One additional study quantified HPV 16 transcription levels in serial biopsies from women with progressive CIN. The results from these studies are summarised in *Table 9*.

The relative rates of progression between HPV-positive and HPV-negative women varied considerably between studies. In three studies (NH30, PR102, NH13) using general primers (GP5/6 and GP5+/6+; the GP5+/6+ primers are an elongation of the GP5/6 primers with improved sensitivity and specificity over the latter) only two out of 1769 women negative for high-risk (or new) HPVs developed high-grade or progressive histological disease compared with 54 of 422 who tested positive for high-risk (or new) HPVs, giving a crude combined relative risk of 113 (Mantel–Haenszel weighted odds ratio, 277; 95% confidence interval, 21–665). All three studies were conducted in The Netherlands by the group of Walboomers and Meijer. A fourth study by the same group published only in abstract (NH74A) used type-specific PCR for 14 high-risk types in two cohorts of women. Among 701 women undergoing routine screening with normal initial smears, the relative risk for subsequent CIN III (after a mean of 4.5 years of follow-up) in women initially positive for HPV was 58. In a second cohort of 1909 women from a hospital outpatient clinic also with a normal first smear, the relative risk (after a mean follow-up of 33 months) was 74. In the combined cohorts just three out of 2507 women initially negative on both cytology and HPV testing developed CIN III in a mean follow-up of 38 months.

Seven other studies (NH12, NH11, NH44, NH57, NH59, NH62, NH54) used other PCR systems, all with much lower odds ratios associated with a positive test result. Flannelly *et al.* (1995, NH12) using semi-quantitative PCR had a crude odds ratio for high-grade CIN on histology of 4.3 in 62 women initially with mild or moderate dyskaryosis on cytology. Londesborough *et al.* (1996, NH57) using the SHARP PCR system found that 43 women testing positive for HPV were at seven times the risk of progressing from mild or moderate dysplasia to high-grade CIN than 129 women who tested negative. Of the 42 women initially testing positive for HPV, 15 had a persistent type-specific infection. All six women with HPV initially who progressed had a persistent infection. The other four studies using PCR all took biopsies at the outset, and this may have altered the natural history of the lesions. Two of them (Downey *et al.,* 1995; NH11, Iwasaka *et al.,* 1996, NH62) found that those testing negative for HPV were the most likely to progress. In one (NH11), with up to 70 months of follow-up, the 51 women positive for HPV were less likely to progress (relative risk 0.63) than the 41 who tested negative. In the other (NH62), 27% of the 26 women negative for HPV progressed to carcinoma *in situ* over a mean of 41 months follow-up, compared with 23% of the 66 women with high-risk HPV, and 11% of 83 women with low, intermediate or unclassified HPV. The other two studies (NH44, NH59) found that women with HPV were about twice as likely to progress as those without. Woodman *et al.* (1996, NH59) found that after 2 years about 40% of 47 women with HPV 16/18 initially progressed from CIN I or CIN II to CIN III compared with about 15% of those testing negative. Romney *et al.* (1997, NH44) simply reported whether CIN (of any grade) was present on biopsy 9 months after the initial diagnosis. They found that the 50 women testing positive for HPV were about twice as likely to have persistent CIN as the ten without.

Four studies (NH4, NH34, NH41, NH27) used old, insensitive HPV assays. The relative risks in three of these studies were 8.6, 11 and 2.5. The fourth study, by Moscicki *et al.* (1998, NH27), presented odds ratios for HSIL (not necessarily histologically

confirmed) of 1.1, 8.9 and 14.1, depending on whether all but one of the previous two, three or four tests were positive for HPV. In an earlier study by this group (ME58) which followed 27 young women initially HPV-positive by both ViraPap and PCR, one woman developed histologically confirmed CIN II after a mean follow-up of 27 months.

One study (Kataja *et al.,* 1992, NH40) related progressive CIN to HPV status as ascertained by *in situ* hybridisation on the first biopsy of women followed as part of a larger study in Finland. Relative to those with no HPV detected, the risk of progressive CIN in 86 women with HPV 16 was 6.6 (relative risk 3.2 after adjusting for age and grade on CIN on initial biopsy).

An abstract by Holladay *et al.* (1999, NH86A) reports that 12 specimens from patients with confirmed histological progression (CIN I–CIN II–CIN III) had increasing transcription levels as measured by quantitative reverse transcript PCR (RT-PCR) for HPV 16 E6/E7 mRNA.

Retrospective evaluation of HPV infection

Ten published studies have evaluated HPV infection in stored material (*Table 10*). Four (NH9, NH52, NH58, NH84A) used archival smears, one (NH23) used previous biopsy specimens, two (NH79A, NH77A) used stored cells from lavage or scrapes, and three (NH10, NH56, NH60) tested for HPV antibodies in stored sera.

Two of these studies (NH23, NH52) did not include controls. They looked at a total of 15 women with invasive cervical cancer and five with CIN III, and examined smears and biopsies taken up to 10 years previously. All stored specimens tested positive for HPV 16, 18 or an unknown type. Chua and Hjerpe (1995, NH9) analysing archival smears used two matched controls per case. They obtained odds ratios of 16, 11 and 176 for invasive squamous, adenocarcinoma and carcinoma *in situ* of the cervix based on 12, 18 and 58 cases, respectively. Walboomers *et al.* (1995, NH58) used women from a gynaecological clinic, some of whom were being treated for CIN, as controls. They used the general primers to probe archival smears and, consistent with other studies from this group, found a very strong association with high-risk HPVs. Sixteen of the 17 women with invasive carcinoma had HPV in archival smears compared with seven of the 43 controls, giving an odds ratio of 49. Further, all nine cases with two archival smears had the same type of HPV detected on both. The smears were taken between 2 months and 6 years prior to cancer diagnosis (median 1 year). By design, all smears were originally classed as normal. On reanalysis, four of the 26 archival smears from the cases were deemed inadequate, and the rest showed severe dyskaryosis or worse. Wallin *et al.* (1999, NH84A) compare archival smears, all of which had normal cytology, from 133 women with subsequent cervical cancer with those from 133 controls. In abstract only, they report that HPV was detected in 24% of the cases, but just 4% of the controls, giving an odds ratio of 8. The PCR in this study used both MY09/MY11 and GP5/6 consensus primers.

Three studies (NH10, NH56, NH60) looked for HPV 16 (or HPV 16 and 18) antibodies in stored sera using a nested case–control design. All three found an increased risk of CIN in women with prior seropositivity to HPV 16. The odds ratios associated with HPV antibodies in these studies ranged from 3 to 13. A longer lag time from sampling of sera to diagnosis was associated with greater relative risk. Chua *et al.* (1996, NH10) estimated progression rates to CIN in women of different ages with and without HPV 16 antibodies. CIN incidence decreased with age as did the relative risk associated with HPV 16 antibodies, whereas seropositivity increased with age in the controls. A possible explanation of this finding is that CIN is associated with an active HPV infection and women who developed antibodies some years earlier no longer necessarily carry the virus. The study also looked at antibodies for HPV 18 and 33, but these were not significantly associated with disease. The largest of the studies (Dillner *et al.,* 1997, NH60) combined cohorts from Finland, Norway and Sweden and included 182 invasive carcinomas. Overall it found relative risks of 2.7 for HPV 16 antibodies and 2.2 for HPV 16, 18 or 33 antibodies. The relative risk associated with HPV 16 antibodies increased to 3.9 in those women with a lag time of over 5 years. The third study looking at antibodies (Lehtinen *et al.,* 1996, NH56) included 27 cases of invasive cancer and 25 carcinomas *in situ*. Overall the odds ratio was 13.2. It was greater for invasive cancer (infinite, 95% confidence interval > 2.0) than for carcinoma *in situ* (6.0, 1.2–29.7) and for lag times of over 5 years (18, 2.3–142) compared with under 5 years (8.6, 1.0–75).

Two others abstracts (Zemio *et al.,* 1999, NH79A; Coker *et al.,* 1999, NH77A) report on nested case–control studies analysing stored cervical samples (cervicovaginal lavage or cervical scrapes). Neither of the studies included any cases of invasive cancer. One abstract (NH77A) reported hazard ratios for

squamous intraepithelial lesions associated with HPV detected by PCR at entry that decrease with time (from 14 for HSIL in the first year to 3 in the fourth). The other abstract (NH79A) on women with prior LSILs and normal smears, finds an odds ratio of just 1.88 for recurrent squamous intraepithelial lesions associated with HPV detected by PCR a mean of 2 years earlier.

Seroconversion

Carter *et al.* (1996, NH8) considered seroconversion (*Table 11*). They serially tested cervical swab specimens and sera of young women for HPV DNA and HPV antibodies. Of 271 women initially seronegative for HPV 16 antibodies, 19 had prevalent HPV 16 infection, 25 initially negative for HPV 16 had a positive test during the 15 months of follow-up and 227 tested negative throughout. Only 4% of the 227 women who were negative for HPV DNA had antibodies for HPV 16 during 15 months of follow-up compared with 67% of the 25 incident cases and 95% of the prevalent ones.

Repeatability of HPV test

Seven papers presented results on sequential testing of HPV with intervals of under 5 months (*Table 12*). Where possible, we have reported the percentage of tests immediately following a positive test that were still positive. Three studies (NH4, NH27, NH63) use dot or slot blot methodology (including ViraPap). All had testing intervals of about 3 or 4 months. Repeatability of the test results were poor. One of the papers (Moscicki *et al.,* 1998, NH27) estimated that three consecutive negative dot blots were required to be reasonably certain that the woman was free of HPV infection. Two of the three studies using PCR found that between 80 and 90% of tests immediately following a previous positive test remained positive. One of these studies (Wheeler *et al.,* 1996, PR115) performed repeat testing every week allowing little time for regression. The other, reported in a letter by Hsing *et al.* (1994, NH39), was conducted in women with biopsy-proven cervical neoplasia, for whom regression was less likely despite the 2–5 month interval between consecutive tests. The third study using PCR (Schneider *et al.,* 1992, PR105) only found 55% of tests taken 5 weeks after an initial positive, in women with no abnormal cytology in the previous 5 years, were also HPV 16-positive. The lower rate of agreement may be due to false-positive as well as false-negative test results in this 'low-risk' population. Giuliano *et al.* (1997, NH53) use HC-I with consensus PCR of those with equivocal results to test women without a history of CIN for HPV. Although only 6.5% of 62 women who initially tested negative were positive on repeat, 49% of the 65 who were initially positive tested negative on repeat after an interval of just 3 months.

Persistence of HPV infection over 6 months or longer

In this section we consider studies that tested women at least twice 6 months apart for HPV and report on either the cross-tabulation of the first and last test results or estimate persistence as a function of time (*Table 13*). As the results from the previous section demonstrated, even using PCR-based assays in women who are likely to still have an HPV infection that was previously detected, at least 10% test negative. Thus the true persistence rates of HPV infection are likely to be greater than those reported in the nine studies summarised here.

Studies that measure persistence as a function of time tend to use Kaplan–Meier estimates. In practice the time at which a woman becomes HPV-negative is not observed exactly. Rather, one has a series of tests, and any change of status must have occurred at some time between two consecutive tests. Such data are said to be interval censored, and special estimates of the survival function (not Kaplan–Meier estimates) should be used.

Studies that provide cross-tabulation of two HPV tests can be summarised in several ways. The proportion of those positive on the first test who are negative on the second test gives a simple estimate of regression. The κ statistic for the 2×2 table is a measure of the agreement of the two test results that takes into account the amount of agreement expected by chance. The κ statistic is most appropriate when the interval between the tests is short so that there is little chance for regression or new infection. The relative risk quantifies how much more likely an individual who is positive on the first test is to have a positive result on the second test compared with those negative on the first test.

Four studies using PCR present data that can be summarised as a 2×2 table of HPV results on the two visits. Surprisingly the concordances of the two test results, as measured by the κ statistic, were poor (they were 0.49, 0.42, 0.03 and 0.17), suggesting that either the majority of infections are only intermittently associated with detectable HPV DNA in a cervical scrape or that (particularly in young women) clearance of infection is generally quite fast, but (re)infection (from the same or a new sexual partner) is quite common.

Although the results of studies included in this subsection are quite variable, they do seem to indicate a persistence rate of no more than about 50%, 12 months after an initial positive HPV test. It is difficult to say categorically that this lack of persistence is due to the absence of the viral infection or to a mixture of initial false-positive and subsequent false-negative tests. But studies such as the one by Moscicki *et al.* (1998, NH27) that take into account the possibility of false-negative test have similar estimates of regression rates.

Discussion and conclusions

In common with much of HPV epidemiology the results in this area are complicated by:

- the variety of HPV assays used
- the different sensitivities and specificities of the assays and of the same assay when used in different laboratories
- the different measures of underlying cervical disease and the lack of close correspondence between them
- the possible effect of biopsy on the future course of a cervical lesion
- the variety of populations studied (different age groups, women with normal cytology, women with dyskaryosis, sexually transmitted disease clinic patients, women with cervical cancer, etc.) and the different relationship that may exist between HPV infection and cervical disease within them.

Nevertheless, certain broad conclusions and recommendations seem possible:

- Women who test negative for high-risk HPVs using the GP5+/6+ primer system and who have normal or borderline changes on cytology are at extremely low risk of developing high-grade CIN over the next 3–4 years (13 per 10,000 tested over 40 months – Rozendaal *et al.*, 1996, PR102). Note that, in the largest of these studies, CIN would only be recorded if it was associated with a sufficiently abnormal smear to warrant colposcopy and biopsy.
- Negativity of other PCR-based systems is also associated with lower risk of future high-grade CIN. However, the risk of progression in those with low-grade cytological or histological disease is not negligible. Thus, some form of additional follow-up would be required in the management of those with abnormal cytology who are negative for HPV on such an assay.
- HPV can be detected in archival smears taken 10 years prior to cancer diagnosis. Too few cases have been studied to reliably estimate the proportion of smears taken 1–2, 3–4, 5–7 or 8–10 years prior to cancer diagnosis that contain detectable HPV DNA. HPV antibodies can also be detected several years prior to diagnosis of invasive cancer, and indeed the association is stronger when analysing samples taken more than 5 years prior to cancer diagnosis. Nevertheless, antibody testing is neither sensitive nor specific enough to cervical cancer to be useful as a screening tool.
- Most testing systems, reliant on **sampling of cervical cells and assays for HPV DNA** are likely to have a sensitivity rate of between 50 and 90%. The sensitivity is likely to depend on viral load and possibly also underlying cervical disease.
- The majority of HPV infections do not persist. It is likely that the median duration is no more than 1 year.
- Persistent infections are more strongly associated with cervical disease than transient ones.

Future research

From a screening prospective, the need for longitudinal rather than cross-sectional studies is mostly linked to determining appropriate screening intervals. It would be useful to examine the cumulative incidence of cervical cancer 1, 3, 5, 10 and 15 years after various screening histories such as:

- HPV-negative, cytology-negative
- HPV-negative (no cytology)
- cytology-negative (no HPV)
- borderline changes on cytology, HPV-negative
- borderline changes on cytology, HPV-positive
- mild dyskaryosis, HPV-negative
- mild dyskaryosis, HPV-positive.

Longitudinal studies can be difficult to interpret because of the need to biopsy suspicious lesions and treat any high-grade lesions. Nevertheless, longitudinal studies are important and provision for at least 6 years of follow-up should be considered in any large-scale study of HPV testing in routine screening.

Analysis of cervical screening databases

Linking of cytology, histology and cancer registry databases should enable one to produce age-specific cumulative incidence curves for invasive cervical cancer up to 5 years after smears tests with different cytological results (normal, borderline,

etc.). Similar curves could be produced for high-grade CIN using records going back to the late 1980s to obtain cumulative incidence 10 or even 15 years after the initial smear test.

Case–control studies testing archival smears for HPV DNA

Despite the medicolegal difficulties in destroying archival smears, it is worth considering ways of testing old smears for HPV DNA. Cases would include women with invasive cancer or CIN III, and all previous smears should be analysed. Control smears should be matched on year of smear, laboratory and age of woman.

Passive follow-up of women previously tested for HPV DNA

Several research groups tested several thousands of 'normal' women using reliable HPV assays in the early and mid-1990s. Tracing such women on cytology databases and recording their subsequent smear results would be an efficient design for learning about the medium-term implications of a negative HPV test.

Long-term surveillance of women with negative HPV tests

It is important to learn the long-term significance of a negative HPV test. Randomised studies comparing two or more screening strategies in terms of future cancer incidence would have to be extremely large. It would nevertheless be of interest to compare the cumulative incidence of high-grade CIN in 6 years after testing negative on both cytology and HPV with the cumulative incidence 3 years after testing negative on cytology alone. From such a comparison, one might conclude whether it is 'safe' to switch from 3-yearly cytology to 6-yearly cytology and HPV. Such a study would require approximately 25,000 women to be screened with cytology alone and 25,000 to be screened (initially) by both cytology and HPV testing. Given the size, consideration should be given to international collaboration and long-term surveillance of women in ongoing HPV screening studies in order to be able to look at subgroups defined by age for instance. Appropriate comparisons could be made without including a randomised cytology only group, but would require approximately 50,000 women to be tested for HPV.

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TABLE 9 *Studies reporting histology at the end of follow-up*

Paper	Author	Year	Assay	Age (years)	Cohort	Follow-up	Biopsy	Results	RR (HSIL)
NH30	Remmink	1995	PCR GP5/6	16–55	The Netherlands Abnormal Smear referred to gynaecology clinic	3–36 months Mean 16.5 months	Colposcopic impression of CIN III in 3+ quadrants	≤ CIN II / CIN III / Total HPV_{hr}+ 150 / 17 / 167 HPV X+ 134 / 2 / 136 HPV_{hr}– and HPV X– 39 / 0 / 39	∞
PR102	Rozendaal	1996	PCR GP 5+/6+	35–54	Routine screening The Netherlands Initial smear normal or borderline	5–73 months Mean 40 months	Colposcopic referral from screening smears	HPV_{hr} / ≤ CIN I / CIN II / CIN III / Total + 78 / 2 / 6 / 86 – 1534 / 1 / 1 / 1536	71.4
NH13	Gaarenstroom	1994	PCR GP5/6 on smears 29% of those with HPV 16 progressed histologically	19–66 Mean 32	Dutch women with abnormal cytology. Punch **biopsy** taken. No treatment in 1st 6 months	6–42 months Mean 20 months	Unclear	HPV / Progress / Total + 21% / 130 – 0% / 97	∞
NH12	Flannelly	1995	Semi-quantitative PCR (Manos) (High level HPV 16)	?	UK Under surveillance for mild or moderate dyskaryosis	0, 6, 12 months Results for 0 and 12 months presented	Loop of everyone	HPV 16 / CIN II+ / Total + 74% / 19 – 40% / 43	1.9
NH11	Downey	1994	Semi-quantitative Type-specific PCR on scrapes		UK women with CIN I or less on biopsy after referral with mild dyskaryosis or more severe cytology	Up to 70 months	Follow-up with cytology every 3 months in 1st year. Biopsy if abnormal cytology	HPV / Progress / Persist / Regress / Total + 11 / 19 / 21 / 51 – 14 / 20 / 7 / 41	0.63
NH44	Romney	1997	PCR MY09/11 'Persistent CIN' – any CIN on final histology	Mean 27	US histologically confirmed **moderate dysplasia** on biopsy 45% Hispanic, 43% black Randomised controlled trial	9 months	Biopsy of everyone	Persistent CIN HPV / No / Yes / Total + 14 / 36 / 50 – 6 / 4 / 10	1.8

hr, high risk; OR, odds ratio; RR, relative risk

continued

TABLE 9 contd *Studies reporting histology at the end of follow-up*

Paper	Author	Year	Assay	Age (years)	Cohort	Follow-up	Biopsy	Results					RR (HSIL)
NH4	Byrne	1990	Slot blot hybridisation	21–38	GUM UK Abnormal smear	Every 4 months Up to 45 months	Severe dyskaryosis on cytology	HPV 16/18 on first test	Negative cytology	Abnormal cytology	CIN III	Total	
								+	4	5	3	12	2.5
								–	10	17	3	30	
								HPV 16/18 on one of first 3 tests	Negative cytology	Abnormal cytology	CIN III	Total	
								+	6	16	5	27	2.8
								–	8	6	1	15	
NH34	Campion	1986	Filter *in situ* HPV 16	< 30 Mean 22	UK colposcopy referral with mild dyskaryosis	17–28 months	Severe dyskaryosis or CIN III on colposcopy	HPV 16	Regress	Persist	CIN III	Total	
								+	0%	44%	56%	39	8.6
								–	11.5%	82%	6.5%	61	
NH41	Koutsky	1992	ViraPap	16–50 Mean 27	US STD clinic Negative cytology 75% white, 17% black	1–65 months Mean 25	Biopsy if cytology or colposcopy suggestive of CIN II			HPV	CIN II/III	Total	
										+	22%	110	11
										–	2%	198	
			Relative risk in Cox model with time-dependent covariate (HPV mostly associated with types 16 and 28)										
NH27	Moscicki	1998	ViraType (1st year) HPV profile (2nd year)	13–22	Positive HPV test No CIN USA	Mean 24 ± 15 months		HPV+ (any type) Cytology negative	Normal 61.2%	LSIL 33.5%	HSIL 5.3%	Total 618	OR for HSIL increased with number of tests positive for high-risk HPV on previous visits
			Relative to those HPV-negative on previous test, 1.1, 8.9 and 14.1 for 1,2 or 3 positive on previous two, three or four tests Details unclear										
NH40	Kataja	1992	*In situ* hybridisation on biopsy	15–66 Mean 28	Finland	Long-term follow-up	Time since initial biopsy unclear If cytology showed HPV with CIN			Progressive	CIN	Total	
										HPV 16+	36%	86	
										HPV 18+	15%	33	
			(Earlier results in NH49) RR (HPV 16) = 6.6 RR (adjusted) = 3.2 RR = 3.6							HPV 31+	19%	32	
										HPV 33+	17%	29	
										HPV 6/11+	10%	107	
										HPV–	5.5%	165	

OR, odds ratio; RR, relative risk

continued

TABLE 9 contd *Studies reporting histology at the end of follow-up*

Paper	Author	Year	Assay	Age (years)	Cohort	Follow-up	Biopsy	Results	RR (HSIL)
NH86A	Holladay	1999	RT-PCR in biopsies (HPV RNA)		USA 6 patients with CIN	Serial biopsies		All 6 had detected HPV 16 E6/E7 transcription. Specimens from patients with CIN progression had increased transcription levels	
NH74A	Meijer	1998	Type-specific PCR (for high-risk HPV)	20–54 Mean 35	The Netherlands Normal smear. No previous cervical dysplasia			CIN III HPV + – Total + 10 73 103 10% 58 – 1 597 598 0.2% 701	
					(1) Routine 3-yearly screening (n = 1913)	Of 701 with at least two HPV tests 0.5–8.3 years Mean 4.5			
					(2) outpatient clinic (n = 2310)	3–69 months Mean 33		CIN III (subsequent) HPV_{hr} + – Total + 29 372 401 8% 74 – 2 1907 1909 0.1%	
NH54	Sichero	1999	Type-specific PCR 16, 18, 31, 33 on biopsies	17–62 Median 28	Denmark All had CIN I or II on biopsy initially	4-monthly Progression 6–62 months Median 10	Biopsy if warranted by cytology or colposcopy. CIN III on biopsy or three normal smears. (No report on numbers not resolved)	Initial CIN / HPV / CIN III / Three normal smears I + 10 11 1.9 I – 5 15	
						Regression 12–89 months Median 23		2 + 17 5 3.1 2 – 2 6	
					Those that neither progressed nor regressed were excluded				
NH59	Woodman	1996	PCR L1 primers for HPV 16/18	30 ± 8	Women with CIN I or II on biopsy UK	4–84 months Median 36 4-monthly cytology and colposcopy	Determined by cytology and colposcopy	n / % CIN III at: 24 months / 48 months HPV at Baseline + 47 40% 50% – 46 15% 20% (Based on Kaplan–Meier curves)	OR 2.3 (1.2–4.3)
NH57	Londesborough	1996	Consensus PCR (Sharp)	19–69 Mean 31	UK Referred with 2 x mild or moderate dyskaryosis colposcopy consistent with no or low-grade lesion	At 1 year if initially HPV-negative; 6-monthly for up to 2 years if HPV-positive	Determined by cytology and colposcopy	Eventual Initial HPV / ≤ CIN I / CIN II / CIN III / Total + 36 2 4 42 – 126 3 0 129	7
								Type-specific HPV: Persistent 9 2 4 15 Transient 27 0 0 29	∞

hr, high risk; OR, odds ratio; RR, relative risk

continued

TABLE 9 contd *Studies reporting histology at the end of follow-up*

Paper	Author	Year	Assay	Age (years)	Cohort	Follow-up	Biopsy	Results			RR (HSIL)
NH62	Iwasaka	1996	Consensus PCR (L1) on cervical scrapes	21–72 Mean 41 ± 10	Japan 101 mild 44 moderate 30 severe dysplasia	Mean 40.4 months Minimum 2 years unless progressed	Punch at entry All progression histologically confirmed carcinoma *in situ* or worse	HPV	*n*	Progress (%)	1.55
								High risk	66	23	Relative to 'rest'. But note highest rate of progression in HPV negatives
								Intermediate risk	27	15	
								Low risk	43	7	
								Unclassified	13	15	
								Negative	26	27	
ME58	Moscicki	1993	ViraPap Type-specific PCR	13–19 Mean 17.8	San Francisco Planned parenthood clinic	4–10 visits (mean 6) over 13–40 months (mean 27)	If indicated by colposcopy	Of 27 initially HPV positive: 0 out of 14 who had two or more negative tests developed high-grade CIN 1 out of 13 who were consistently (3) or intermittently (on both tests) developed high-grade CIN			

OR, odds ratio; RR, relative risk

TABLE 10 *Studies retrospectively analysing stored samples for HPV DNA or antibodies*

Paper	Author	Year	Assay	Follow-up	Setting	Age (years)	Case	Control	Material
NH9	Chua	1996	PCR (nested): (i) MY09/11 (ii) GP5+/6+	2–7 years Mean ~3 years	Sweden	17–68	Adenocarcinoma (12) Squamous cell (18) Carcinoma *in situ* (58)	No carcinoma *in situ* for 5 years post-smear (but some history of abnormality) (Age matched)	Archival smears
								Case: *n* / HPV+ (%); Control: *n* / HPV+ (%) Carcinoma *in situ*: 58 / 71; 58 / 12 Invasive squamous cell: 18 / 67; 18 / 11 Adenocarcinoma: 12 / 58; 12 / 8	
NH23	Konno	1992	*In situ* hybridisation PCR of negatives	< 10 years	Japan		CIN III (5) Microinvasive (2) Invasive carcinoma (1)	None	Hysterectomy sections
			HPV 16 found in all previous biopsy specimens				All with HPV 16/18 on hysterectomy section		
NH52	de Roda Husman	1995	General primer PCR	2–9 years Mean 5.8	The Netherlands Screening programme		Cervical cancer (12)	None	Archival smears
			HPV found in archival smears of all 12 cases. Same type found in smear and biopsy of tumour. Seven had type 16, four type 18, one unknown type						
NH10	Chua	1996	Serology L1 and L2 capsids for HPV 16 antibodies	< 6.5 years Mean 3 years	Sweden	27–61 Mean 39	CIN II/III (41) CIN I (10) CIN not otherwise specified (23)	Population based Match on age, date of blood Probability of CIN within 33 months given HPV seropositivity	Sera
						n	Seropositive (%)	Age (years) / + / –	
						CIN II–III: 41	37	25–34: 0.034 / 0.005	
						CIN I: 10	20	35–44: 0.016 / 0.006	
						CIN not otherwise specified: 23	45–64: 0.002 / 0.002 43		
						Controls: 148	16		
NH79A	Zemio	1999	MY09*/MY11	Maximum: 51 months Mean 23 months	USA From a cohort of over 2000 womenwith untreated LSIL and a normal smear on entry.		Recurrent abnormal smear or biopsy (*n* = 130) OR for recurrent SIL 1.88	No abnormal smear or biopsy after entry (*n* = 130)	Cervicovaginal lavage

continued

TABLE 10 contd *Studies retrospectively analysing stored samples for HPV DNA or antibodies*

Paper	Author	Year	Assay	Follow-up	Setting	Age (years)	Case	Control	Material
NH77A	Coker	1999	Consensus PCR	< 5 years	USA family planning cohort of 6284 screened in 1991–92. 4386 followed		22 HSIL 404 LSIL Sample normal follow-up with cytology		'Cervical samples'
							Adjusted hazard ratio for oncogenic HPV at entry and subsequent HSIL (LSIL) development: year 1, 13.8 (5.6); year 2, 10.3 (4.0); year 3, 5.6 (2.0); year 4, 3.1 (1.0)		
NH84A	Wallin	1999	MY09/11 and GP5/6	Median 3.8 years?	Sweden	Mean 44	133 cancers (with prior negative smears)	133	Archival smears (and biopsies)
								HPV + / HPV – Case: 32 / 101 (133) Control: 5 / 128 (133) OR = 7.7	
							OR for associated HPV on both prediagnostic smear and diagnostic sample = 110		
NH56	Lehtinen	1996	HPV 16 L1 and L2 capsid antibodies	0.7–22.8 years Mean 10 years	Finland 18,814 women flagged to cancer registry	Mean 39 at baseline 49 at diagnosis	27 invasive carcinomas 25 carcinomas *in situ*	143 individually matched	Stored sera
							HPV 16 antibodies in 24% of cases and 2% of controls, conditional OR 13.2		
							OR for invasive cancer diagnosis ∞ (2.0 to ∞), for carcinoma *in situ* 6.0 (1.2–29.7)		
							OR for < 5 years since sampling 8.6 (1.0–75); over 5 years 18 (2.3–142)		
NH60	Dillner	1997	L1 and L2 capsids to HPV 16, 18 and 33 antibodies	14% under a year 33% over 5 years	Finland, Norway and Sweden population-based serum banks	< 40 (45%) > 45 (26%)	182 invasive carcinomas	~3 matched controls per case (total 538) n / HPV 16+ / HPV 16, 18, 33+ Case: 182 / 16% / 37% Control: 538 / 7% / 19% RR: 2.7 / 2.2	Stored sera
							For HPV 16, RR increased with increasing lag time 3.9 (1.6–9.6) over 5 years		
NH58	Walboomers	1995	General practitioner PCR	2 months – 6 years Median 1 year	The Netherlands 3-yearly screening programme		17 cancers with normal archival smears	50 controls from gynaecology clinic including women with CIN Archival HPV_{hr} + / – / Total Women / (Smears) Case: 16 / 1 / 17 / (26) OR = 49 Control: 7 / 43 / 50 / (88)	Archival smears
							All nine cases with two archival smears had the same viral type on both		
							On rescreening 26 archival smears from the cases, four were inadequate and the rest (22) were all severe dyskaryosis or worse		

TABLE 11 *Studies following women for development of HPV antibodies*

Paper	Author	Year	DNA	Antibody	Cohort	Age (years)	Initial state	Seroconversion by 15 months (%)
NH8	Carter	1996	PCR MY09/11	HPV 16, L1, ELISA	University, USA	18–20	Incident HPV 16, n = 25 Prevalent HPV 16, n = 19 HPV-negative, n = 227	67 95 4

ELISA, enzyme-linked immunoassay

TABLE 12 *Studies retesting women at intervals of between 1 week and 4 months*

Paper	Author	Year	Assay	'Test 1'-positive	'Test 2'-positive	Percentage still positive on repeat	Interval	Cohort
NH4	Byrne	1990	Slot blot Hybridisation Spatula	50	18	36	~4 months	Mild/moderate dyskaryosis on smear Genitourinary medicine clinic
NH27	Moscicki	1998	Dot blot Dacron swab Using hidden Markov model estimated three consecutive negative tests required to be 'certain that woman is HPV-negative	513	~275[a]	54	~4 months	Young women with positive initial test and no CIN
PR105	Schneider	1992	PCR, HPV 16 E1 Cotton swab	40	22	55	~5 weeks	Self-selected. Normal smear within previous 5 years
PR115	Wheeler	1996	Type-specific PCR Swab and lavage	220	183	83	1 week	Students, USA
NH39	Hsing	1994	Consensus PCR (Manos) Cervical swabs 33 of 34 had same type in both samples (Of 52 negative on test 1, 92% were still negative on test 2. κ = 0.82)	38	34	89	2–5 months	Women with biopsy proven cervical neoplasia Test 2: + / – / Total Test 1 +: 34 / 4 / 38 Test 1 –: 4 / 48 / 52
NH53	Giuliano	1997	HC (intermediate and high risk) Consensus (L1 primers) PCR on equivocal 4 (6.5%) of 62 initially HPV-negative were positive on repeat κ = 0.44	65	33	51	3 months	USA. Hispanic, low income. Non-smokers. No previous treatment for CIN
NH63	Change-Claude	1995	ViraPap/ViraType (Of 1161 negative on test 1, 1131 (97.4%) were also negative on test 2. κ = 0.25)	49	13	26	~3 months	Germany – University Women's clinic. 108 pregnant and 192 non-pregnant women

[a] *Estimate from Kaplan–Meier survival function*

TABLE 13 *Studies following women initially testing positive for HPV infection for at least 4 months*

Paper	Author	Year	Assay	Age (years)	Cohort	Follow-up	Results	Persistence (%)	RR
NH17	Hildesheim	1994	PCR, L1	18–65 Median 26	Negative cytology No prior CIN 90% white US	9–30 month Median 15 months	HPV (2) + / – / Total HPV (1) +: 64 / 38 / 102 HPV (1) –: 39 / 252 / 291 35/86 had type-specific persistence (53% within 12 months, 28% over 18 months) κ = 0.49	63	4.68
NH19	Ho	1998	PCR consensus and SB (HPV-positive if either test positive)	20 ± 3	Students in US 57% white, 13% Hispanic, 12% black	Mean 2.2 years Maximum: 3.4 years 6-monthly	HPV– 399 HPV+ HPV+ 43% by 3 years[a] HPV– 70% by 1 year Increased incidence in younger women and ethnic minorities Increased persistence in older women and women with multiple HPV types	30	
NH27	Moscicki	1998	Three dot blots (~4 months apart)		Positive HPV Negative cytology US	1 year[a]	HPV+ 303 HPV_{hr}+ HPV– ~185 (60%)	40	
NH37	Hinchcliffe	1995	PCR GP5/6	18–35	366 women with negative smears in contraceptive trial	4 months	HPV (2) + / – / Total HPV (1) +: 12 / 15 / 27 HPV (1) –: 13 / 326 / 339 Same viral type in just two of 12 with HPV in both tests. OR = 20 κ = 0.42	44	11.6
NH45	Rosenfeld	1992	SB (lavage)	13–21 Mean 17	Smear test in Bronx clinic	6–36 months Median 13 months	HPV (2) + / – / Total HPV (1) +: 4 / 16 / 20 HPV (1) –: 9 / 22 / 31 One of four with two positive results had same type on both tests κ = –0.10	20	0.69
PR72	Kotloff	1998	PCR MY09/11	17–44 Mean 22	US students 78% white	Median duration of high-risk HPV 9 months (Kaplan–Meier) (based on 52 women with high-risk HPV)		< 50	
PR103	Saito	1995	HPV 16/18 using E6	17–68 Mean 23	Japan HPV 16/18-positive normal cytology	12–48 months Mean 23 months	HPV (2) + / – / Total HPV (1) +: 4 / 41 / 49	8	
PR111	Smith	1997	Consensus PCR	45–64	US postmenopausal clinical trial	24 months	HPV (2) + / – / Total HPV (1) +: 11 / 29 / 40 HPV (1) –: 13 / 52 / 81	28	1.38

continued

TABLE 13 contd *Studies following women initially testing positive for HPV infection for at least 4 months*

Paper	Author	Year	Assay	Age (years)	Cohort	Follow-up	Results	Persistence (%)	RR
PR40	Evander	1995	PCR MY09/11 GP5/6 Only two of 12 had type-specific persistence HPV not limited to high-risk types	19–25	Sweden	11–37 months Median 24	HPV (2) HPV (1) + – Total + 12 47 59 – 11 206 253	20	4.01
NH74A	Meijer	1998	Type-specific PCR	(1) –	(1) The Netherlands screening. Normal smear. No previous abnormality	(1) Routine 3-yearly 0.5–8.3 years Mean 4.5 years	HPV (2) HPV (1) + – Total + 33 70 103 – 15 583 598	32	12.8
				(2) 20–54 Mean 35	(2) Outpatient clinic. Normal smear. No previous abnormality	(2) 3–69 months Mean 33	(2) Survival analysis at 6 years	15	
NH75A	Coker	1999	HC (high risk)	'Young'	USA SIL or ASCUS at baseline	Every 4.5 months	After 4.5 months	65	
NH83A	Coker	1999			*n* = 188	13.5 months	After 9 months Persistence associated with young age	46	
NH81A	Van Duin	1999			The Netherlands 44 with HPV DNA on smear at entry		HPV 16 variants Progression to CIN III in 57%	68	
NH80A	Kjaer	1999	GP5+/6+ and TS		Denmark Initial cohort 11,000 8700 examined twice	Examined ~ every 2 years		50 Of 501 initially HPV-positive	
ME54	McNichol	1994	Type-specific PCR Spatula and swab Note: very high attrition rate	?	Canada HPV (PCR) or koilocytotic smear. No CIN on colposcopy	4–13 months Mean 8	HPV (2) HPV (1) + – + 8 14 –[b] 5 10 κ = 0.03	36 (33% positivity)	
NH55	Fairley	1995	PCR MY09/MY11 Note: (1) All 59 originally tested positive. 51 were positive on reanalysis of stored samples (2) No difference between those who did and did not cease smoking	37 ± 10	Australia smoking cessation study. All with initially positive HPV	At 1 year	Reanalysis of initial Follow-up HPV HPV + – Total + 23 18 51 – 2 6 8 κ = 0.17	45	3.8
ME58	Moscicki	1993	ViraPap PCR	13–19 Mean 17.8	San Francisco Planned parenthood clinic	13–40 months Mean 27 months Mean 6 visits	27 initially positive by both tests	48	

[a] *Kaplan–Meier estimate;* [b] *After a previous positive test*

Chapter 6
Prevalence

Introduction

A number of issues other than disease state affect the prevalence of HPV in a population. This is particularly important for 'normal' populations, where lifestyle factors are the dominant force. It is well known that HPV is a sexually transmitted disease, and that the dominant epidemiological factors are a number of sexual partners in the last few years, and age at first intercourse. Thus, higher prevalences would be expected in samples taken in sexually transmitted disease clinics, or in big cities. Likewise, lower rates would be expected in private surgeries, especially in rural or settled suburban areas. Age is also an important factor. HPV infection rates peak in the early twenties and decline steadily thereafter up to about age 45 years, where they stabilise and may actually begin to rise again. This will be dealt with more fully below.

Even within disease categories these lifestyle factors will have some influence on HPV prevalence, especially for low-grade CIN, which is little more than a cytological manifestation of HPV infection. More importantly, the method of disease ascertainment varies across studies, and this can affect results, even for high-grade lesions.

We have striven to use histological disease categories, but several studies are based on cytology only. There is considerable variation between the two, especially for low-grade cytology, where the histopathological findings are widely varying, typically being 20% high-grade CIN, 50% low-grade CIN, and 30% less than CIN or normal. In addition, at the lower end there are three 'normal' groups – negative cytology, no cytology result, or abnormal cytology, but histology or colposcopically negative. We would expect an increasing gradient of positivity across these groups, all other things being equal.

In addition to population or disease state factors, there are factors related to sample collection and assay procedures which can affect the observed prevalence. We have focused on sample collection methods that would be suitable for screening. Thus, all studies in which HPV was measured in a biopsy have been excluded. This has excluded much of the data which have shown that a very high percentage of cervical cancers contain HPV and that the relative risk of cancer in infections is typically in excess of 30-fold. Much of this data has been reviewed in an IARC (1995) monograph. A good example is the study by Bosch *et al.* (1995) of 932 cancer biopsies from around the world. An initial analysis found HPV in 93% of the cancers, and a more refined approach using different sets of primers (Jacobs *et al.,* 1997) has now found HPV in over 99% of these samples.

Serological assays have also been used for epidemiological studies, especially when serum samples on large cohorts followed up for cancer and or CIN III were available, and also to document the time from infection to seroconversion. We have not included these studies in this section because currently the sensitivity is too low (typically less than 50% for established disease) and blood samples are unattractive as a source of screening material.

A little material exists on collection methods for which adequate sensitivity is not fully established, but for which there is much potential in screening. These include urine, tampons, and other self-sampling devices. However, the main methods for sample collection are the spatula, some sort of brush, a swab, or a saline cervicovaginal lavage. Each of these can be subdivided further. Spatulas can be wooden or plastic, and come in a range of designs from the classic Ayres spatula to the more pointed Aylesbury spatula. Even more variability exists in brushes from the classic Cytobrush®, useful only for endocervical sampling, to a broad Cervex Brush® with plastic fronds for a complete sample, to the specially designed Digene HPV conical brush sampler. Swabs can be cotton or Dacron, and used with or without a speculum.

Lastly, but of great importance, is the fact that HPV detection rates depend very substantially on the type of assay used. We have chosen to exclude all non-amplified assays, as these are not considered to be sensitive enough to be useful as a screening test on smear material, although some, such as Southern blot are the gold standard, when sufficient tissue exists, such as a biopsy. Methods excluded are FISH, NISH, dot and slot blot hybridisation

methods such as ViraPap and classical Southern blot hybridisation. In a few cases, studies employing a sensitive Southern blot with radioactive probes have been included because of their demonstrated high sensitivity. These have been flagged by a footnote.

Thus, we have only included methods where some form of amplification is employed, either target amplification (PCR) or signal amplification (HC). These are discussed more fully in the methods section. The only commercially currently available method is HC, which comes in two formats, either as a tube test (HC-I), or in a microwell plate (HC-II). The system is based on a hybridisation between the target DNA and a set of whole genome RNA probes for the types of interest and is well standardised. By contrast, PCR is a highly variable technique, and the results depend on a variety of factors which are discussed below.

Primers

Either a consensus system that amplifies a range of types or a type-specific system can be used. There are two widely used consensus systems:

(1) **MY09/11**. This amplifies an approximately 450 bp region in the L1 gene and, by using a range of different primers, can amplify more than 25 known types and a range of uncharacterised types.
(2) **GP5/6 or GP5+/6+**. This is based on 140 bp region within the MY09/11 region and amplifies a similar but not identical spectrum of types.

Two other consensus systems have also been used by more than one group. These are those developed by Gregoire *et al.* (1989) and Yoshikawa *et al.* (1990).

A wide range of type-specific primers have been used. These of course can only amplify one type of HPV, so are often used in combination, either as completely separate amplifications or combined into one PCR by multiplexing. They can have higher sensitivity and specificity than a consensus system but are more labour-intensive. Often they are used as a second stage for typing samples which are positive by a consensus PCR.

Detection system

The detection system after PCR amplification is also variable. A basic ethidium bromide staining and ultraviolet visualisation procedure is often used, and can be followed by Southern blot hybridisation with radiolabelled probes to increase sensitivity or for typing if type-specific probe are used. Dot blot hybridisation can also be employed to increase sensitivity, or for typing, but is less specific. Another approach to typing is to use restriction fragment length polymorphisms (RFLPs) with a variety of sequence specific 'restriction' enzyme DNA cutters.

Amount of amplification

Sensitivity can also be affected by the number of PCR cycles or the use of nested PCR, where amplification is performed in two stages using different sets of primers, the second set being 'nested' inside the first. Addition of a dilution series of standards with known amounts of HPA DNA can give an overall measure of the sensitivity, but an appropriate background of HPV free human DNA should also be included. Quality control issues such as positive and negative controls, tests for DNA adequacy, and replicated samples also influence the reliability of the results obtained.

Results

Study description

The results are summarised in three main tables (*Tables 14–16*) and six figures (*Figures 1–6*). These details have been split according to the primary assay used in the HPV analysis. The Manos consensus system using the MY09/11 primers is the most widely used, especially in North America, and these papers are grouped separately. The second most common system is the GP5/6 consensus system developed by Walboomers and colleagues. This has been most widely used in Europe. A refinement of it, the GP5+/6+ system, in which the primers have been extended to 23 and 25 mers to improve sensitivity and specificity, has also been included with this group. A few other consensus systems have been employed on a limited basis, and they are all grouped together in the third section of the table. Of these, a Japanese system in E6 based on the work of Yoshikawa *et al.* (1990), is most widely employed, but the CP 1–2 system of Gregoire has also been used by more than one group.

The published papers using either the HC-I or HC-II system are also grouped together. This is the only commercially available assay, so its potential value in screening merits careful evaluation. Unfortunately, much of the available data have not yet been published, although they have been widely disseminated at meetings and in abstracts. This is especially true for the HC-II microtitre system, where fully published reports are very scant.

The final grouping consists of papers in which one or more type-specific PCRs have been

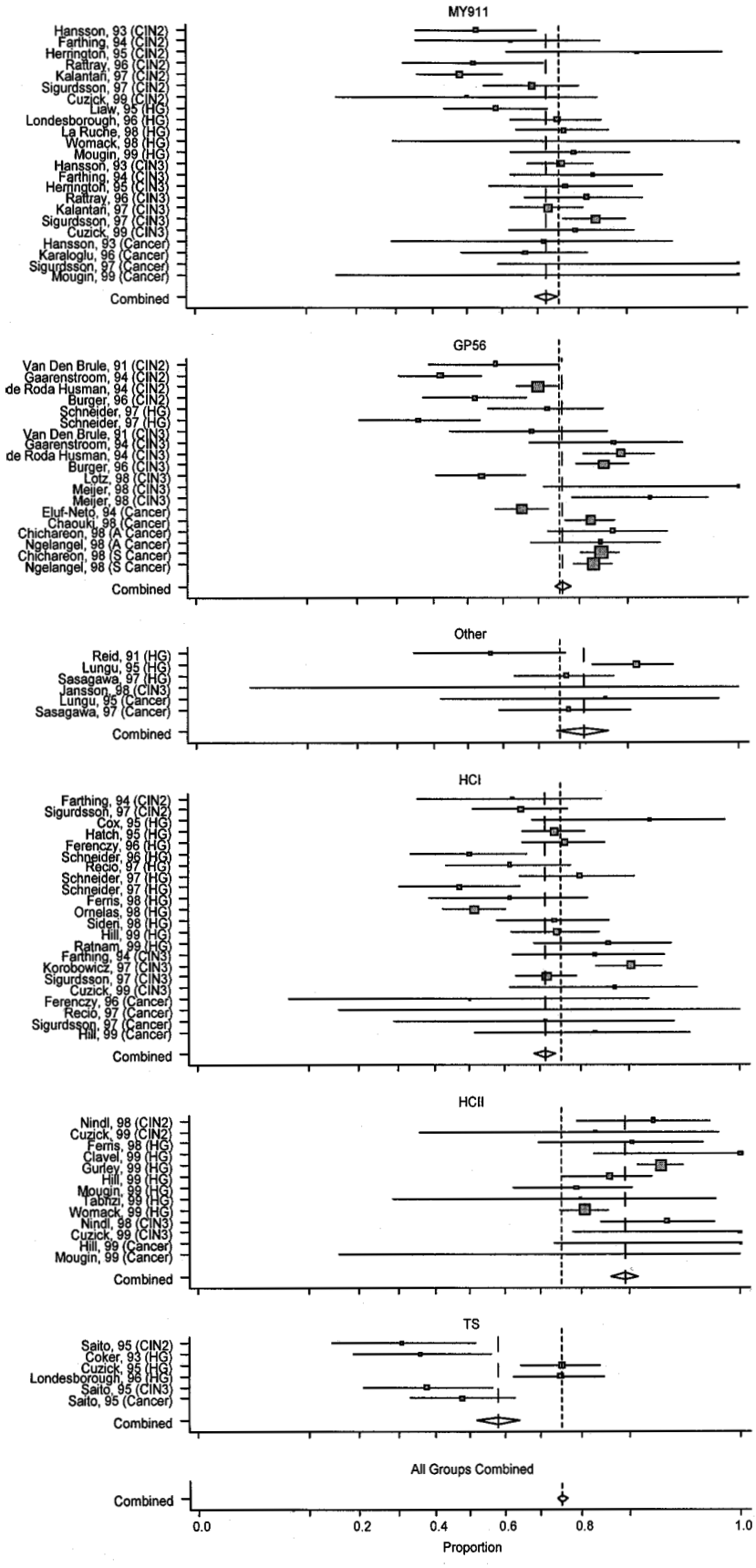

FIGURE 1 *Forest plots for prevalence of high-risk HPV type in high-grade CIN and cancer*

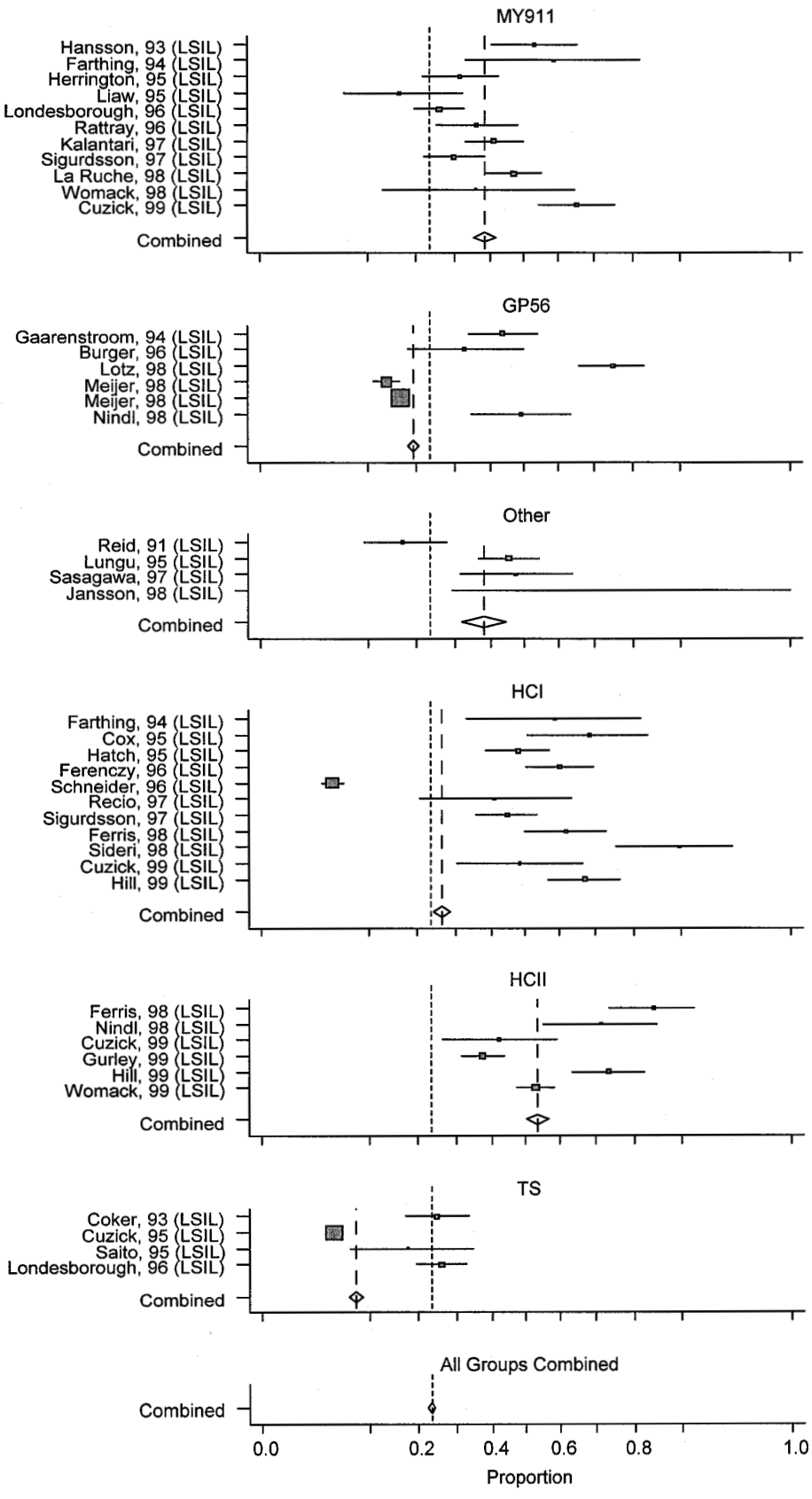

FIGURE 2 *Forest plots for prevalence of high-risk HPV type in low-grade CIN*

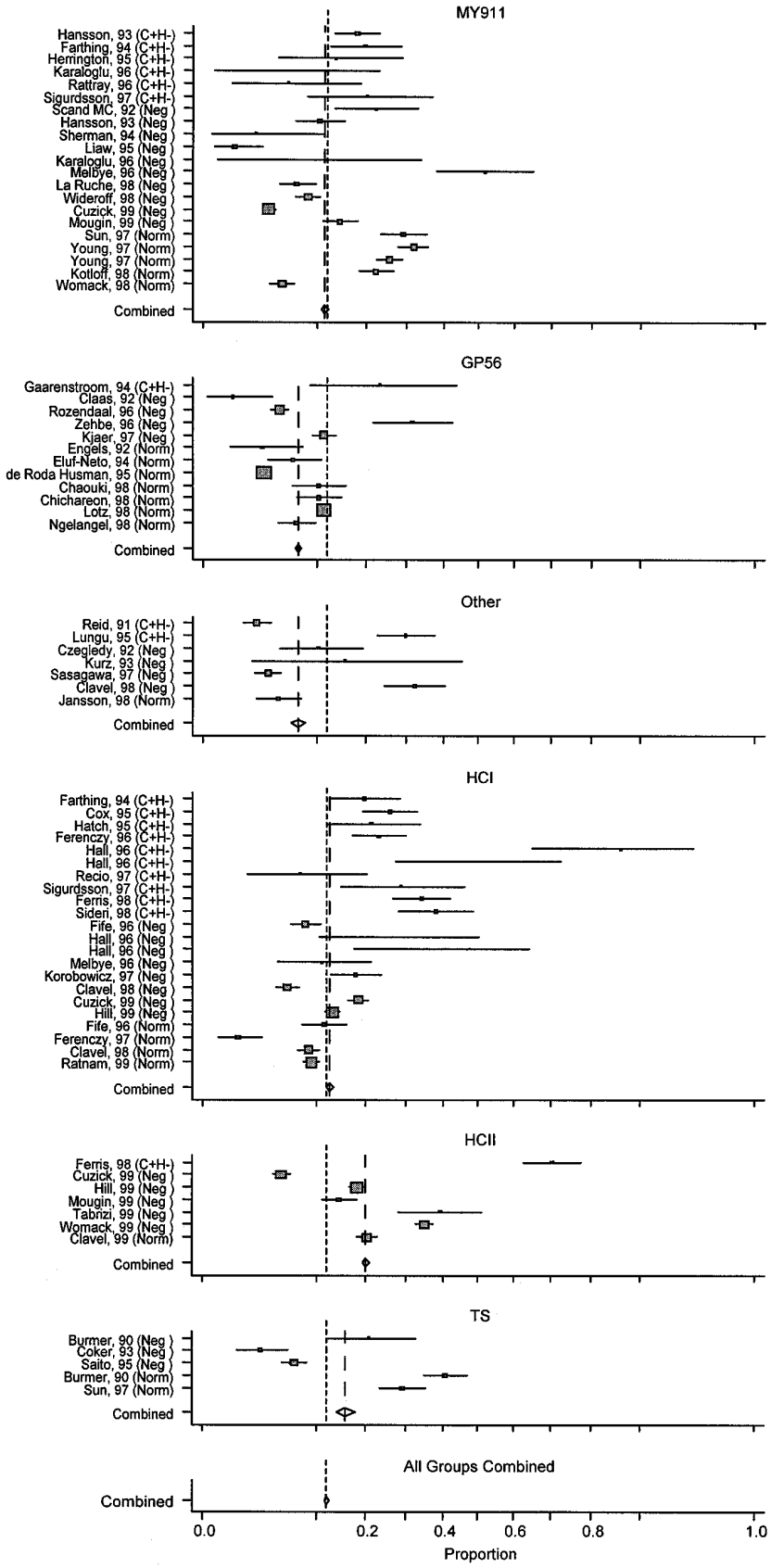

FIGURE 3 *Forest plots for prevalence of high-risk HPV type in normal populations*

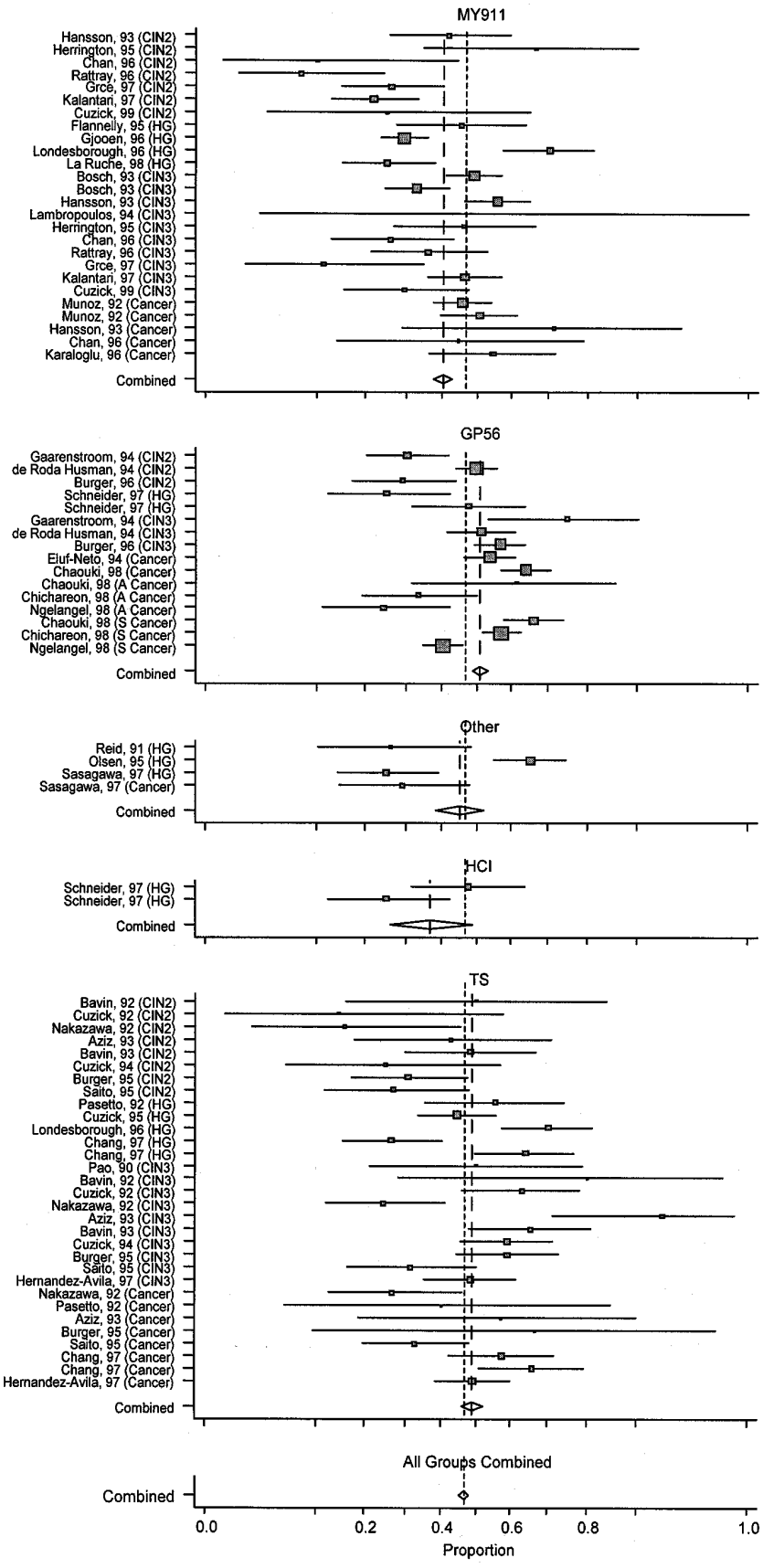

FIGURE 4 *Forest plots for prevalence of HPV 16 in high-grade CIN and cancer*

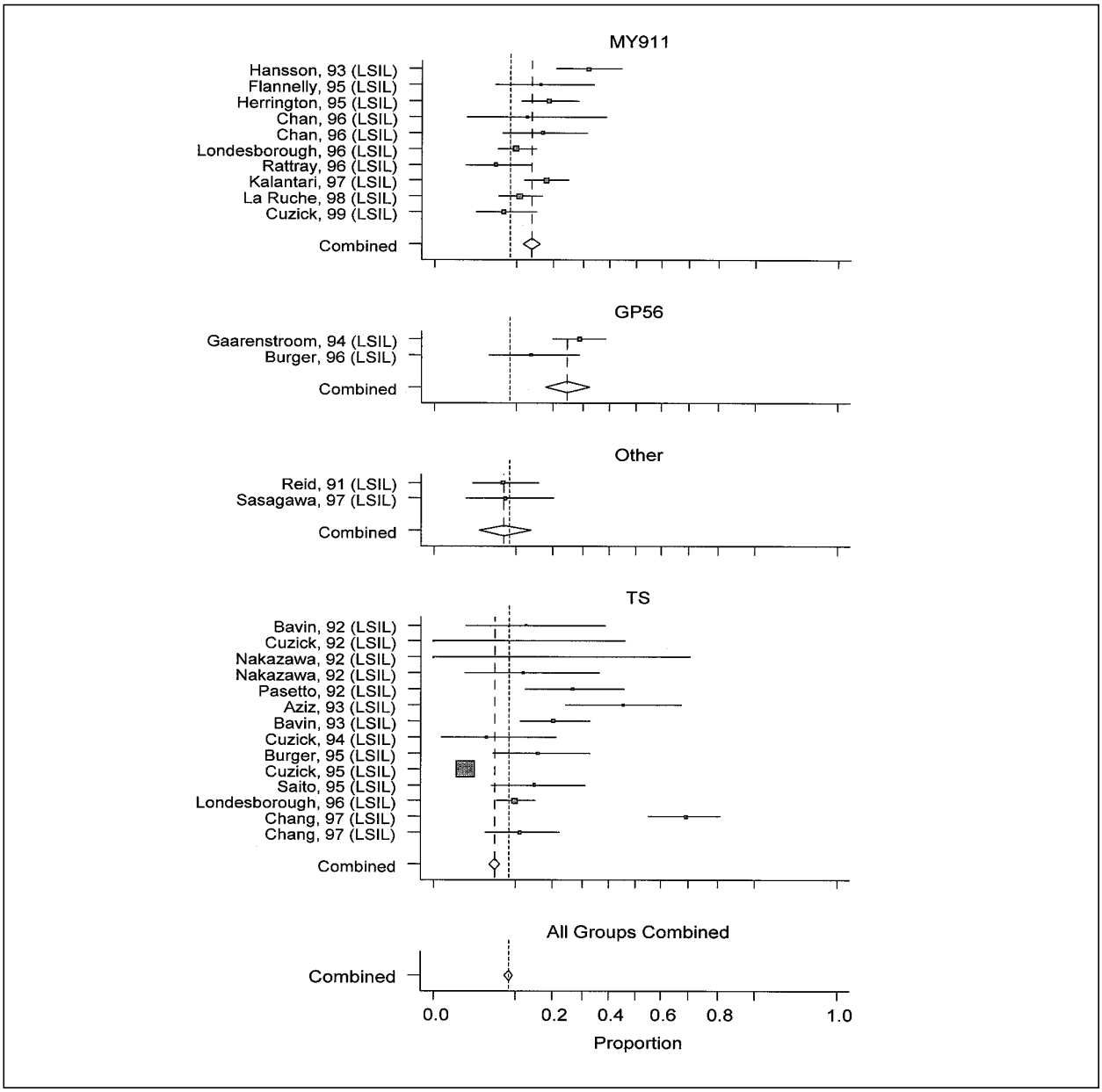

FIGURE 5 *Forest plots for prevalence of HPV 16 in low-grade CIN*

employed as the main analysis tool. These were quite diverse and difficult to further categorise. Type-specific PCR is often employed as a second step following a positive consensus PCR test. Papers using type-specific PCR only in this way have not been listed in the type-specific groupings, but the results have been used in the main tables to specify the type-specific positivity rate. This is a particularly common practice following testing with the GP5/6 system, where positive samples are often typed for HPV 6/11, 16, 18, 31 or 33 by separate type-specific PCR reactions.

In some cases more than two acceptable assays have been used on all samples. In that case the study will appear in more than one of the subsections. This is only done when both assays are considered 'primary' and are done on (virtually) all samples.

Table 14 summarises the methodologies used in the different studies. The papers are identified by the first author, date of publication and our internal identification number. The location (city, country) of the study and the venue at which patients were seen is specified next. There is a wide variety of possible choices, ranging from population screening through referral outpatient gynaecological clinics to hospital patients. Each of these tends to have a different spectrum of patients; the population studies have truly representative normal patients, but very few cancers, and in many cases very few women with high-grade CIN. In contrast,

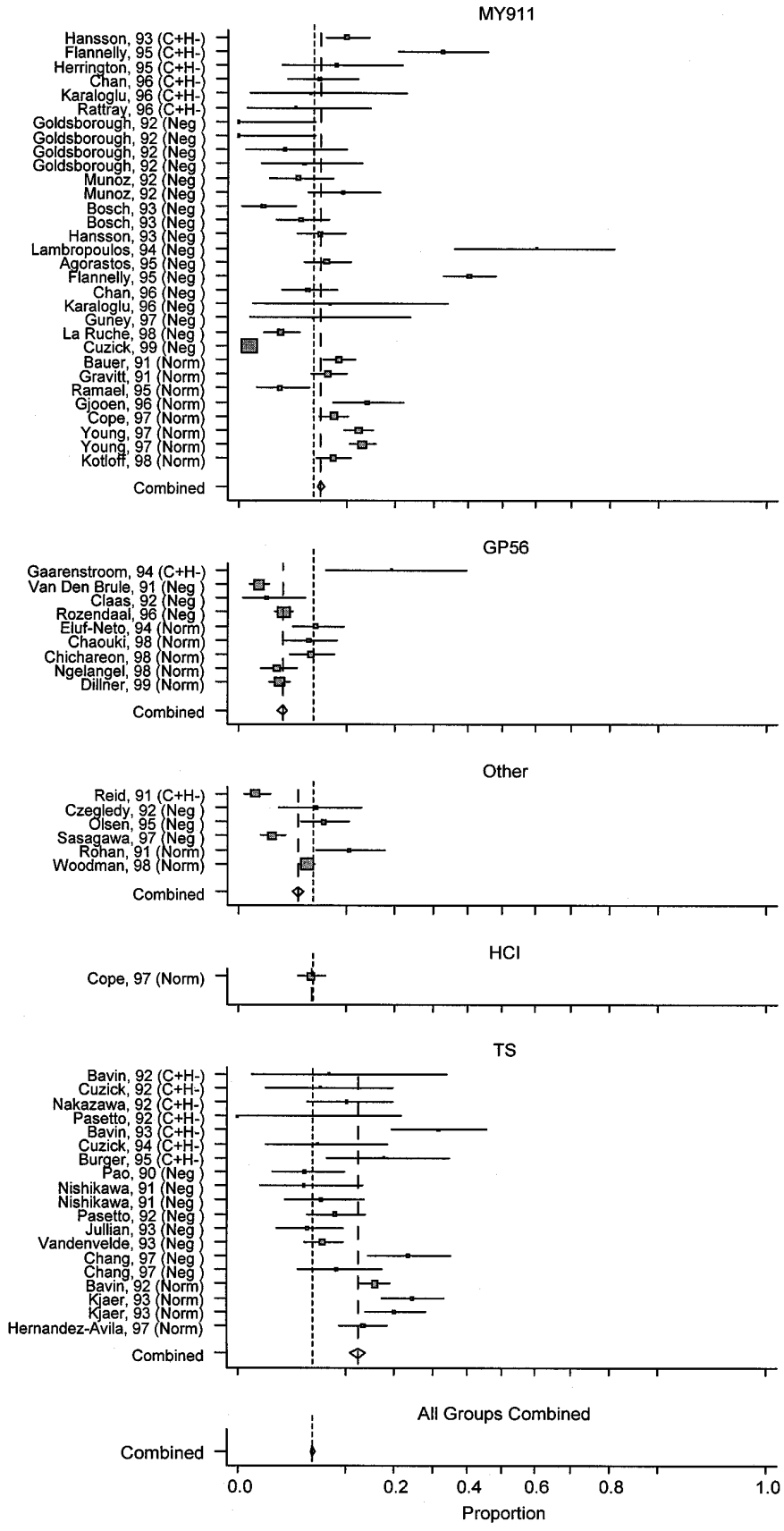

FIGURE 6 *Forest plots for prevalence of HPV 16 in normal populations*

the colposcopy clinics, and to a greater extent the hospital inpatients, have much more disease, so that good data is available on sensitivity for cancer and high-grade CIN, but usually the 'normal' patients are those with a current or previous cytological abnormality, for which colposcopy and/or biopsy was unable to identify a lesion. These women are not representative of the normal population, and reported specificities in these studies need to be carefully interpreted. The same caveat applies to cohorts of women seen at clinics for various other conditions. This includes antenatal clinics, sexually transmitted disease clinics, HIV-positive women, and women with other gynaecological symptoms.

Details of the age distribution of the population are given next. Where available, any or all of the following are given: mean (with standard deviation), median, minimum age, maximum age. The method of sample collection is then recorded, which was usually by spatula, brush, cervical swab, vaginal swab or lavage, but in a few studies, samples were taken by a tampon or urine sample. The basic amplification system is then indicated along with the detection system, which was most often ethidium bromide visualisation by ultraviolet light on a gel, followed by Southern or dot blot hybridisation. Other detection systems were also used either for overall positivity or typing. Typing was done either by separate type-specific PCR, hybridisation with type-specific probes or RFLPs using a variety of enzyme DNA cutters.

When given, the number of cycles for PCR, the use of positive and negative controls, and the degree of sample replication was noted. Often this was not stated, but reference to a standard source for GP5/6 or MY09/11 suggested that these standard procedures probably had been employed. However, the column was left blank unless a specific statement about controls or replication was made. The use of a control gene to verify the suitability of the sample for DNA amplification was also noted. This was most often β-globin, but a range of other cellular DNA targets were also used, including HLA genes, GAPDH, and the cystic fibrosis gene.

Lastly, when provided, the estimated assay sensitivity is given. This is not a very reliable measure, since sensitivity for plasmid HPV DNA is much greater than for clinical samples, and often the reported sensitivity is for the former. Sensitivities depend upon a number of factors, including number of amplification cycles, the intrinsic efficiency of a particular pair of primers, the detection system used, and the existence of inhibitors in this sample. As a general rule we decided that any PCR system or HC was adequate with regards to sensitivity. A more serious concern is overly sensitive assays, since there is some evidence that low levels of HPV may not be predictive of high-grade CIN, and without a (semi)quantitative assay, very high HPV sensitivity will only lead to poorer specificity when high-grade CIN is the end-point.

Prevalence by disease category

Table 15 provides the positivity rates for the different assays for different disease groups on a study-by-study basis. The results are also summarised in *Figures 1–6*. These plot the positivity rate in each study (on a arcsine square-root scale) with (exact binomial) 95% confidence intervals for each study and for each group of studies in 'normal' women and those with low-grade or high-grade histological disease. Disease categories are further subdivided in the plots: 'normal' being split into negative cytology, no cytology or positive cytology with negative histology, and high-grade disease being split into CIN II, any HSIL, CIN III/0, cancer, systemic cancer or adenocarcinoma. There is a wide spread of results, depending partly on the population under study, and the assay used, but probably also relating to the quality of the study. This is difficult to quantify, but it is well recognised that PCR is, to some extent, still an art, and experienced laboratories produce more consistent and reliable results. Positivity rates for high-risk types in normal populations appear to be higher for the MY09/11 system (approximately 20%) than for the GP5/6 system (5–10%), but this to a large extent reflects the younger age distribution in the larger studies that employed the MY09/11 system.

In the larger studies employing either MY09/11 or GP5/6 consensus primers or HC-II, there is greater consistency regarding sensitivity for detecting high-grade CIN or cancer (*Figure 1*). These are typically in the 60–90% range for high-risk types both for cancer and CIN III, with somewhat lower values for CIN II. The sensitivity for HC-II appears to be at least as high as for the PCR techniques. For CIN II/III and cancer, about two-thirds of the positives are HPV 16. Where available, the comparisons with cytology generally indicate a higher sensitivity for the HPV test (*Table 17*).

A bigger concern is test specificity. There are more highly variable access studies, typically ranging from 2 to 30%. Test specificity depends on a number of factors, and these were not always provided in the published articles. A key factor is age. HPV infection rates are much higher in younger women (see below), being highest in the 20–25 year age group and declining after 30 years of age. Most of these

infections in younger women are transient and are cleared naturally by the immune system. It is well established that cervical neoplasia requires a persistent HPV infection. Unfortunately there is currently no direct method of establishing persistence from a single test, as there is for hepatitis B infection, and surrogates such as age, and possibly viral load, are all that can be used to improve specificity for a single test. Studies in women aged 30 years or older all show lower positivity rates, and the more recent larger studies suggest rates in the 2–10% range. This is still higher than what is typically found for cytology, and specificity is a key issue in evaluating the role of HPV testing in primary screening.

Post-treatment surveillance

Studies of the use of HPV testing after treatment for cervical disease are summarised in *Table 18*. None of these studies adequately addresses the issue, but all of the data generally support the thesis that successful local treatment is accompanied by disappearance of HPV, and the persistence of the virus is an early indication of incomplete excision. The ideal study would measure and type HPV in the treatment biopsy and then monitor positivity for this type in follow-up smears. The goal of such a study would be to demonstrate that disappearance of the virus provides adequate evidence of complete excision and that prolonged surveillance is not necessary.

Key papers

A number of papers have been influential in current knowledge regarding the potential role of HPV testing in cervical screening. To help provide coherence in a complicated field, the results of major papers are briefly summarised below. The choice of papers is unavoidably subjective.

(1) Reid *et al.* (1991) were the first to demonstrate a role for HPV testing in a screening context. This study was carried out on high-risk women from sexually transmitted disease clinics and gynaecologist specialists, and used a sensitive (low stringency) Southern blot hybridisation for HPV detection. A total of 1012 women were enrolled, and cervicography was also considered as a possible adjunct to cytology. Twenty-three CIN II/III lesions were found altogether, but only 12 were detected by cytology (sensitivity 52%, specificity 92%). HPV testing found 16 high-grade lesions (sensitivity 14/23, specificity 1–104/989). The authors suggested that using all three test models would be more cost-effective than when used singly or in pairs.

(2) Bauer *et al.* (1991) report an early PCR-based study using MY09/11 primers in young women attending for routine smears (college students). They found a positivity rate of 46% in 467 women, which was much higher than for the dot blot assay (11%).

(3) van der Brule *et al.* (1991) using GP5/6 primers showed a very strong correlation of HPV positivity with cervical neoplasia as assessed by cytology. In older women (aged 35–55 years) with negative cytology the HPV positivity rate was only 3.5%, and this was reduced to 1.5% if only types 16, 18, 31 and 33 were considered, while women with histological carcinoma *in situ* were all HPV-positive, and 90% had one of the four above types. Women with less severe cytological abnormalities had lower HPV positivity rates in a graded way, showing a clear trend.

(4) de Roda Husman *et al.* (1994) expanded these observations by looking at a further 1373 women with abnormal smears. This study also confirmed an increasing positivity rate with increasing severity of smear result. They also noted that the level of HPV heterogeneity decreased from 22 types for low-grade smears to ten 'high-risk' types for high-grade smears. This paper did not include any cytologically negative women, nor was cytological disease confirmed histologically.

(5) Cuzick *et al.* (1992, 1994) were the first to report that HPV testing provided useful information for the triage of cytological abnormalities detected during random screening. In a study of 133 women, referral for colposcopy they found a positive predictive value of 42%, which was similar to that for moderate dyskaryosis. The results were most striking for HPV 16, where 39 of 42 HPV 16-positive women were found to have high-grade CIN on biopsy. This study pointed out the importance of assessing viral load and only considered high levels of high-risk types as positive.

(6) Cox *et al.* (1995) demonstrated a role for HPV testing by HC-I for triaging women with borderline smears. This test was performed on 217 such women from a college referral service, and a sensitivity of 93% was found for CIN II/III compared with 73% for repeat cytology. High viral load was found to further improve performance by reducing false positives. When 5 RLU was taken as a cut-off, a PPV of approximately 24% was found with no loss of sensitivity.

(7) Cuzick *et al.* (1995) evaluated HPV testing in a primary screening context in 1985 women attending for routine screening at a family planning clinic. Sensitivity using type-specific PCR for the four common HPV types (75%) exceeded

that of cytology (46%), and the PPV for a positive HPV test (42%) was similar to that for moderate dyskaryosis (43%).

(8) Several ongoing studies will provide definitive information on the prevalence of HPV using the best currently available test (see *Table 17*). Preliminary results from some of these studies have been published in abstract form and are included in this review.

(9) Elfgren *et al.* (1996) produced the first of a handful of papers showing a role for HPV testing in the surveillance of women treated for CIN. In a study of 23 women with conisation or treatment for CIN, the four who were HPV-positive were found to be the only ones who remained HPV-positive after treatment. All 19 who did not recur became HPV-negative.

Age distribution

Table 16 examines the data on the relationship between HPV positivity and age in 'normal' women. Many of these studies only give information on any type of HPV, as opposed to the more useful 'high-risk' category. In almost all studies prevalence decreases with age. The exceptions are Kalantari *et al.* (1997) where the referral pattern led to more disease in older women and Sasagawa *et al.* (1997), de Roda Husman *et al.* (1995) and Schneider *et al.* (1992), where prevalence was low at all ages. In large studies looking only at high-risk types, the prevalence is typically 10–30% at 20–30 years of age and falls to 3–10% after the age of 30 years. There is still controversy as to whether positivity falls still further after age 40 years or begins to rise again, and more data are needed in older women to complete the picture. Moscicki *et al.* (1996) and Evander *et al.* (1992) document the increased levels of infection found thorough adolescence and in the early twenties.

Discussion and conclusions

The variability of methods used to evaluate HPV and recent improvements in the tests make it difficult to draw detailed or far-reaching conclusions. However, the one point that emerges fairly clearly is that HPV testing has a high sensitivity for cervical neoplasia, which in most comparative studies exceeds that of conventional cytology. There is less evidence available about the degree of independence between the two tests, and this will have a major impact on the question as to whether this should be used in combination (i.e. HPV plus cytology at primary screening) or whether it is sufficient to use only one of the tests.

Most of the studies also indicate that HPV testing has a lower specificity than cytology. This is a serious concern, and more work is necessary to determine if this can be improved. Viral persistence is the key factor in HPV-induced cervical neoplasia, and one approach would be to require at least two positive tests separated by 6 months or more in the absence of any cytological abnormality before referral for colposcopy. If used in this way, a positive test would be treated in the same way as a mild/borderline smear. One approach would be to treat HPV and cytology as two separate tests and to augment this current scoring system (1 point for borderline smears, 2 points for mild smears, 3 points needed for colposcopy referral) to add 1 point when the HPV test is positive, and to consider that an additional negative test has been performed when the HPV test is negative.

However, other factors may influence persistence, and in certain circumstances a single positive test may be grounds for referral. Those factors include:

(1) **Age**. Positivity rates are lower after 30–35 years of age, and more of the infections are likely to be persistent.
(2) **Viral load**. Some evidence suggests that low-level infections are more likely to be transient and not associated with CIN. Whether or not this is a real biological factor or reflects assay variability is still uncertain.
(3) **Viral type**. HPV 16 appears to be more often related to high-grade CIN and cancer than other 'high-risk' types, especially in the UK. More work is needed to clarify this point.
(4) **Viral integration**. Integration generally implies persistence, but the reverse is not always true. About 20–30% on average of the invasive cancers contain only episomal DNA whereas this is true for more than 95% of low-grade cervical lesions. However, some of the new tests may be able to reliably detect integrated DNA from smears, and if reliable this could be a useful second-stage test with high sensitivity but poor specificity to help determine persistence in HPV-positive samples.
(5) **Viral RNA transcripts**. Newer tests may be able to detect accurately viral RNA by RT-PCR on smear material, if it is stored appropriately. The presence of high-grade lesions appears to be associated with a switch from L1 to E6/E7 transcripts, and the ratio of these may be useful for deciding which women have high-grade lesions in need of immediate referral.

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TABLE 14a *Characteristics of studies employing MY09/11*

Author, year	Paper	Location	Clinic	Age (years)					Collection device	Amplification system	Detection system	No. of cycles	Controls			DNA amplification	Sensitivity
				Mean	SD	Median	Minimum	Maximum					Positive	Negative	Replication		
Cuzick, 1999	PR150Aa		Routine screening				34	70	Sp, CBr	MY09/11	ELISA		Y	Y			
Mougin, 1999	PR154A		Routine screening							MY09/11, HC-II							
del Mistro, 1998	PR137Aa		Normal smears			34				MY09/11	Gel						
del Mistro, 1998	PR137Ab		Abnormal smears			31				MY09/11	Gel						
Womack, 1998	PR139A		Routine screening				> 35			MY09/11							
Wideroff, 1998	PR116	Oregon	Screening (controls)	33					CVL	MY09/11			Y	Y	Y	β-Globin	
Wideroff, 1998	PR116	Oregon	Screening (cases)	32					CVL	MY09/11			Y	Y	Y	β-Globin	
Kotloff, 1998	PR72	USA	Gynaecology	22.5			17	44		MY09/11	DB	40	Y	Y		β-Globin	
La Ruche, 1998	PR158	Ivory Coast	Gynaecology			28				MY09/11	Gel, RFLP					β-Globin	
Sigurdsson, 1997	PR110b	Iceland	Colposcopy			33	18	71	CSw	MY09/11	Gel, DB	35	Y	Y		β-Globin	
Smith, 1997	PR111	Iowa	PEPI trial of HRT				45	64	CSw	MY09/11	DB				Y		
Sun, 1997	PR136		Sexually transmitted diseases clinic – HIV seronegative	35						MY09/11, TS 16, 18	Gel					K-ras	
Young, 1997	PR117a	Canada	Health clinic – aboriginal					30	Sp, CBr, CSw	MY09/11	Gel, DB	30	Y	Y		β-Globin	
Young, 1997	PR117b	Canada	Health clinic – non-aboriginal					30	Sp, CBr, CSw	MY09/11	Gel, DB	30	Y	Y		β-Globin	
Cope, 1997	PR26b	Oregon	Normal cohort						CVL	MY09/11	DB						
Grce, 1997	PR54	Croatia	Colposcopy – abnormal Pap				17	64	Sp, CBr	MY09/11, TS 6, 11, 16, 18, 31, 33	Gel		Y	Y		β-Globin	
Guney, 1997	PR56	Turkey	Antenatal				17	36	CBr	MY09/11	Gel + SB	35	Y	Y		β-Globin	
Kalantari, 1997	PR65	Stockholm	Private gynaecology				15	74	CBr	MY09/11, TS 6, 11, 16, 18, 31, 33						HLA	
Rattray, 1996	PR100	Jamaica	Colposcopy	34					CSw	MY09/11						β-Globin	

Sp, spatula; TS, type specific; HLA, human leukocyte antigen

continued

TABLE 14a contd *Characteristics of studies employing MY09/11*

Author, year	Paper	Location	Clinic	Age (years)					Collection device	Amplification system	Detection system	No. of cycles	Controls			DNA amplification	Sensitivity
				Mean	SD	Median	Minimum	Maximum					Positive	Negative	Replication		
Chan, 1996	PR15a	Hong Kong	Colposcopy	35.8			16	76	Sp	MY09/11,TS 6, 11, 16, 18, 31, 33	Gel, SB	40				β-Globin	
Chan, 1996	PR15b	Hong Kong	Antenatal				16	76	Sp	MY09/11,TS 6, 11, 16, 18, 31, 33	Gel, SB	40				β-Globin	
Chan, 1996	PR15c	Hong Kong	Gynaecology	41.6			16	76	Sp	MY09/11,TS 6, 11, 16, 18, 31, 33	Gel, SB	40				β-Globin	
Gjooen, 1996	PR50	Oslo	Gynaecology (controls)	32.7					CBr	MY09/11, nest primer,TS 6/11, 16, 18, 31, 33	Gel	30, 30, 40	Y	Y		β-Globin	
Gjooen, 1996	PR50	Oslo	Gynaecology (cases)	31.8					CBr	MY09/11, nest primer,TS 6/11, 16, 18, 31, 33	Gel	30, 30, 40	Y	Y		β-Globin	
Karaloglu, 1996	PR66	Turkey	Hospital	51					CBr	MY09/11	SB	35	Y	Y			
Londesborough, 1996	NH65	London	Abnormal cytology – colposcopy clinic	31			16	69		MY09/11,TS 16, 18, 31, 33, 35	ELISA						
Melbye, 1996	PR83b	Denmark	HIV clinics (HIV–)			25	19	53	CSw	MY09/11	SB	30				β-Globin	
Melbye, 1996	PR83b	Denmark	HIV clinics (HIV+)			30	19	53	CSw	MY09/11	SB	30				β-Globin	
Agorastos, 1995	PR1	N. Greece	Gynaecology – normal Pap				20	55	CBr	MY09/11		30		Y			
Shen, 1995	PR107		Gynaecology and hysterectomy specimens	47.7			19	81	CBr	MY09/11	Gel, RFLP			Y			
Flannelly, 1995	PR48	Scotland	Family practitioner, general practitioner	31.6	10.6				Sp	MY09/11,TS 16	Gel (TS 16)					β-Globin	
Herrington, 1995	PR60	England	Colposcopy – mild borderline/wart virus						Sp	MY09/11	DB		Y	Y		β-Globin	0–10
Baken, 1995	PR7	Seattle	Sexually transmitted disease	26.5			17		CSw	MY09/11, HC-I	Gel		Y	Y	Y		
Liaw, 1995	PR78	Taiwan	Population (HSIL)	41			30	64	CSw	MY09/11			Y	Y	Y		
Liaw, 1995	PR78	Taiwan	Population (LSIL)	47			30	64	CSw	MY09/11			Y	Y	Y		
Liaw, 1995	PR78	Taiwan	Population (control)	43			30	64	CSw	MY09/11			Y	Y	Y		

Sp, spatula; TS, type specific

continued

TABLE 14a contd *Characteristics of studies employing MY09/11*

Author, year	Paper	Location	Clinic	Age (years)					Collection device	Amplification system	Detection system	No. of cycles	Controls			DNA amplification	Sensitivity
				Mean	SD	Median	Minimum	Maximum					Positive	Negative	Replication		
Ramael, 1995	PR98	Belgium	Screening	34.2			19	43	CBr	GP1/2, MY09/11, TS 6, 11, 16, 18, 33	Gel	40	Y	Y		β-Globin	< 50
Sherman, 1994	PR108	Oregon							CVL	MY09/11							
Kuhler-Obbarius, 1994	PR160		Screening and outpatient	35						MY09/11	Gel					β-Globin	
Farthing, 1994	PR43		Colposcopy						Sp	MY09/11, HC-I	SB	35				β-Globin	10
Lambropoulos, 1994	PR76	N. Greece	Routine Pap				17	45	CBr	MY09/11	Gel, DB	30		Y			
Bosch, 1993	PR11a	Spain	Screening and family practitioner	36			15	70	CBr or CSw	MY09/11	DB	35	Y	Y		β-Globin	
Bosch, 1993	PR11b	Colombia	Screening and family practitioner	39			15	70	CBr or CSw	MY09/11	DB	35	Y	Y		β-Globin	
Hansson, 1993	PR58a	Sweden	Screening				20	29	CBr	MY09/11, TS 6, 11, 16, 18, 31, 33, 35						β-Globin	
Hansson, 1993	PR58b	Sweden	Colposcopy – abnormal Pap	37			17	79	CBr	MY09/11, TS 6, 11, 16, 18, 31, 33, 35						β-Globin	
Scand MC, 1992	PR3	Scandinavia	Gynaecology						CBr	MY09/11, Affiprobe®, ViraType	SB	40	Y	Y			1000
Evander, 1992	PR39a	Sweden	All women in Umea	22			19	25	VSw	MY09/11	Gel, SB	40	Y	Y			
Fairley, 1992	PR41	Australia	General practitioner, students	18			13	41	T	MY09/11	SB		Y	Y		β-Globin	10
Goldsborough, 1992	PR51a	Detroit	Colposcopy, screening				< 40		CSw	MY09/11, TS 16	Gel	35	Y	Y		β-Globin	Gel 1000, TS 10
Goldsborough, 1992	PR51b	Detroit	Colposcopy, screening				< 40		CSw	MY09/11, TS 16	SB	35	Y	Y		β-Globin	SB < 10, TS 10
Munoz, 1992	PR89a	Columbia	Hospital cancers	46.5				< 70	CSw, Sp, CBr	MY09/11		35	Y	Y		β-Globin	
Munoz, 1992	PR89a	Columbia	Population control	47.5				< 70	CSw, Sp, CBr	MY09/11		35	Y	Y		β-Globin	
Munoz, 1992	PR89b	Spain	Population control	52.3				< 70	CSw, Sp, CBr	MY09/11		35	Y	Y		β-Globin	
Munoz, 1992	PR89b	Spain	Hospital cancers	52.2				< 70	CSw, Sp, CBr	MY09/11		35	Y	Y		β-Globin	

Sp, spatula; T, tampon; TS, type specific

continued

TABLE 14a contd *Characteristics of studies employing MY09/11*

Author, year	Paper	Location	Clinic	Age (years)					Collection device	Amplification system	Detection system	No. of cycles	Controls			DNA amplification	Sensitivity
				Mean	SD	Median	Minimum	Maximum					Positive	Negative	Replication		
Gravitt, 1991	PR53a	N. Carolina	Routine						CSw	MY09/11, ViraPap	SB + restriction 6, 11, 16, 18	40				Cystic fibrosis gene	19 by plasmids
Gravitt, 1991	PR53b	N. Carolina	Routine						CSw	TS 6, 16, 18, ViraPap						Cystic fibrosis gene	
Ley, 1991	PR77	California	Students	22.9			17	50	CSw, VSw	MY09/11							
Bauer, 1991	PR8	California	Students	22.9					CSw, VSw, vulvar	MY09/11	Gel	35	Y	Y		β-Globin	

TS, type specific

TABLE 14b *Characteristics of studies employing GP5/6 or GP5+/6+*

Author, year	Paper	Location	Clinic	Age (years)					Collection device	Amplification system	Detection system	No. of cycles	Controls			DNA amplification	Sensitivity
				Mean	SD	Median	Minimum	Maximum					Positive	Negative	Replication		
Dillner, 1999	PR151A		Routine smears	35			32	38		GP5+/6+							
Chaouki, 1998	PR18	Morocco	Hospital cases	49.7			21	73	CBr	GP5+/6+	SB			Y		β-Globin	
Chaouki, 1998	PR18	Morocco	Hospital controls	46.7			18	70	CSc	GP5+/6+	SB			Y		β-Globin	
Chicareon, 1998	PR19	Thailand	Hospital control without cancer	49.7					CSc, CBr	GP5+/6+	SB			Y		β-Globin	
Chicareon, 1998	PR19	Thailand	Diagnosed cancer (adenocarcinoma)	46.1					CSc, CBr	GP5+/6+	SB			Y		β-Globin	
Chicareon, 1998	PR19	Thailand	Diagnosed cancer (squamous cell)	50.3					CSc, CBr	GP5+/6+	SB			Y		β-Globin	
Kruger-Kjaer, 1998	PR73	Copenhagen	Abnormal Pap in cohort						CSw	GP5+/6+	Gel, SB	40	Y	Y			
Lotz, 1998	PR130A		Routine screening	32			18	70		GP5+/6+	DB					β-Globin	
Meijer, 1998	PR131Aa		Routine screening	44			35	54		GP5+/6+							
Meijer, 1998	PR131Ab		Outpatient gynaecological	35			20	54		GP5+/6+							
Ngelangel, 1998	PR92	Philippines	Outpatient (squamous)	47.2					CSc, CBr	GP5+/6+	SB		Y	Y		β-Globin	
Ngelangel, 1998	PR92	Philippines	Outpatient (adenocarcinoma)	48.4					CSc, CBr	GP5+/6+	SB		Y	Y		β-Globin	
Ngelangel, 1998	PR92	Philippines	Outpatient (control)	46.8					CSc, CBr	GP5+/6+	SB		Y	Y		β-Globin	
Nindl, 1998	PR132A		Histology CIN I	29			17	52		GP5+/6+							
Schneider, 1997	PR106a	Germany	Screening	36.2			15	72	CSw	GP5/6+, TS 6, 11, 16, 18, 31, 33	Gel, SB						< 1 pg
Kjaer, 1997	PR70	Copenhagen	Population			25	20	29	CSw	GP5/6	SB						
Burger, 1996	NH3		Gynaecology						CSc, CBr	GP5/6, TS 6, 11, 16, 18, 31, 33							
Elfgren, 1996	PR123	Sweden	Post-treatment (conisation)		35.8		20	51	CBr	GP5/6		40	Y	Y		β-Globin	

TS, type specific

continued

TABLE 14b contd *Characteristics of studies employing GP5/6 or GP5+/6+*

Author, year	Paper	Location	Clinic	Age (years)					Collection device	Amplification system	Detection system	No. of cycles	Controls			DNA amplification	Sensitivity
				Mean	SD	Median	Minimum	Maximum					Positive	Negative	Replication		
Rozendaal, 1996	PR102	Amsterdam	Screening	42			34	54	CBr	GP5+/6+	SB					β-Globin	
Zehbe, 1996	PR118	Sweden	Sexually transmitted diseases			25			CBr	GP5+/6+	Gel, DB	40	Y	Y			
de Roda Husman, 1995	PR32	Amsterdam	Screening				15	49	CSc, CBr	GP5/6,TS 6, 11, 16, 18, 31, 33	SB, gel	40, ?	Y	Y		β-Globin	SB 10, gel 10,000
Gaarenstroom, 1994	NH13	Amsterdam	Colposcopy – abnormal Pap	32			19	66	CSc, CBr	GP5/6,TS 6, 11, 16, 18, 31, 33	SB						
de Roda Husman, 1994	PR31	Amsterdam	Abnormal smears – outpatient						CSc, CBr	GP5/6,TS 6, 11, 16, 18, 31, 33	Gel, DB	40	Y	Y			
Eluf-Neto, 1994	PR37	Brazil	Hospital (controls)	52.4					CSc, CBr	GP5/6,TS 6, 11, 16, 18, 31, 33	SB					β-Globin	
Eluf-Neto, 1994	PR37	Brazil	Hospital (cases)	52.1					CSc, CBr	GP5/6,TS 6, 11, 16, 18, 31, 33	SB					β-Globin	
Melkert, 1993	PR85a	Amsterdam	Screening – routine				15	55	CSc	GP5/6,TS 6, 11, 16, 18, 31, 33	SB		Y	Y		β-Globin	
Melkert, 1993	PR85b	Amsterdam	Screening – gynaecology				15	55	CSc	GP5/6,TS 6, 11, 16, 18, 31, 33	SB		Y	Y		β-Globin	
Claas, 1992	PR21	Netherlands	Screening, colposcopy, sexually transmitted diseases						CSc	GP5/6,TS 6, 11, 16, 18, 31, 32	SB, SB	40, 40	Y	Y		β-Globin	
Engels, 1992	PR38	Kenya	Family practitioner and sexually transmitted diseases						CBr	GP5/6	DB	40					
Van Den Brule, 1991	PR112	Netherlands	Screening				35	55	CBr	GP5/6	SB	40	Y	Y		β-Globin	
Van Den Brule, 1991	PR112	Netherlands	Gynaecology				18	80	CBr	GP5/6	SB	40	Y	Y		β-Globin	

TS, type specific

TABLE 14c *Characteristics of studies employing other consensus PCR*

Author, year	Paper	Location	Clinic	Age (years)					Collection device	Amplification system	Detection system	No. of cycles	Controls			DNA amplification	Sensitivity
				Mean	SD	Median	Minimum	Maximum					Positive	Negative	Replication		
Sasagawa, 1999	PR142A		Referred							LCR-47, HC-II							
Clavel, 1998	PR22	France	Obstetrics, gynaecology			32			CBr	E6/E7	EIA (ELISA)	30	Y	Y			< 100 fg
Jansson, 1998	PR138A		Antenatal clinic	32.4													
Woodman, 1998	PR134A		Young women														
Sasagawa, 1997	PR104	Japan	Population				16	82	CBr	E6/E7	Gel, RFLP, SB	27				β-Globin	1
Duggan, 1997	PR36	Canada	Colposcopy – mild smear	28					Sp	Yoshikawa, TS 6, 11, 16, 18, 31, 33, 35	DB					β-Globin	
Lungu, 1995	PR81	NY/Montreal	Colposcopy						CSw	E6	ELISA	38	Y	Y			
Olsen, 1995	PR94	Oslo	Cases – colposcopy clinic	31.8			20	44	CBr	L1						β-Globin	
Olsen, 1995	PR94	Oslo	Control population based	32.7			20	44	CBr	L1						β-Globin	
Duggan, 1994	PR35	Canada	Colposcopy						Sp	Saiki, TS 6, 11, 16, 18, 31, 33, 35	DB (TS)	30	Y	Y		β-Globin	TS 1–20, consensus 2– 250
Kurz, 1993	PR74	Canada	Colposcopy						CSw	Paper and co-workers, TS 16, 18, 33, 6/11, 31	Gel, SB	45, 35–40	Y	Y		GAPDH	
Czegledy, 1992	PR30	Kenya	Family practitioner	25.8					CSw	GP60/124, E7/E1	Gel, DB	35	Y	Y		β-Globin	
Evander, 1992	PR39b	Sweden	All women in Umea	22			19	25	VSw	MY09/11 + GP5/6	Gel, SB	20/30	Y	Y			
Reid, 1991	PR126	USA	Sexually transmitted diseases and gynaecology				18	35	Sp, CBr	Low-stringency SB							
Rohan, 1991	PR101	Toronto	Screening	23					Sp	CP1/2, TS 6/11, 16, 18	Gel	35, ?				β-Globin	

TS, type specific

TABLE 14d *Characteristics of studies employing HC-I*

Author, year	Paper	Location	Clinic	Age (years)					Collection device	Amplification system	Detection system	No. of cycles	Controls			DNA amplification	Sensitivity
				Mean	SD	Median	Minimum	Maximum					Positive	Negative	Replication		
Cuzick, 1999	PR150Ab		Routine screening				34	70	Sp, CBr	HC-I			Y	Y			
Hill, 1999	PR153Aa		Unscreened women							HC-I							
Ratnam, 1999	PR155A		Routine screening				25	49		HC-I							
Sideri, 1998	PR109	Milan, Italy	Colposcopy						CSw	HC-I							
Clavel, 1998	PR23	Reims, France	Routine smears	36.1			14	68	CBr	HC-I			Y	Y			
Ferris, 1998	PR46a	Georgia, MA, NY	Colposcopy				18+		CSw	HC-I							
Ornelas, 1998	PR133A		CIN II/III	37					CSw	HC-I							
Ferenczy, 1997	PR45	Montreal	Postmenopausal	57			50	70	Endocervical/ exocervical	HC-I			Y	Y			
Korobowicz, 1997	PR71	Lublin, Poland	Hospital (in- and outpatients)				18	34	CSw	HC-I							
Recio, 1997	PR157A	USA	Referral for abnormal cytology	30.5			18	38		HC-I							
Schneider, 1997	PR106b	Germany	Screening	36.2			15	72	CSw	HC-I	Gel, SB						< 1 pg
Sigurdsson, 1997	PR110a	Iceland	Colposcopy			33	18	71	CSw	HC-I			Y	Y		β-Globin	
Cope, 1997	PR26a	Oregon	Normal cohort						CVL	HC-I							
Ferenczy, 1996	PR44	Montreal/NY	Colposcopy	33			17	73	CBr	HC-I							
Fife, 1996	PR47	USA	Sexually transmitted diseases	28.2			18	45	CVL	HC-I			Y	Y			
Fife, 1996	PR47	USA	Gynaecology	29.2			18	45	CVL	HC-I			Y	Y			
Fife, 1996	PR47	USA	Obstetrics	22.8			18	45	CVL	HC-I			Y	Y			
Hall, 1996	PR57a	Baltimore, USA	Colposcopy – abnormal Pap						CBr	HC-I							
Hall, 1996	PR57b	Baltimore, USA	Colposcopy – abnormal Pap						CVL	HC-I							
Melbye, 1996	PR83a	Denmark	HIV clinics (HIV+)			30	19	53	CSw	HC-I						β-Globin	
Melbye, 1996	PR83a	Denmark	HIV clinics (HIV–)			25	19	53	CSw	HC-I						β-Globin	

continued

TABLE 14d contd *Characteristics of studies employing HC-I*

Author, year	Paper	Location	Clinic	Age (years)					Collection device	Amplification system	Detection system	No. of cycles	Controls			DNA amplification	Sensitivity
				Mean	SD	Median	Minimum	Maximum					Positive	Negative	Replication		
Schneider, 1996	PR159		Routine screening	37.1			15	76	CSw	HC-I							
Baken, 1995	PR7	Seattle	Sexually transmitted diseases	26.5			17		CSw	MY09/11, HC-I	Gel		Y	Y	Y		
Cox, 1995	PR121	California	Student health service	21			18	22	CBr	HC-I			Y	Y			
Hatch, 1995	PR124	USA and Germany	Abnormal smears – colposcopy						CSw	HC-I			Y	Y	Y		
Farthing, 1994	PR43		Colposcopy						Sp	MY09/11, HC-I	SB	35				β-Globin	10

TABLE 14e *Characteristics of studies employing HC-II*

Author, year	Paper	Location	Clinic	Age (years)					Collection device	Amplification system	Detection system	No. of cycles	Controls			DNA amplification	Sensitivity
				Mean	SD	Median	Minimum	Maximum					Positive	Negative	Replication		
Clavel, 1999	PR149A		Routine screening							HC-II							
Cuzick, 1999	PR150Ac	London	Routine screening				34	70	Sp, CBr	HC-II			Y	Y			
Gurley, 1999	PR141A	Australia	Low-grade or borderline abnormal cytology							HC-II							
Hill, 1999	PR153Ab		Unscreened women							HC-II							
Mougin, 1999	PR154A		Routine screening							MY09/11, HC-II							
Sasagawa, 1999	PR142A		Referred							LCR-47, HC-II							
Tabrizi, 1999	PR146A	Rural Australia							T	HC-II							
Womack, 1999	PR140A	Zimbabwe	Screen – 50% HIV+				25	56		HC-II							
Ferris, 1998	PR46b	Georgia, MA, NY	Colposcopy				18+		CBr	HC-II							
Nindl, 1998	PR156A	Germany	Abnormal cytology, colposcopy referral, CIN+						CBr	HC-II							

TABLE 14f *Characteristics of studies employing type-specific PCR*

Author, year	Paper	Location	Clinic	Age (years)					Collection device	Amplification system	Detection system	No. of cycles	Controls			DNA amplification	Sensitivity
				Mean	SD	Median	Minimum	Maximum					Positive	Negative	Replication		
Sun, 1997	PR136		Sexually transmitted diseases clinic – HIV seronegative	35						MY09/11, TS 16, 18		Gel					K-ras
Chang, 1997	PR17a	Taiwan	Outpatient, gynaecology (cancer)	51.9	32	69			Sp	TS 6, 11, 16, 18	Gel, DB	? (2 step)		Y			0.0000001 pg
Chang, 1997	PR17a	Taiwan	Outpatient, gynaecology (normal)	38			16	65	Sp	TS 6, 11, 16, 18	Gel, DB	? (2 step)		Y			0.0000001 pg
Chang, 1997	PR17a	Taiwan	Outpatient, gynaecology (LSIL/HSIL)	41.2			25	66	Sp	TS 6, 11, 16, 18	Gel, DB	? (2 step)		Y			0.0000001 pg
Chang, 1997	PR17b	Taiwan	Outpatient, gynaecology (LSIL/HSIL)	41.2			25	66	Sp	TS 6, 11, 16, 18	Gel, DB	35 (1 step)		Y			0.01 pg
Chang, 1997	PR17b	Taiwan	Outpatient, gynaecology (cancer)	51.9			32	69	Sp	TS 6, 11, 16, 18	Gel, DB	35 (1 step)		Y			0.01 pg
Chang, 1997	PR17b	Taiwan	Outpatient, gynaecology (normal)	38			16	65	Sp	TS 6, 11, 16, 18	Gel, DB	35 (1 step)		Y			0.01 pg
Hernandez-Avila, 1997	PR59	Mexico	Hospital (invasive)	49.9						TS 16, 18	Gel	40	Y	Y			
Hernandez-Avila, 1997	PR59	Mexico	Population (control)	44.3						TS 16, 18	Gel	40	Y	Y			
Hernandez-Avila, 1997	PR59	Mexico	Hospital (carcinoma *in situ*)	44.9						TS 16, 18	Gel	40	Y	Y			
Wheeler, 1996	PR115	New Mexico	Students			27	18	35	CSw, VSw, CVL				Y	Y	Y	β-Globin	
Burk, 1996	PR13	New York	Medical/drug treatment	31			18	50	CVL						Y		
Gradilone, 1996	PR52	Rome	Gynaecology – negative smears	37.7			17	70	Sp	TS 16, 18	SB	30		Y	Y	β-Globin	
Londesborough, 1996	NH65	London	Abnormal cytology – colposcopy clinic	31			16	69		MY09/11, TS 16, 18, 31, 33, 35	ELISA						
Moscicki, 1996	PR88	USA	Planned parenthood				13	19									
Cuzick, 1995	PR122	England	Routine screening – family practitioner clinic			29	20	45	Sp, CBr	TS 16, 18, 31, 33	Gel	35	Y	Y			

TS, type specific

continued

TABLE 14f contd *Characteristics of studies employing type-specific PCR*

Author, year	Paper	Location	Clinic	Age (years)					Collection device	Amplification system	Detection system	No. of cycles	Controls			DNA amplification	Sensitivity
				Mean	SD	Median	Minimum	Maximum					Positive	Negative	Replication		
Saito, 1995	PR103	Osaka, Japan	Students	40.9	10		18	72	CSw	TS 16, 18	Gel, DB		Y	Y			< 10
Burger, 1995	PR12	Netherlands	Gynaecology – abnormal Pap														
Cuzick, 1994	PR29	England	Colposcopy – abnormal Pap						Sp	TS 6/11, 16, 18, 31, 33, 35	Gel	35	Y	Y			
Fairley, 1994	PR42	Australia	Gynaecology	27	4.5		18	35	T								
Vandenvelde, 1993	PR113	Brussels	Screening and colposcopy						Sp	TS 16, 18, 33		40	Y	Y	Y		100–500
Coker, 1993	PR24	S. Carolina	Family practitioner clinics	23.5					Sp, CBr	TS 6/11, 16, 18, 33			Y	Y		β-Globin, β-lactamase	
Aziz, 1993	PR4	Montreal	Colposcopy – abnormal Pap	24			16	69	CBr, CSw,	TS 6/11, 16, 18	Gel	40	Y	Y		β-Globin	
Bavin, 1993	PR127a	London	Colposcopy – mild smear (positive)	29					Sp	TS 16	Gel		Y	Y	Y		5
Bavin, 1993	PR127b	London	Colposcopy – mild smear (high level)	29					Sp	TS 16	Gel		Y	Y	Y		5
Jullian, 1993	PR64	France	Screening							TS 16, 18	Gel, RFLP	40	Y	Y		Myosin heavy chain	15–30
Kjaer, 1993	PR69a	Denmark	Population	28			20	39	CSw	TS 11, 16, 18, 33	Gel, SB	30	Y	Y			
Kjaer, 1993	PR69b	Greenland	Population	28			20	39	CSw	TS 11, 16, 18, 33	Gel, SB	30	Y	Y			
Cuzick, 1992	PR27	England	Colposcopy						Sp	TS 16	Gel	35	Y	Y			
Bavin, 1992	PR9	England	General practitioner	38.4			18	76	Sp	TS 16	SB	35	Y	Y	Y		
Nakazawa, 1992	PR91	Osaka, Japan	Outpatient clinic				21	55	CSw	TS 16, 18	Gel, SB	25	Y	Y			20
Pasetto, 1992	PR96	Rome	Colposcopy				19	65	Sp	TS 16	Gel, RFLP	40	Y	Y			
Morrison, 1991	PR87		Gynaecology, family practitioner						CVL	TS 16, 18, 33	Gel, SB	30	Y	Y		β-Globin	
Nishikawa, 1991	PR93	Japan	Gynaecology	38.5			18	73	Sp	TS 16, 18, 33	Gel, DB	30	Y	Y		β-Globin	< 10
Burmer, 1990	PR14	Seattle	Family practitioner, general practitioner						CSw	TS 6/11, 16, 18	SB	30					10,000
Pao, 1990	PR95	Taiwan							CVL	TS 6, 11, 16, 18, 33	Gel, DB		Y	Y			50–300

TS, type specific

TABLE 15a *Overall and type-specific prevalence by disease category for studies employing MY09/11*

Author, year	Paper	Group	Number	TS 6/11	TS 16	TS 18/45	TS 31	TS 33	TS 30s	TS 50s	High risk	Low risk	Any
Cuzick, 1999	PR150Aa	Cytology negative	2855		3 (0.1)	1 (0.03)	3 (0.1)	1 (0.03)			97 (3.4)		93 (3.3)
Cuzick, 1999	PR150Aa	Histology CIN I	84		6 (7.1)	0 (0)	5 (6)	1 (1.2)			55 (66)		50 (59.5)
Cuzick, 1999	PR150Aa	Histology CIN II	8		2 (25)	1 (12.5)	1 (12.5)	0 (0)			4 (50)		4 (50)
Cuzick, 1999	PR150Aa	Histology CIN III/carcinoma *in situ*	34		10 (29.4)	3 (8.8)	9 (26.5)	0 (0)			27 (79)		26 (46.5)
Mougin, 1999	PR154A	Cytology negative	422								60 (14.2)	23 (5.4)	
Mougin, 1999	PR154A	ASCUS	37								15 (40.5)	5 (13.5)	
Mougin, 1999	PR154A	Cytology LSIL	96								60 (62.5)	4 (4.2)	
Mougin, 1999	PR154A	Cytology HSIL	38								30 (78.9)	1 (2.6)	
Mougin, 1999	PR154A	Cancer	2								2 (100)		
del Mistro, 1998	PR137Aa	Normal	129										10 (7.7)
del Mistro, 1998	PR137Ab	Abnormal cytology	75										32 (42.6)
Womack, 1998	PR139A	Normal	843								41 (4.9)	48 (5.7)	
Womack, 1998	PR139A	Histology CIN I	14								5 (35.7)	6 (42.9)	
Womack, 1998	PR139A	Histology CIN II/III	3								3 (100)	0 (0)	
Wideroff, 1998	PR116	Cytology negative	806								69 (8.6)		123 (15.3)
Wideroff, 1998	PR116	Abnormal cytology	251								68 (27.1)		105 (41.8)
Kotloff, 1998	PR72	Normal	414		32 (7.7)	23 (5.6)	8 (1.9)	1 (.2)			92 (22.2)	21 (5.1)	145 (35)
Kotloff, 1998	PR72	Abnormal cytology	15										14 (93.3)
La Ruche, 1998	PR158	Cytology negative	391		6 (1.5)	2 (0.5)	3 (0.8)	0 (0)			27 (6.9)		95 (24.3)
La Ruche, 1998	PR158	Histology CIN I	151		16 (10.6)	1 (0.7)	8 (5.3)	8 (5.3)			71 (47)		103 (68.2)
La Ruche, 1998	PR158	Histology CIN II/III	60		15 (25)	5 (8.3)	3 (5)	4 (6.7)			46 (76.7)		49 (81.7)
La Ruche, 1998	PR158	Cancer	13										10 (76.9)
Sigurdsson, 1997	PR110b	Abnormal cytology/histology negative	35								7 (20)	0 (0)	
Sigurdsson, 1997	PR110b	Histology CIN I	128								38 (29.7)	2 (1.6)	
Sigurdsson, 1997	PR110b	Histology CIN II	57								39 (68.4)	0 (0)	
Sigurdsson, 1997	PR110b	Histology CIN III/carcinoma *in situ*	131								110 (84)	2 (1.5)	
Sigurdsson, 1997	PR110b	Cancer	7								7 (100)	0 (0)	

TS, type specific

continued

TABLE 15a contd *Overall and type-specific prevalence by disease category for studies employing MY09/11*

Author, year	Paper	Group	Number	TS 6/11	TS 16	TS 18/45	TS 31	TS 33	TS 30s	TS 50s	High risk	Low risk	Any
Smith, 1997	PR111	Normal	105										40 (38.1)
Sun, 1997	PR136	Normal	231			13 (5.6)				16 (6.9)	67 (29)	12 (5.2)	103 (44.6)
Young, 1997	PR117a	Normal	530	64 (12.1)	64 (12.1)	78 (14.7)	35 (6.6)	35 (6.6)			168 (31.7)		178 (33.6)
Young, 1997	PR117b	Normal	733	70 (9.5)	95 (13)	71 (9.7)	30 (4.1)	38 (5.2)			187 (25.5)		233 (31.8)
Cope, 1997	PR26b	Normal	596		46 (7.7)		12 (2)			44 (7.4)			134 (22.5)
Cope, 1997	PR26b	Cytology negative											
Cope, 1997	PR26b	Abnormal cytology											
Grce, 1997	PR54	Cytology CIN I	183	22 (12)	8 (4.4)	1 (.5)	11 (6)	2 (1.1)					65 (35.5)
Grce, 1997	PR54	Cytology CIN II	128	15 (11.7)	10 (7.8)	6 (4.7)	14 (10.9)	5 (3.9)					61 (47.7)
Grce, 1997	PR54	Cytology CIN III	50	3 (6)	13 (26)	1 (2)	3 (6)	2 (4)					26 (52)
Grce, 1997	PR54	Cytology CIN IV	18	0 (0)	2 (11.1)	1 (5.6)	1 (5.6)	2 (11.1)					11 (61.1)
Guney, 1997	PR56	Cytology negative	21		1 (4.8)								2 (9.5)
Kalantari, 1997	PR65	Previous condyloma or dysplasia	171	55 (32.2)	23 (13.5)	14 (8.2)	15 (8.8)	8 (4.7)			47 (27.5)		136 (79.5)
Kalantari, 1997	PR65	Histology CIN I	141	33 (23.4)	25 (17.7)	20 (14.2)	15 (10.6)	9 (6.4)			58 (41.1)		100 (70.9)
Kalantari, 1997	PR65	Histology CIN II	69	11 (15.9)	15 (21.7)	7 (10.1)	13 (18.8)	11 (15.9)			33 (47.8)		56 (81.2)
Kalantari, 1997	PR65	Histology CIN III/carcinoma *in situ*	95	8 (8.4)	44 (46.3)	7 (7.4)	14 (14.7)	17 (17.9)			69 (72.6)		80 (84.2)
Rattray, 1996	PR100	Cytology positive–negative histology	36		1 (2.8)	0 (0)	1 (2.8)	0 (0)			2 (5.6)		9 (25)
Rattray, 1996	PR100	Histology CIN I	72		4 (5.6)	8 (11.1)	4 (5.6)	6 (8.3)			26 (36.1)		36 (50)
Rattray, 1996	PR100	Histology CIN II	27		2 (7.4)	3 (11.1)	2 (7.4)	2 (7.4)			14 (51.9)		21 (77.8)
Rattray, 1996	PR100	Histology CIN III/carcinoma *in situ*	39		14 (35.9)	6 (15.4)	4 (10.3)	3 (7.7)			32 (82.1)		37 (94.9)
Chan, 1996	PR15a	Cytology positive–negative histology	105	0 (0)	6 (5.7)	1 (1)		0 (0)					11 (10.5)
Chan, 1996	PR15a	Histology CIN I	16	1 (6.3)	2 (12.5)	3 (18.8)		3 (18.8)					9 (56.3)
Chan, 1996	PR15a	Histology CIN II	10	0 (0)	1 (10)	1 (10)		0 (0)					5 (50)
Chan, 1996	PR15a	Histology CIN III/carcinoma *in situ*	35	2 (5.7)	9 (25.7)	3 (8.6)		1 (2.9)					20 (57.1)
Chan, 1996	PR15a	Histology cancer	9	0 (0)	4 (44.4)	2 (22.2)		1 (11.1)					7 (77.8)
Chan, 1996	PR15a	Condyloma/HPV	42	3 (7.1)	7 (16.7)	2 (4.8)		0 (0)					13 (31)
Chan, 1996	PR15b	Cytology negative	101										
Chan, 1996	PR15c	Cytology negative	170		7 (4.1)								

TS, type specific

continued

TABLE 15a contd *Overall and type-specific prevalence by disease category for studies employing MY09/11*

Author, year	Paper	Group	Number	TS 6/11	TS 16	TS 18/45	TS 31	TS 33	TS 30s	TS 50s	High risk	Low risk	Any
Gjooen, 1996	PR50	Normal	101	5 (5)	14 (13.9)	3 (3)	6 (5.9)	1 (1)					34 (33.7)
Gjooen, 1996	PR50	Histology CIN II/III	222		65 (29.3)	4 (1.8)	9 (4.1)	3 (1.4)					92 (41.4)
Agorastos, 1995	PR1	Cytology negative	226		15 (6.6)	3 (1.3)							82 (36.3)
Karaloglu, 1996	PR66	Cytology negative	14		1 (7.1)	0 (0)					1 (7.1)		
Karaloglu, 1996	PR66	Cytology positive–negative histology	22		1 (4.5)	0 (0)					1 (4.5)		
Karaloglu, 1996	PR66	Histology cancer	33		18 (54.5)	15 (45.5)					22 (66.7)		
Londesborough, 1996	NH65	Histology CIN I	194		19 (9.8)	7 (3.6)	24 (12.4)	8 (4.1)			50 (26)		
Londesborough, 1996	NH65	Histology CIN II/III	64		45 (70.3)	9 (14.1)	35 (54.7)	13 (20.3)			48 (75)		
Melbye, 1996	PR83b	Cytology negative, HIV-negative	58								30 (51.7)		
Melbye, 1996	PR83b	Abnormal cytology, HIV-negative	4								3 (75)		
Melbye, 1996	PR83b	Cytology normal, HIV-positive	52								2 (3.8)		
Melbye, 1996	PR83b	Cytology abnormal, HIV-positive	11								11 (100)		
Shen, 1995	PR107	Normal	417	2 (.5)			1 (.2)						7 (1.7)
Shen, 1995	PR107	Cytology positive–negative histology	16										2 (12.5)
Shen, 1995	PR107	Histology CIN II/III	27										16 (59.3)
Shen, 1995	PR107	High risk of neoplasia	43	1 (2.3)	11 (25.6)	2 (4.7)	2 (4.7)						16 (37.2)
Flannelly, 1995	PR48	Cytology negative	167		67 (40.1)								
Flannelly, 1995	PR48	Cytology positive–negative histology	62		20 (32.3)								
Flannelly, 1995	PR48	Histology CIN I	31		5 (16.1)								
Flannelly, 1995	PR48	Histology CIN II/III	31		14 (45.2)								
Herrington, 1995	PR60	Cytology positive–negative histology	37		3 (8.1)	1 (2.7)					5 (13.5)		8 (21.6)
Herrington, 1995	PR60	Histology CIN I	86		16 (18.6)	2 (2.3)					27 (31.4)		36 (41.9)
Herrington, 1995	PR60	Histology CIN II	12		8 (66.7)	0 (0)	2 (16.7)				11 (91.7)		11 (91.7)
Herrington, 1995	PR60	Histology CIN III/carcinoma *in situ*	26		12 (46.2)	3 (11.5)	4 (15.4)				20 (76.9)		24 (92.3)
Baken, 1995	PR7	Cytology negative	42										21 (50)
Baken, 1995	PR7	Squamous intraepithelial lesion on cytology	4										4 (100)

TS, type specific

continued

TABLE 15a contd *Overall and type-specific prevalence by disease category for studies employing MY09/11*

Author, year	Paper	Group	Number	TS 6/11	TS 16	TS 18/45	TS 31	TS 33	TS 30s	TS 50s	High risk	Low risk	Any
Liaw, 1995	PR78	Cytology negative	260								2 (.8)	11 (4.2)	24 (9.2)
Liaw, 1995	PR78	Histology CIN I	37								6 (16.2)	6 (16.2)	20 (54.1)
Liaw, 1995	PR78	Histology CIN II/III and cancers	48								28 (58.3)	1 (2.1)	44 (91.7)
Ramael, 1995	PR98	Normal	200		3 (1.5)	1 (.5)							8 (4)
Sherman, 1994	PR108	Cytology negative	46								1 (2.2)	9 (19.6)	
Sherman, 1994	PR108	Cytology positive	14								12 (85.7)	3 (21.4)	
Sherman, 1994	PR108	Cytology negative (1 pathology)											
Sherman, 1994	PR108	Cytology (1 pathology)											
Farthing, 1994	PR43	Cytology positive–negative histology	107								21 (19.6)		
Farthing, 1994	PR43	Histology CIN I	17								10 (58.8)		
Farthing, 1994	PR43	Histology CIN II	16								10 (62.5)		
Farthing, 1994	PR43	Histology CIN III/carcinoma *in situ*	24								20 (83.3)		
Kuhler-Obbarius, 1994	PR160	Cytology negative	101										23 (22.8)
Kuhler-Obbarius, 1994	PR160	Abnormal cytology	550										309 (56.2)
Lambropoulos, 1994	PR76	Cytology negative	20		12 (60)	2 (10)							8 (40)
Lambropoulos, 1994	PR76	Histology CIN III/carcinoma *in situ*	1		1 (100)	1 (100)							
Bosch, 1993	PR11a	Cytology negative	193	0 (0)	1 (.5)	0 (0)	1 (.5)	1 (.5)	2 (1)				9 (4.7)
Bosch, 1993	PR11a	Histology CIN III/carcinoma *in situ*	157	0 (0)	77 (49)	1 (.6)	2 (1.3)	9 (5.7)	12 (7.6)				111 (70.7)
Bosch, 1993	PR11b	Cytology negative	181	3 (1.7)	6 (3.3)	0 (0)	0 (0)	1 (.6)	1 (.6)				19 (10.5)
Bosch, 1993	PR11b	Histology CIN III/carcinoma *in situ*	125	0 (0)	41 (32.8)	0 (0)	3 (2.4)	3 (2.4)	8 (6.4)				79 (63.2)
Hansson, 1993	PR58a	Cytology negative	210	1 (.5)	12 (5.7)	4 (1.9)	5 (2.4)	2 (1)	11 (5.2)		22 (10.5)		47 (22.4)
Hansson, 1993	PR58a	Cytology CIN I	15	2 (13.3)	1 (6.7)		1 (6.7)		3 (20)		3 (20)		8 (53.3)
Hansson, 1993	PR58a	Cytology CIN II	4	1 (25)	1 (25)				1 (25)		1 (25)		3 (75)
Hansson, 1993	PR58a	Cytology CIN III	1										0 (0)
Hansson, 1993	PR58b	Cytology positive–negative histology	252	0 (0)	25 (9.9)	9 (3.6)	6 (2.4)	8 (3.2)	20 (7.9)		45 (17.9)		78 (31)
Hansson, 1993	PR58b	Histology CIN I	66	5 (7.6)	21 (31.8)	3 (4.5)	8 (12.1)	8 (12.1)	18 (27.3)		35 (53)		50 (75.8)
Hansson, 1993	PR58b	Histology CIN II	36	3 (8.3)	15 (41.7)	2 (5.6)	2 (5.6)	3 (8.3)	5 (13.9)		19 (52.8)		25 (69.4)
Hansson, 1993	PR58b	Histology CIN III/carcinoma *in situ*	120	2 (1.7)	67 (55.8)	7 (5.8)	15 (12.5)	16 (13.3)	36 (30)		91 (75.8)		109 (90.8)
Hansson, 1993	PR58b	Histology cancer	7	0 (0)	5 (71.4)	0 (0)	0 (0)	1 (14.3)	1 (14.3)		5 (71.4)		6 (85.7)

TS, type specific

continued

TABLE 15a contd *Overall and type-specific prevalence by disease category for studies employing MY09/11*

Author, year	Paper	Group	Number	TS 6/11	TS 16	TS 18/45	TS 31	TS 33	TS 30s	TS 50s	High risk	Low risk	Any
Scand MC, 1992	PR3	Cytology negative	77	10 (13)							17 (22.1)		27 (35.1)
Scand MC, 1992	PR3	Cytology CIN I	156	23 (14.7)							36 (23.1)		52 (33.3)
Scand MC, 1992	PR3	Cytology CIN II/III	81	11 (13.6)							39 (48.1)		46 (56.8)
Scand MC, 1992	PR3	Cytology carcinoma *in situ*	12										7 (58.3)
Evander, 1992	PR39a	Cytology negative	539										30 (5.6)
Evander, 1992	PR39a	Cytology positive–negative histology	19										5 (26.3)
Fairley, 1992	PR41	Normal	55										0 (0)
Goldsborough, 1992	PR51a	Cytology negative	53	0 (0)	1 (1.9)	0 (0)	0 (0)	0 (0)					4 (7.5)
Goldsborough, 1992	PR51a	Abnormal cytology	36	5 (13.9)	5 (13.9)	0 (0)	0 (0)	1 (2.8)					21 (58.3)
Goldsborough, 1992	PR51a	Cytology negative (routine smear)	70	0 (0)	0 (0)	0 (0)	2 (2.9)	0 (0)					13 (18.6)
Goldsborough, 1992	PR51a	Cytology positive (routine smear)	29	0 (0)	9 (31)	0 (0)	3 (10.3)	1 (3.4)					23 (79.3)
Goldsborough, 1992	PR51b	Cytology negative	53	2 (3.8)	2 (3.8)	0 (0)	0 (0)	3 (5.7)					32 (60.4)
Goldsborough, 1992	PR51b	Abnormal cytology	36	5 (13.9)	6 (16.7)	1 (2.8)	0 (0)	3 (8.3)					32 (88.9)
Goldsborough, 1992	PR51b	Cytology negative (routine smear)	70	0 (0)	0 (0)	0 (0)	2 (2.9)	0 (0)					23 (32.9)
Goldsborough, 1992	PR51b	Cytology positive (routine smear)	29	0 (0)	9 (31)	0 (0)	3 (10.3)	0 (0)					28 (96.6)
Munoz, 1992	PR89a	Cytology negative	98		9 (9.2)	2 (2)	0 (0)	0 (0)	1 (1)				13 (13.3)
Munoz, 1992	PR89a	Cancer	87		44 (50.6)	5 (5.7)	5 (5.7)	0 (0)	8 (9.2)				63 (72.4)
Munoz, 1992	PR89b	Cytology negative	130		4 (3.1)	0 (0)	1 (.8)	1 (.8)	2 (1.5)				6 (4.6)
Munoz, 1992	PR89b	Cancer	142		65 (45.8)	5 (3.5)	5 (3.5)	5 (3.5)	12 (8.5)				98 (69)
Gravitt, 1991	PR53a	Normal	362	22 (6.1)	25 (6.9)	18 (5)	1 (.3)						118 (32.6)
Gravitt, 1991	PR53b	Normal		12 (.)	19 (.)	8 (.)							
Ley, 1991	PR77	Normal	467										213 (45.6)
Ley, 1991	PR77	Abnormal cytology	33										28 (84.8)
Ley, 1991	PR77	Previous abnormal cytology	34										21 (61.8)
Ley, 1991	PR77	Previous warts	41										27 (65.9)
Bauer, 1991	PR8	Normal	467	16 (3.4)	40 (8.6)	24 (5.1)	22 (4.7)	12 (2.6)		21 (4.5)			154 (33)
Bauer, 1991	PR8	Cytology negative	421										130 (30.9)
Bauer, 1991	PR8	Cytology CIN I	28										20 (71.4)
Bauer, 1991	PR8	Abnormal cytology	5										4 (80)

TS, type specific

TABLE 15b *Overall and type-specific prevalence by disease category for studies employing GP5/6*

Author, year	Paper	Group	Number	TS 6/11	TS 16	TS 18/45	TS 31	TS 33	TS 30s	TS 50s	High risk	Low risk	Any
Dillner, 1999	PR151A	Normal	1029		15 (1.5)		23 (2.2)		26 (2.5)	8 (0.8)			57 (5.7)
Chaouki, 1998	PR18	Normal	185		8 (4.3)	5 (2.7)			2 (1.1)	4 (2.2)	19 (10.3)		38 (20.5)
Chaouki, 1998	PR18	Cancer biopsy	197		126 (64)	24 (12.2)			7 (3.6)	6 (3)	163 (82.7)		176 (89.3)
Chaouki, 1998	PR18	Histology adenocarcinoma	13		8 (61.5)	1 (7.7)							12 (92.3)
Chaouki, 1998	PR18	Squamous cancer	139		92 (66.2)	19 (13.7)							132 (95)
Chichareon, 1998	PR19	Normal	261		12 (4.6)	7 (2.7)	3 (1.1)	1 (.4)		2 (.8)	27 (10.3)		41 (15.7)
Chichareon, 1998	PR19	Histology adenocarcinoma	39		13 (33.3)	21 (53.8)	0 (0)	0 (0)		0 (0)	34 (87.2)		35 (89.7)
Chichareon, 1998	PR19	Squamous cancer	338		193 (57.1)	57 (16.9)	7 (2.1)	5 (1.5)		10 (3)	287 (84.9)		322 (95.3)
Kruger-Kjaer, 1998	PR73	Cytology negative	994										155 (15.6)
Kruger-Kjaer, 1998	PR73	Cytology ASCUS	126										82 (65.1)
Kruger-Kjaer, 1998	PR73	Cytology CIN I	119										86 (72.3)
Kruger-Kjaer, 1998	PR73	Cytology CIN II/III	79										71 (89.9)
Lotz, 1998	PR130A	Normal	3510								394 (11.2)		
Lotz, 1998	PR130A	Histology CIN I/II	116								87 (75)		
Lotz, 1998	PR130A	Histology CIN III/carcinoma *in situ*/cancer	63								34 (54)		
Meijer, 1998	PR131Aa	Histology CIN III/carcinoma *in situ*	11								11 (100)		
Meijer, 1998	PR131Aa	< CIN III	690								92 (13.3)		
Meijer, 1998	PR131Ab	Histology CIN III/carcinoma *in situ*	31								29 (93.5)		
Meijer, 1998	PR131Ab	< CIN III	2279								372 (16.3)		
Ngelangel, 1998	PR92	Normal	381		5 (1.3)	11 (2.9)	2 (.5)				26 (6.8)		35 (9.2)
Ngelangel, 1998	PR92	Histology squamous cancer	323		130 (40.2)	118 (36.5)	2 (.6)				269 (83.3)		303 (93.8)
Ngelangel, 1998	PR92	Histology adenocarcinoma	33		8 (24.2)	22 (66.7)					28 (84.8)		33 (100)
Nindl, 1998	PR132A	Histology CIN I	49								24 (47)		
Schneider, 1997	PR106a	Incident histology CIN II/III	36		9 (25)	1 (2.8)	0 (0)	4 (11.1)			13 (36.1)	1 (2.8)	25 (69.4)
Schneider, 1997	PR106a	Prevalent histology CIN II/III	40		19 (47.5)	1 (2.5)	5 (12.5)	6 (15)			29 (72.5)	1 (2.5)	38 (95)
Kjaer, 1997	PR70	Cytology negative	956								108 (11.3)	44 (4.6)	147 (15.4)
Burger, 1996	NH3	Histology CIN I	37	1 (2.7)	5 (13.5)	8 (21.6)		2 (5.4)			12 (32.4)		18 (48.6)
Burger, 1996	NH3	Histology CIN II	48	1 (2.1)	14 (29.2)	6 (12.5)	7 (14.6)	2 (4.2)			25 (52.1)		33 (68.8)
Burger, 1996	NH3	Histology CIN III/carcinoma *in situ*	180	2 (1.1)	102 (56.7)	15 (8.3)	19 (10.6)	11 (6.1)			154 (85.6)		154 (85.6)
Elfgren, 1996	PR123	Recurrent CIN	4										4 (100)
Elfgren, 1996	PR123	Non-recurrent CIN	19										0 (0)

TS, type specific

continued

TABLE 15b contd *Overall and type-specific prevalence by disease category for studies employing GP5/6*

Author, year	Paper	Group	Number	TS 6/11	TS 16	TS 18/45	TS 31	TS 33	TS 30s	TS 50s	High risk	Low risk	Any
Rozendaal, 1996	PR102	Cytology negative	1622		29 (1.8)	14 (.9)	13 (.8)	3 (.2)			75 (4.6)	12 (.7)	98 (6)
Zehbe, 1996	PR118	Normal cytology	83								26 (31.3)		36 (43.4)
Zehbe, 1996	PR118	Abnormal cytology	11								5 (45.5)		10 (90.9)
de Roda Husman, 1995	PR32	Normal – not pregnant	3948								116 (2.9)		432 (10.9)
de Roda Husman, 1995	PR32	Pregnant – cytology negative	709								22 (3.1)		68 (9.6)
Gaarenstroom, 1994	NH13	Cytology positive–negative histology	26	1 (3.8)	5 (19.2)	0 (0)	1 (3.8)	0 (0)			6 (23.1)		8 (30.8)
Gaarenstroom, 1994	NH13	Histology CIN I	101	3 (3)	29 (28.7)	7 (6.9)	8 (7.9)	1 (1)			44 (43.6)		55 (54.5)
Gaarenstroom, 1994	NH13	Histology CIN II	76	1 (1.3)	23 (30.3)	7 (9.2)	1 (1.3)	3 (3.9)			32 (42.1)		43 (56.6)
Gaarenstroom, 1994	NH13	Histology CIN III/carcinoma *in situ*	24	0 (0)	18 (75)	2 (8.3)	1 (4.2)	0 (0)			21 (87.5)		24 (100)
de Roda Husman, 1994	PR31	Pap IIIa (mild/moderate)	971	24 (2.5)	240 (24.7)	52 (5.4)	67 (6.9)	37 (3.8)			435 (44.8)		695 (71.6)
de Roda Husman, 1994	PR31	Pap IIIb (severe)	295	4 (1.4)	147 (49.8)	23 (7.8)	19 (6.4)	6 (2)			206 (69.8)		252 (85.4)
de Roda Husman, 1994	PR31	Pap IVa (carcinoma *in situ*/cancer)	107	1 (.9)	55 (51.4)	13 (12.1)	13 (12.1)	9 (8.4)			95 (88.8)		107 (100)
Eluf-Neto, 1994	PR37	Normal	190	1 (.5)	10 (5.3)	2 (1.1)			0 (0)		12 (6.3)		32 (16.8)
Eluf-Neto, 1994	PR37	Histology cancer	186	0 (0)	100 (53.8)	16 (8.6)			6 (3.2)		122 (65.6)		157 (84.4)
Claas, 1992	PR21	Cytology negative	143		1 (.7)						1 (.7)		2 (1.4)
Claas, 1992	PR21	Abnormal cytology (Pap IIIA or higher)	46		19 (41.3)	5 (10.9)	2 (4.3)	5 (10.9)			30 (65.2)		33 (71.7)
Claas, 1992	PR21	Sexually transmitted diseases (Pap IIIA or higher)	101		5 (5)	1 (1)	1 (1)				7 (6.9)		11 (10.9)
Engels, 1992	PR38	Normal – family practitioner	109	1 (.9)							3 (2.8)		4 (3.7)
Engels, 1992	PR38	Normal – sexually transmitted diseases	97	1 (1)							15 (15.5)		16 (16.5)
Van Den Brule, 1991	PR112	Cytology negative	1346	2 (.1)	5 (.4)	6 (.4)	5 (.4)	3 (.2)					47 (3.5)
Van Den Brule, 1991	PR112	Cytology negative, outpatient no history CIN	239			6 (2.5)							22 (9.2)
Van Den Brule, 1991	PR112	Cytology negative, outpatient history CIN	177		20 (11.3)	1 (.6)	3 (1.7)				1 (.6)		38 (21.5)
Van Den Brule, 1991	PR112	Cytology IIIa	124								51 (41.1)		87 (70.2)
Van Den Brule, 1991	PR112	Cytology IIIb	31								18 (58.1)		26 (83.9)
Van Den Brule, 1991	PR112	Cytology IV	22								15 (68.2)		22 (100)

TS, type specific

TABLE 15c *Overall and type-specific prevalence by disease category for studies employing other consensus PCR*

Author, year	Paper	Group	Number	TS 6/11	TS 16	TS 18/45	TS 31	TS 33	TS 30s	TS 50s	High risk	Low risk	Any
Sasagawa, 1999	PR142A	Cytology negative	64										5 (7.8)
Sasagawa, 1999	PR142A	LSIL	137										71 (51.8)
Sasagawa, 1999	PR142A	HSIL	101										87 (86.1)
Sasagawa, 1999	PR142A	Cancer	50										39 (78)
Clavel, 1998	PR22	Cytology negative	137								44 (32.1)	29 (21.2)	52 (38)
Clavel, 1998	PR22	Cytology CIN I	20								12 (60)	5 (25)	13 (65)
Clavel, 1998	PR22	Cytology CIN II/III	24								23 (95.8)	0 (0)	23 (95.8)
Jansson, 1998	PR138A	Normal	269								12 (4.5)		17 (6.6)
Jansson, 1998	PR138A	Histology CIN I	3								3 (100)		3 (100)
Jansson, 1998	PR138A	Histology CIN III	1								1 (100)		1 (100)
Woodman, 1998	PR134A	Normal	2011		83 (4)	33 (1.6)	18 (0.9)	40 (2)					362 (18)
Sasagawa, 1997	PR104	Cytology negative	778		8 (1)	0 (0)	11 (1.4)	1 (.1)		4 (.5)	26 (3.3)		35 (4.5)
Sasagawa, 1997	PR104	Histology CIN I	40		3 (7.5)	1 (2.5)	5 (12.5)			8 (20)	19 (47.5)		24 (60)
Sasagawa, 1997	PR104	Histology CIN II/III	52		13 (25)	2 (3.8)	6 (11.5)	1 (1.9)		9 (17.3)	40 (76.9)		48 (92.3)
Sasagawa, 1997	PR104	Histology cancer	31		9 (29)	3 (9.7)	3 (9.7)	1 (3.2)		2 (6.5)	24 (77.4)		26 (83.9)
Duggan, 1997	PR36	Cytology or colposcopy ≤ CIN I	332	12 (3.6)					33 (9.9)		85 (25.6)		149 (44.9)
Duggan, 1997	PR36	Cytology or colposcopy ≥ CIN II	193	4 (2.1)					22 (11.4)		62 (32.1)		100 (51.8)
Lungu, 1995	PR81	Cytology positive–negative histology	155								46 (29.7)		
Lungu, 1995	PR81	Histology CIN I	128								58 (45.3)		
Lungu, 1995	PR81	Histology CIN II/III	81								74 (91.4)		
Lungu, 1995	PR81	Histology cancer	7								6 (85.7)		
Olsen, 1995	PR94	Cytology negative	221		14 (6.3)								34 (15.4)
Olsen, 1995	PR94	Histology CIN II/III	98		64 (65.3)								89 (90.8)
Kurz, 1993	PR74	Cytology negative	13								2 (15.4)		2 (15.4)
Kurz, 1993	PR74	Cytology CIN I	25								12 (48)		14 (56)
Kurz, 1993	PR74	Cytology CIN II/III	7								6 (85.7)		7 (100)
Kurz, 1993	PR74	Cytology atypia	102								10 (9.8)		18 (17.6)
Czegledy, 1992	PR30	Cytology negative	77		4 (5.2)	3 (3.9)					8 (10.4)		15 (19.5)
Evander, 1992	PR39b	Cytology negative	530										102 (19.2)
Evander, 1992	PR39b	Cytology positive–negative histology	19										16 (84.2)
Reid, 1991	PR126	LSIL/CIN I	71		5 (7)	3 (4.2)					12 (16.9)	11 (15.5)	32 (45.1)
Reid, 1991	PR126	Histology CIN II/III	23		6 (26.1)	3 (13)					13 (56.5)	1 (4.3)	16 (69.6)
Reid, 1991	PR126	Equivocal histology	164		6 (3.7)	2 (1.2)					13 (7.9)	6 (3.7)	34 (20.7)
Reid, 1991	PR126	Negative histology	754		2 (0.3)	6 (0.8)					17 (2.3)	4 (0.5)	38 (5)
Rohan, 1991	PR101	Normal	105	3 (2.9)	11 (10.5)	0 (0)		0 (0)					19 (18.1)

TS, type specific

TABLE 15d *Overall and type-specific prevalence by disease category for studies employing HC-I*

Author, year	Paper	Group	Number	TS 6/11	TS 16	TS 18/45	TS 31	TS 33	TS 30s	TS 50s	High risk	Low risk	Any
Cuzick, 1999	PR150Ab	Cytology negative	1238								227 (18.3)		
Cuzick, 1999	PR150Ab	Histology CIN I	31								15 (48)		
Cuzick, 1999	PR150Ab	Histology CIN III/carcinoma *in situ*	16								14 (88)		
Hill, 1999	PR153Aa	Cytology negative	2544								331 (13)		
Hill, 1999	PR153Aa	Histology CIN I	95								64 (67)		
Hill, 1999	PR153Aa	Histology CIN II/III	66								49 (74)		
Hill, 1999	PR153Aa	Cancer	12								10 (83)		
Ratnam, 1999	PR155A	Normal	2098								193 (9.2)		
Ratnam, 1999	PR155A	Histology CIN II/III	29								25 (86.2)		
Sideri, 1998	PR109	Histology negative	92								35 (38)		
Sideri, 1998	PR109	Histology CIN I	39								35 (89.7)		
Sideri, 1998	PR109	Histology CIN II/III	42								31 (73.8)		
Clavel, 1998	PR23	Normal	1028								90 (8.8)	19 (1.8)	108 (10.5)
Clavel, 1998	PR23	Cytology negative	981								56 (5.7)	12 (1.2)	68 (6.9)
Clavel, 1998	PR23	Cytology CIN I	57								24 (42.1)	7 (12.3)	31 (54.4)
Clavel, 1998	PR23	Cytology CIN II/III	26								19 (73.1)	0 (0)	19 (73.1)
Ferris, 1998	PR46a	Cytology positive–negative histology	150								51 (34)		
Ferris, 1998	PR46a	Histology CIN I	71								44 (62)		
Ferris, 1998	PR46a	Histology CIN II/III	21								13 (61.9)		
Ornelas, 1998	PR133A	Histology CIN II/III	128								66 (51.5)	19 (14.8)	77 (60.2)
Ferenczy, 1997	PR45	Normal	306								3 (1)		
Korobowicz, 1997	PR71	Cytology negative	204								36 (17.6)	24 (11.8)	54 (26.5)
Korobowicz, 1997	PR71	Cytology CIN I	200								60 (30)	150 (75)	180 (90)
Korobowicz, 1997	PR71	Cytology Pap 4	124								112 (90.3)	10 (8.1)	118 (95.2)
Recio, 1997	PR157A	Cytology positive–negative histology	40								3 (7.5)		
Recio, 1997	PR157A	Histology CIN I	22								9 (40.9)		
Recio, 1997	PR157A	Histology CIN II/III	34								21 (61.8)		
Recio, 1997	PR157A	Cancer	2								2 (100)		
Schneider, 1997	PR106b	Incident histology CIN II/III	36		9 (25)	1 (2.8)	0 (0)	4 (11.1)			17 (47.2)	4 (11.1)	18 (50)
Schneider, 1997	PR106b	Prevalent histology CIN II/III	40		19 (47.5)	1 (2.5)	5 (12.5)	6 (15)			32 (80)	1 (2.5)	32 (80)

TS, type specific

continued

TABLE 15d contd *Overall and type-specific prevalence by disease category for studies employing HC-I*

Author, year	Paper	Group	Number	TS 6/11	TS 16	TS 18/45	TS 31	TS 33	TS 30s	TS 50s	High risk	Low risk	Any
Sigurdsson, 1997	PR110a	Abnormal cytology/histology negative	35								10 (28.6)	1 (2.9)	
Sigurdsson, 1997	PR110a	Histology CIN I	128								57 (44.5)	3 (2.3)	
Sigurdsson, 1997	PR110a	Histology CIN II	57								37 (64.9)	2 (3.5)	
Sigurdsson, 1997	PR110a	Histology CIN III/carcinoma *in situ*	131								94 (71.8)	0 (0)	
Sigurdsson, 1997	PR110a	Cancer	7								5 (71.4)	0 (0)	
Cope, 1997	PR26a	Normal	596		28 (4.7)					31 (5.2)			81 (13.6)
Cope, 1997	PR26a	Cytology negative	499										
Cope, 1997	PR26a	Abnormal cytology	97										
Ferenczy, 1996	PR44	Cytology positive–negative histology	178								41 (23)		
Ferenczy, 1996	PR44	Histology CIN I	106								64 (60.4)		
Ferenczy, 1996	PR44	Histology CIN II/III	76								58 (76.3)		
Ferenczy, 1996	PR44	Histology cancer	4								2 (50)		
Ferenczy, 1996	PR44	All	364								164 (45.1)		
Fife, 1996	PR47	Cytology negative	591								49 (8.3)	69 (11.7)	103 (17.4)
Fife, 1996	PR47	Cytology CIN I	104								22 (21.2)	60 (57.7)	52 (50)
Fife, 1996	PR47	Cytology CIN II/III	11								5 (45.5)	2 (18.2)	5 (45.5)
Fife, 1996	PR47	Normal – pregnant	245								61 (24.9)	31 (12.7)	76 (31)
Fife, 1996	PR47	Normal – sexually transmitted diseases	248								33 (13.3)	22 (8.9)	44 (17.7)
Fife, 1996	PR47	Normal – gynaecology	246								28 (11.4)	23 (9.3)	46 (18.7)
Hall, 1996	PR57a	Cytology negative	18								7 (38.9)	0 (0)	7 (38.9)
Hall, 1996	PR57a	Cytology CIN I	20								16 (80)	4 (20)	20 (100)
Hall, 1996	PR57a	Cytology CIN II/III	15								14 (93.3)	0 (0)	14 (93.3)
Hall, 1996	PR57a	Cytology positive–negative histology	22								19 (86.4)	1 (4.5)	20 (90.9)
Hall, 1996	PR57b	Cytology negative	22								6 (27.3)	1 (4.5)	7 (31.8)
Hall, 1996	PR57b	Cytology CIN I	23								20 (87)	2 (8.7)	22 (95.7)
Hall, 1996	PR57b	Cytology CIN II/III	11								6 (54.5)	0 (0)	6 (54.5)
Hall, 1996	PR57b	Cytology positive–negative histology	20								10 (50)	1 (5)	11 (55)
Melbye, 1996	PR83a	Cytology negative, HIV-negative	64								7 (10.9)		
Melbye, 1996	PR83a	Abnormal cytology, HIV-negative	4								2 (50)		
Melbye, 1996	PR83a	Cytology normal, HIV-positive	64								1 (1.6)		
Melbye, 1996	PR83a	Cytology abnormal, HIV-positive	14								14 (100)		
Schneider, 1996	PR159	< CIN II/III	929								41 (4.4)		
Schneider, 1996	PR159	Histology CIN II/III	38								19 (50)		

TS, type specific

continued

TABLE 15d contd *Overall and type-specific prevalence by disease category for studies employing HC-I*

Author, year	Paper	Group	Number	TS 6/11	TS 16	TS 18/45	TS 31	TS 33	TS 30s	TS 50s	High risk	Low risk	Any
Baken, 1995	PR7	Cytology negative	42										21 (50)
Baken, 1995	PR7	SIL on cytology	4										4 (100)
Cox, 1995	PR121	Cytology positive/negative histology	167								43 (25.8)	14 (8.4)	48 (28.8)
Cox, 1995	PR121	Histology CIN I	35								24 (68.6)	8 (22.9)	29 (82.9)
Cox, 1995	PR121	Histology CIN II/III	15								14 (92.3)	2 (13.03)	14 (92.3)
Hatch, 1995	PR124	Cytology positive/negative histology	61								13 (21.3)		
Hatch, 1995	PR124	Histology CIN I	115								55 (47.8)		
Hatch, 1995	PR124	Histology CIN II/III	126								93 (73.8)		
Farthing, 1994	PR43	Cytology positive/negative histology	107								21 (19.6)		
Farthing, 1994	PR43	Histology CIN I	17								10 (58.8)		
Farthing, 1994	PR43	Histology CIN II	16								10 (62.5)		
Farthing, 1994	PR43	Histology CIN III/carcinoma *in situ*	24								20 (83.3)		

TS, type specific

TABLE 15e *Overall and type-specific prevalence by disease category for studies employing HC-II*

Author, year	Paper	Group	Number	TS 6/11	TS 16	TS 18/45	TS 31	TS 33	TS 30s	TS 50s	High risk	Low risk	Any
Clavel, 1999	PR149A	Normal	1203								244 (20.3)		
Clavel, 1999	PR149A	Histology CIN II/III	20								20 (100)		
Cuzick, 1999	PR150Ac	Cytology negative	1644								81 (4.9)		
Cuzick, 1999	PR150Ac	Histology CIN I	38								16 (42)		
Cuzick, 1999	PR150Ac	Histology CIN II	6								5 (83)		
Cuzick, 1999	PR150Ac	Histology CIN III/carcinoma *in situ*	15								15 (100)		
Gurley, 1999	PR141A	≤ CIN I	255								95 (37)		
Gurley, 1999	PR141A	Histology CIN II/III	252								239 (95)		
Hill, 1999	PR153Ab	Cytology negative	2544								458 (18)		
Hill, 1999	PR153Ab	Histology CIN I	95								70 (74)		
Hill, 1999	PR153Ab	Histology CIN II/III	66								57 (86)		
Hill, 1999	PR153Ab	Cancer	12								12 (100)		
Mougin, 1999	PR154A	Cytology negative	422								60 (14.2)	23 (5.4)	
Mougin, 1999	PR154A	ASCUS	37								15 (40.5)	5 (13.5)	
Mougin, 1999	PR154A	Cytology LSIL	96								60 (62.5)	4 (4.2)	
Mougin, 1999	PR154A	Cytology HSIL	38								30 (78.9)	1 (2.6)	
Mougin, 1999	PR154A	Cancer	2								2 (100)		
Sasagawa, 1999	PR142A	Cytology negative	64										5 (7.8)
Sasagawa, 1999	PR142A	LSIL	137										71 (51.8)
Sasagawa, 1999	PR142A	HSIL	101										87 (86.1)
Sasagawa, 1999	PR142A	Cancer	50										39 (78)
Tabrizi, 1999	PR146A	Cytology negative	74								29 (39.2)		
Tabrizi, 1999	PR146A	Cytology low-grade	54								36 (66.7)		
Tabrizi, 1999	PR146A	Cytology high-grade	5								4 (80)		
Womack, 1999	PR140A	Cytology negative	1579								553 (35)		
Womack, 1999	PR140A	Histology CIN I	346								183 (53)		
Womack, 1999	PR140A	Histology CIN II/III	215								174 (81)		
Ferris, 1998	PR46b	Cytology positive–negative histology	150								106 (70.7)		
Ferris, 1998	PR46b	Histology CIN I	71								60 (84.5)		
Ferris, 1998	PR46b	Histology CIN II/III	21								19 (90.5)		
Nindl, 1998	PR156	Histology CIN I	39								28 (72)		
Nindl, 1998	PR156	Histology CIN II	32								30 (94)		
Nindl, 1998	PR156	Histology CIN III/carcinoma in situ	44								42 (95)		

TS, type specific

TABLE 15f *Overall and type-specific prevalence by disease category for studies employing type-specific PCR*

Author, year	Paper	Group	Number	TS 6/11	TS 16	TS 18/45	TS 31	TS 33	TS 30s	TS 50s	High risk	Low risk	Any
Sun, 1997	PR136	Normal	231			13 (5.6)				16 (6.9)	67 (29)	12 (5.2)	103 (44.6)
Chang, 1997	PR17a	Cytology negative, negative pathology	72	28 (38.9)	17 (23.6)	12 (16.7)	5 (6.9)						
Chang, 1997	PR17a	Low-grade squamous intraepithelial lesion pathology	55	28 (50.9)	38 (69.1)	20 (36.4)	8 (14.5)						
Chang, 1997	PR17a	Histology CIN II/III	53	14 (26.4)	34 (64.2)	14 (26.4)	8 (15.1)						
Chang, 1997	PR17a	Histology cancer	47	5 (10.6)	31 (66)	10 (21.3)	5 (10.6)						
Chang, 1997	PR17b	Cytology negative, negative pathology	72	21 (29.2)	6 (8.3)	10 (13.9)	1 (1.4)						
Chang, 1997	PR17b	Low-grade squamous intraepithelial lesion pathology	55	12 (21.8)	6 (10.9)	18 (32.7)	2 (3.6)						
Chang, 1997	PR17b	Histology CIN II/III	53	8 (15.1)	14 (26.4)	12 (22.6)	2 (3.8)						
Chang, 1997	PR17b	Histology cancer	47	5 (10.6)	27 (57.4)	10 (21.3)	4 (8.5)						
Hernandez-Avila, 1997	PR59	Normal	204		27 (13.2)	0 (0)							
Hernandez-Avila, 1997	PR59	Histology CIN III/carcinoma *in situ*	60		29 (48.3)	0 (0)							
Hernandez-Avila, 1997	PR59	Histology cancer	88		43 (48.9)	10 (11.4)							
Wheeler, 1996	PR115	Normal	72										26 (36.1)
Londesborough, 1996	NH65	Histology CIN I	194		19 (9.8)	7 (3.6)	24 (12.4)	8 (4.1)			50 (26)		
Londesborough, 1996	NH65	Histology CIN II/III	64		45 (70.3)	9 (14.1)	35 (54.7)	13 (20.3)			48 (75)		
Moscicki, 1996	PR88	Normal	2300										483 (21)
Cuzick, 1995	PR122	Histology CIN II/III	81		36 (44.4)	8 (9.9)	20 (24.7)	7 (8.6)			61 (75.3)		
Cuzick, 1995	PR122	≤ CIN I	1904		30 (1.6)	16 (0.8)	26 (1.4)	15 (0.8)			85 (4.5)		
Saito, 1995	PR103	Cytology negative	800								53 (6.6)		
Saito, 1995	PR103	Histology CIN I	34		5 (14.7)	1 (2.9)					6 (17.6)		
Saito, 1995	PR103	Histology CIN II	26		7 (26.9)	1 (3.8)					8 (30.8)		
Saito, 1995	PR103	Histology CIN III/carcinoma *in situ*	32		10 (31.3)	2 (6.3)					12 (37.5)		
Saito, 1995	PR103	Histology cancer	46		15 (32.6)	7 (15.2)					22 (47.8)		
Saito, 1995	PR103	Histology negative, but pregnant	170								23 (13.5)		

TS, type specific

continued

TABLE 15f contd *Overall and type-specific prevalence by disease category for studies employing type-specific PCR*

Author, year	Paper	Group	Number	TS 6/11	TS 16	TS 18/45	TS 31	TS 33	TS 30s	TS 50s	High risk	Low risk	Any
Burger, 1995	PR12	Cytology positive–negative histology	34	1 (2.9)	6 (17.6)	5 (14.7)	0 (0)	2 (5.9)					12 (35.3)
Burger, 1995	PR12	Histology CIN I	32	1 (3.1)	5 (15.6)	6 (18.8)	0 (0)	2 (6.3)					14 (43.8)
Burger, 1995	PR12	Histology CIN II	39	1 (2.6)	12 (30.8)	3 (7.7)	6 (15.4)	2 (5.1)					27 (69.2)
Burger, 1995	PR12	Histology CIN III/carcinoma *in situ*	49	1 (2)	29 (59.2)	4 (8.2)	6 (12.2)	4 (8.2)					42 (85.7)
Burger, 1995	PR12	Histology cancer	3	0 (0)	2 (66.7)	0 (0)	0 (0)	0 (0)					3 (100)
Cuzick, 1994	PR29	Cytology positive–negative histology	36		2 (5.6)	3 (8.3)	1 (2.8)	2 (5.6)					
Cuzick, 1994	PR29	Histology CIN I	24		1 (4.2)	0 (0)	5 (20.8)	3 (12.5)					
Cuzick, 1994	PR29	Histology CIN II	12		3 (25)	2 (16.7)	0 (0)	4 (33.3)					
Cuzick, 1994	PR29	Histology CIN III/carcinoma *in situ*	61		36 (59)	4 (6.6)	14 (23)	7 (11.5)					
Fairley, 1994	PR42	Normal	298										92 (30.9)
Vandenvelde, 1993	PR113	Cytology negative	323		20 (6.2)	8 (2.5)		26 (8)					
Coker, 1993	PR24	Cytology negative	223	4 (1.8)							6 (2.7)		
Coker, 1993	PR24	Histology CIN I	114	3 (2.6)							28 (24.6)		
Coker, 1993	PR24	Histology CIN II/III	28	0 (0)							10 (35.7)		
Coker, 1993	PR24	Atypia	115	4 (3.5)							7 (6.1)		
Coker, 1993	PR24	Infection or inflammation	140	3 (2.1)							15 (10.7)		
Aziz, 1993	PR4	Histology CIN I	22	4 (18.2)	10 (45.5)	1 (4.5)			5 (22.7)				
Aziz, 1993	PR4	Histology CIN II	14	0 (0)	6 (42.8)	1 (7.1)			2 (6.5)				
Aziz, 1993	PR4	Histology CIN III/carcinoma *in situ*	17	2 (11.8)	16 (94.1)	4 (23.5)			0 (0)				
Aziz, 1993	PR4	Histology cancer	7	1 (14.3)	4 (57.1)	1 (14.3)			1 (14.3)				
Bavin, 1993	PR127a	Cytology positive–negative histology (positive)	54		34 (63)								
Bavin, 1993	PR127a	Histology CIN I (positive)	59		29 (49)								
Bavin, 1993	PR127a	Histology CIN II (positive)	31		20 (64)								
Bavin, 1993	PR127a	Histology CIN III/carcinoma *in situ* (positive)	35		26 (74)								
Bavin, 1993	PR127b	Cytology positive–negative histology (high level)	54		17 (31)								
Bavin, 1993	PR127b	Histology CIN I (high level)	59		12 (20)								
Bavin, 1993	PR127b	Histology CIN II (high level)	31		15 (48)								
Bavin, 1993	PR127b	Histology CIN III/carcinoma *in situ* (high level)	35		23 (66)								
Jullian, 1993	PR64	Cytology negative	120		5 (4.2)	0 (0)							

TS, type specific

continued

TABLE 15f contd *Overall and type-specific prevalence by disease category for studies employing type-specific PCR*

Author, year	Paper	Group	Number	TS 6/11	TS 16	TS 18/45	TS 31	TS 33	TS 30s	TS 50s	High risk	Low risk	Any
Kjaer, 1993	PR69a	Normal	126	4 (3.2)	31 (24.6)	25 (19.8)		11 (8.7)					
Kjaer, 1993	PR69b	Normal	129	8 (6.2)	26 (20.2)	19 (14.7)		12 (9.3)					
Cuzick, 1992	PR27	Cytology positive–negative histology	34		2 (5.9)								
Cuzick, 1992	PR27	Histology CIN I	6		0 (0)								
Cuzick, 1992	PR27	Histology CIN II	7		1 (14.3)								
Cuzick, 1992	PR27	Histology CIN III/carcinoma *in situ*	38		24 (63.2)								
Bavin, 1992	PR9	Normal	471		74 (15.7)								
Bavin, 1992	PR9	Cytology positive–negative histology	14		1 (7.1)								
Bavin, 1992	PR9	Histology CIN I	16		2 (12.5)								
Bavin, 1992	PR9	Histology CIN II	8		4 (50)								
Bavin, 1992	PR9	Histology CIN III/carcinoma *in situ*	5		4 (80)								
Nakazawa, 1992	PR91	Cytology positive–negative histology	69		7 (10.1)	5 (7.2)							11 (15.9)
Nakazawa, 1992	PR91	Histology CIN I	17		2 (11.8)	3 (17.6)							5 (29.4)
Nakazawa, 1992	PR91	Histology CIN II	13		2 (15.4)	0 (0)							2 (15.4)
Nakazawa, 1992	PR91	Histology CIN III/carcinoma *in situ*	37		9 (24.3)	1 (2.7)							10 (27)
Nakazawa, 1992	PR91	Histology cancer	30		8 (26.7)	4 (13.3)							11 (36.7)
Nakazawa, 1992	PR91	Condyloma	3		0 (0)	0 (0)							0 (0)
Pasetto, 1992	PR96	Cytology negative	148		12 (8.1)								
Pasetto, 1992	PR96	Cytology positive–negative histology	15		0 (0)								
Pasetto, 1992	PR96	Histology CIN I	30		8 (26.7)								
Pasetto, 1992	PR96	Histology CIN II/III	27		15 (55.6)								
Pasetto, 1992	PR96	Histology cancer	5		2 (40)								
Nishikawa, 1991	PR93	Cytology negative	83		5 (6)	0 (0)		0 (0)					
Nishikawa, 1991	PR93	Cytology negative – non-pregnant	52		2 (3.8)								
Nishikawa, 1991	PR93	Cytology negative – pregnant	51		3 (5.9)								
Burmer, 1990	PR14	Normal	270	40 (14.8)							110 (40.7)		134 (49.6)
Burmer, 1990	PR14	Cytology negative	67	5 (7.5)							14 (20.9)		15 (22.4)
Burmer, 1990	PR14	Cytology CIN I	105	22 (21)							53 (50.5)		69 (65.7)
Burmer, 1990	PR14	Cytology CIN II/III	39	5 (12.8)							26 (66.7)		27 (69.2)
Burmer, 1990	PR14	Cytology indefinite	59	8 (13.6)							17 (28.8)		23 (39)
Pao, 1990	PR95	Cytology negative	102	3 (2.9)	4 (3.9)	7 (6.9)		2 (2)					43 (42.2)
Pao, 1990	PR95	Histology CIN III/carcinoma *in situ*	12	2 (16.7)	6 (50)	6 (50)							12 (100)

TS, type specific

TABLE 16a *Positivity by age in 'normal' populations for studies employing MY09/11*

Author, year	Paper	Group	Age group (years)	Number	TS 6/11	TS 16	TS 18/45	TS 31	TS 33	TS 30s	TS 50s	High risk	Low risk	Any
Kotloff, 1998	PR72	Other	< 20	74										24 (32.4)
Kotloff, 1998	PR72	Other	20–24	260										97 (37.3)
Kotloff, 1998	PR72	Other	25–29	53										10 (18.9)
Kotloff, 1998	PR72	Other	30+	27										7 (25.9)
Grce, 1997	PR54	Other	< 20	41	11 (26.8)	4 (9.8)	2 (4.9)	5 (12.2)	2 (4.9)					28 (68.3)
Grce, 1997	PR54	Other	21–30	208	17 (8.2)	19 (9.1)	2 (1)	17 (8.2)	6 (2.9)					86 (41.3)
Grce, 1997	PR54	Other	31–40	63	7 (11.1)	3 (4.8)	1 (1.6)	5 (7.9)	1 (1.6)					21 (33.3)
Grce, 1997	PR54	Other	41–50	48	4 (8.3)	5 (10.4)	0 (0)	1 (2.1)	2 (4.2)					16 (33.3)
Grce, 1997	PR54	Other	> 51	19	3 (15.8)	2 (10.5)	3 (15.8)	1 (5.3)	0 (0)					12 (63.2)
Kalantari, 1997	PR65	Other	≤ 24	215	34 (16)	26 (12)	34 (16)	26 (12)	32 (15)			125 (58)		189 (88)
Kalantari, 1997	PR65	Other	25–34	182	22 (12)	29 (16)	9 (5)	15 (8)	42 (23)			95 (52)		149 (82)
Kalantari, 1997	PR65	Other	35–44	37	2 (6)	5 (14)	4 (10)	8 (22)	7 (20)			24 (66)		32 (86)
Kalantari, 1997	PR65	Other	45–54	33	4 (11)	2 (5)	10 (29)	7 (20)	2 (5)			19 (59)		27 (81)
Kalantari, 1997	PR65	Other	55–64	8	0 (0)	3 (37.5)			3 (37.5)					7 (88)
Kalantari, 1997	PR65	Other	65–74	1	0 (0)									1 (100)
Gjooen, 1996	PR50	Not pregnant	20–24	13										3 (23.1)
Gjooen, 1996	PR50	Not pregnant	25–29	65										15 (23.1)
Gjooen, 1996	PR50	Not pregnant	30–34	69										9 (13)
Gjooen, 1996	PR50	Not pregnant	35–39	48										4 (8.3)
Gjooen, 1996	PR50	Not pregnant	40–45	27										3 (11.1)
Baken, 1995	PR7	Any site	≤ 25	25										21 (84)
Baken, 1995	PR7	Any site	> 25	25										15 (60)
Evander, 1992	PR39a	Other	19	69										1 (1.4)
Evander, 1992	PR39a	Other	21	158										6 (3.8)
Evander, 1992	PR39a	Other	23	221										15 (6.8)
Evander, 1992	PR39a	Other	25	140										13 (9.3)
Evander, 1992	PR39b	Other	19	69										12 (17.4)
Evander, 1992	PR39b	Other	21	158										24 (15.2)
Evander, 1992	PR39b	Other	23	218										39 (17.9)
Evander, 1992	PR39b	Other	25	135										43 (31.9)
Ley, 1991	PR77	Other	17–19	79										38 (48.1)
Ley, 1991	PR77	Other	20–21	135										59 (43.7)
Ley, 1991	PR77	Other	22–23	93										51 (54.8)
Ley, 1991	PR77	Other	24–25	58										30 (51.7)
Ley, 1991	PR77	Other	26–29	77										27 (35.1)
Ley, 1991	PR77	Other	30–50	25										8 (32)

TS, type specific

TABLE 16b *Positivity by age in 'normal' populations for studies employing GP5/6 or GP5+/6+*

Author, year	Paper	Group	Age group (years)	Number	TS 6/11	TS 16	TS 18/45	TS 31	TS 33	TS 30s	TS 50s	High risk	Low risk	Any
Kjaer, 1997	PR70	Cytology negative	20–23	288										56 (19.4)
Kjaer, 1997	PR70	Cytology negative	24–26	311										44 (14.1)
Kjaer, 1997	PR70	Cytology negative	27–29	357										47 (13.2)
de Roda Husman, 1995	PR32	Not pregnant	15–19	169								7 (4.1)		29 (17.2)
de Roda Husman, 1995	PR32	Not pregnant	20–24	486								31 (6.4)		101 (20.8)
de Roda Husman, 1995	PR32	Not pregnant	25–29	775								27 (3.5)		106 (13.7)
de Roda Husman, 1995	PR32	Not pregnant	30–34	890								26 (2.9)		86 (9.7)
de Roda Husman, 1995	PR32	Not pregnant	35–39	734								16 (2.2)		50 (6.8)
de Roda Husman, 1995	PR32	Not pregnant	40–49	894								9 (1)		60 (6.7)
Melkert, 1993	PR85a	Cytology negative	< 35	156								6 (3.8)		22 (14.1)
Melkert, 1993	PR85a	Cytology negative routine	35–55	1555								14 (0.9)		65 (4.2)
Melkert, 1993	PR85b	Cytology negative	< 35	2320								91 (3.9)		322 (13.9)
Melkert, 1993	PR85b	Cytology negative gynaecology	35–55	1826								27 (1.5)		120 (6.6)

TS, type specific

TABLE 16c *Positivity by age in 'normal' populations for studies employing other consensus PCR*

Author, year	Paper	Group	Age group (years)	Number	TS 6/11	TS 16	TS 18/45	TS 31	TS 33	TS 30s	TS 50s	High risk	Low risk	Any
Sasagawa, 1997	PR104	Cytology negative	≤ 24	102										5 (4.9)
Sasagawa, 1997	PR104	Cytology negative	25–34	260										10 (3.8)
Sasagawa, 1997	PR104	Cytology negative	35–44	141										6 (4.3)
Sasagawa, 1997	PR104	Cytology negative	45–54	151										8 (5.3)
Sasagawa, 1997	PR104	Cytology negative	55+	124										6 (4.8)

TS, type specific

TABLE 16d *Positivity by age in 'normal' populations for studies employing HC-I*

Author, year	Paper	Group	Age group (years)	Number	TS 6/11	TS 16	TS 18/45	TS 31	TS 33	TS 30s	TS 50s	High risk	Low risk	Any
Clavel, 1998	PR23	Other	< 20	50								6 (12)	0 (0)	6 (12)
Clavel, 1998	PR23	Other	20–29	220								42 (19.1)	6 (2.7)	48 (21.8)
Clavel, 1998	PR23	Other	30–39	310								26 (8.4)	6 (1.9)	32 (10.3)
Clavel, 1998	PR23	Other	40–49	261								11 (4.2)	6 (2.3)	17 (6.5)
Clavel, 1998	PR23	Other	50–59	102								4 (3.9)	1 (1)	5 (4.9)
Clavel, 1998	PR23	Other	> 60	35								1 (2.9)	0 (0)	1 (2.9)
Schneider, 1996	PR159	Other	< 20	40								2 (5)		
Schneider, 1996	PR159	Other	20–24	123								15 (12)		
Schneider, 1996	PR159	Other	25–29	152								16 (10.5)		
Schneider, 1996	PR159	Other	30–34	129								11 (8.3)		
Schneider, 1996	PR159	Other	35–39	135								8 (5.8)		
Schneider, 1996	PR159	Other	40–44	119								1 (0.8)		
Schneider, 1996	PR159	Other	45–49	85								1 (1.2)		
Schneider, 1996	PR159	Other	50–54	98								6 (6)		
Schneider, 1996	PR159	Other	55+	86								2 (2.2)		
Baken, 1995	PR7	Any site	≤ 25	25										21 (84)
Baken, 1995	PR7	Any site	> 25	25										15 (60)

TS, type specific

TABLE 16e *Positivity by age in 'normal' populations for studies employing HC-II*

Author, year	Paper	Group	Age group (years)	Number	TS 6/11	TS 16	TS 18/45	TS 31	TS 33	TS 30s	TS 50s	High risk	Low risk	Any
Schneider, 1996	PR159	Other	< 20	40								2 (5)		
Schneider, 1996	PR159	Other	20–24	123								15 (12)		
Schneider, 1996	PR159	Other	25–29	152								16 (10.5)		
Schneider, 1996	PR159	Other	30–34	129								11 (8.3)		
Schneider, 1996	PR159	Other	35–39	135								8 (5.8)		
Schneider, 1996	PR159	Other	40–44	119								1 (0.8)		
Schneider, 1996	PR159	Other	45–49	85								1 (1.2)		
Schneider, 1996	PR159	Other	50–54	98								6 (6)		
Schneider, 1996	PR159	Other	55+	86								2 (2.2)		
Baken, 1995	PR7	Any site	≤ 25	25										21 (84)
Baken, 1995	PR7	Any site	> 25	25										15 (60)

TS, type specific

TABLE 16f *Positivity by age in 'normal' populations for studies employing type-specific PCR*

Author, year	Paper	Group	Age group (years)	Number	TS 6/11	TS 16	TS 18/45	TS 31	TS 33	TS 30s	TS 50s	High risk	Low risk	Any
Burk, 1996	PR13	Normal	< 25	119										40 (33.6)
Burk, 1996	PR13	Normal	25–29	93										23 (24.7)
Burk, 1996	PR13	Normal	30–34	83										13 (15.7)
Burk, 1996	PR13	Normal	35–39	66										6 (9.1)
Burk, 1996	PR13	Normal	40–44	42										4 (9.5)
Burk, 1996	PR13	Normal	45–50	36										1 (2.8)
Gradilone, 1996	PR52	Cytology negative	17–25	48		11 (22.9)	1 (2.1)							
Gradilone, 1996	PR52	Cytology normal	26–35	30		3 (10)	1 (3.3)							
Gradilone, 1996	PR52	Cytology normal	36–50	32		2 (6.3)	1 (3.1)							
Gradilone, 1996	PR52	Cytology normal	51–70	33		1 (3)	0 (0)							
Moscicki, 1996	PR88	Other	13	38								5 (13.2)	3 (7.9)	7 (18.4)
Moscicki, 1996	PR88	Other	14	121								23 (19)	2 (1.7)	24 (19.8)
Moscicki, 1996	PR88	Other	15	242								34 (14)	10 (4.1)	44 (18.2)
Moscicki, 1996	PR88	Other	16	333								40 (12)	27 (8.1)	53 (15.9)
Moscicki, 1996	PR88	Other	17	440								66 (15)	26 (5.9)	79 (18)
Moscicki, 1996	PR88	Other	18	479								96 (20)	38 (7.9)	115 (24)
Moscicki, 1996	PR88	Other	19	591								100 (16.9)	47 (8)	130 (22)
Moscicki, 1996	PR88	Other	20	51								9 (17.6)	4 (7.8)	13 (25.5)
Fairley, 1994	PR42	Other	20	27										11 (40.7)
Fairley, 1994	PR42	Other	21–25	81										30 (37)
Fairley, 1994	PR42	Other	26–30	108										34 (31.5)
Fairley, 1994	PR42	Other	31–35	74										18 (24.3)
Coker, 1993	PR24	Other	< 25	366										
Coker, 1993	PR24	Other	≥ 25	254										
Kjaer, 1993	PR69a	Other	20–24	32		8 (25)								
Kjaer, 1993	PR69a	Other	25–29	26		8 (30.8)								
Kjaer, 1993	PR69a	Other	30–34	34		8 (23.5)								
Kjaer, 1993	PR69a	Other	35–39	34		7 (20.6)								
Kjaer, 1993	PR69b	Other	20–24	43		11 (25.6)								
Kjaer, 1993	PR69b	Other	25–29	35		5 (14.3)								
Kjaer, 1993	PR69b	Other	30–34	32		4 (12.5)								
Kjaer, 1993	PR69b	Other	35–39	19		6 (31.6)								
Morrison, 1991	PR87	Cytology negative	< 25	26										14 (53.8)
Morrison, 1991	PR87	Cytology negative	25–34	23										7 (30.4)
Morrison, 1991	PR87	Cytology negative	35+	10										2 (20)
Morrison, 1991	PR87	Histology squamous intraepithelial lesion	< 25	23										20 (87)
Morrison, 1991	PR87	Histology squamous intraepithelial lesion	25–34	26										23 (88.5)
Morrison, 1991	PR87	Histology squamous intraepithelial lesion	35+	16										12 (75)

TS, type specific

TABLE 17 *Ongoing or unpublished studies of HPV testing*

Principal investigators	Location	Population	Approximate size	Investigations	Outcomes	Status
Meijers/ Walboomers[a]	Netherlands	Women with borderline/ mild smears	353	HPV with GP5+/6+ Persistence of HPV	CIN III	Submitted for publication
Cuzick[a]	London, UK	Routine screening Age 34–65 years	2988	HPV with MY09/11 HC-I and HC-II	High-grade CIN	Submitted for publication
Manos/Kinney	N. California	Women with ASCUS smears	1000 ASCUS smears from 46,000 screened women	HPV with HC-II	HSIL	Submitted for publication
Schiffman	Guanacaste, Costa Rica	Routine screening	9175	HC Cytology, Cervigram Papnet	High-grade CIN and cancer	Completed
Ratnam/ Ferenczy[a]	Newfoundland	Routine screening Age 25–49 years	2100	HPV by HC-II	High-grade CIN	Completed
Schiffman	USA (ASCUS/LSIL Triage Study)	Women with ALTS ASCUS/mild smears (mild dropped)	1500 ASCUS smears from 40,000 screened	HPV with HC-II Cervicography Liquid cytology	CIN	Ongoing
Cuzick	UK	Routine smears Age 30–60 years	12,000	HPV with HC-II	High-grade CIN Persistence of HPV	Ongoing
Schneider	Jena, Germany	Screening Age 18–70 years	5000+	HPV by GP5/6 Colposcopy and cytology	High-grade CIN	Ongoing
Franco/Villa	Sao Paulo	Long-term follow-up study since 1993	~900	HPV MY09/11	Persistence HSIL	Ongoing
Moscicki	San Francisco	Young sexually active cohort	900	HPV	Development of CIN and HPV	Ongoing
Dillner	Sweden	Screening Age 32–38 years	10,000	HPV randomised	Viral persistence CIN	Ongoing
Meijers/ Walboomers	Netherlands	Routine screening	44,000	HPV GP5+/6+		Pilot
Syrjanen	Russia	Routine screening	13,000	HPV by GP5/6 and HC-II		Advanced planning
Hakama	Finland/ Nordic (?)		~100,000	HPV and other new technologies		Planning
Iffner/Petri	Germany	Routine screening Age 30–60 years	4000	HPV by HC-II	High-grade CIN	About to start
Jenkins/Little	UK Tombola	Mild cytological abnormalities				Advanced planning

[a] *For papers published or received since report first submitted, see end of appendix 3*

TABLE 18 *Direct comparisons of HPV with cytology*

Author	HPV method	Sensitivity for HSIL		Specificity for HSIL		Comments
		Cytology ≥ LSIL	HPV	Cytology < LSIL	HPV	
Reid 1991	SB	52	55	92.3	95.8	
Cuzick 1995	TS PCR	46	75	96.4	95.5	Only HPV 16, 18, 31, 33
Schneider 1996	HC	29	50	96	96	
Ratnam 1999	HC	37.9	86.2	95.6	91.9	
Womack 140a	HC-II(HR)	44	81	NA	62	Zimbabwe – high HIV rate
Gurley 141A	HC-II(HR)	50	95	NA	37	
Clavel 149A[a]	HC	75	97.4	97.3	86.4	
Cuzick 150A	HC-II(HR)	79	95.2	98.7	95.1	Age ≥ 35 years
Schiffman 1999	HC-II	75.2	89.6	96.5	89.1	

[a] *For papers published or received since report first submitted, see end of appendix 3*

Chapter 7

Assessing effectiveness, costs and cost-effectiveness of cervical cancer screening and HPV testing

Introduction

A proper economic assessment of the introduction of HPV testing in cervical cancer screening would bring together data on costs of screening and follow-up, and estimates of effectiveness in reducing mortality and morbidity from cervical cancer. Estimates of effectiveness would use data on the numbers of cases detected (by CIN/invasive cancer category). Since the wider objective is health benefits (and not cases detected), it is necessary to use modelling techniques to estimate effects of detecting and treating more cases on survival and morbidity, and also to look at the potentially harmful consequences of additional anxiety and treatment. There are several possible contexts within which HPV testing could be introduced as a primary screening test. The economic evaluation should therefore compare these in terms of how each contributes health benefits and at what cost. The most likely options are HPV testing alongside the current cytology programmes, HPV testing in combination with new or amended models of cytology screening, and HPV with no cytology screening. In principle, any role for HPV testing in reducing the burden of cervical cancer should be compared with other prevention or treatment strategies, such as better quality control in cytology screening or primary prevention strategies. However, in this review the focus is only on screening and secondary prevention, and the use of HPV testing to supplement or partly to replace cytology-based screening and follow-up care. Modelling is used to inform possible changes in cervical screening programmes and is based on our current understanding of the role of HPV in the development of CIN and invasive cervical cancer.

In this review, some different strategies for the use of HPV testing have been compared, based on the best assessments of the performance of tests, prevalence of the virus, likely numbers of cases progressing to preinvasive or invasive cancers and effects on survival. In doing this it has been possible to identify the likely range within which the cost-effectiveness of HPV testing lies, but, perhaps more importantly, it has helped to identify areas where the research evidence is inadequate.

As with any intervention that aims to extend life and improve health-related quality of life, the measurement of outcome should take both these dimensions into account. However, no studies have provided data on quality of life in the context of cervical cancer from which quality-adjusted life-years (QALYs) could reliably be calculated. Given this constraint, the appropriate main outcome measure for assessing the cost-effectiveness of HPV testing is the cost per year of life gained. A proxy for this might be cancers and premature deaths prevented, although factors such as age and other morbidity must then be taken into account. But it is important also to identify (if not measure) some of the factors that might affect the quality of life of patients and their experiences, such as false-positive rates in screening, experience of treatment and side-effects of preventable disease, and the extent of treatment of non-life-threatening disease.

The economic context

A review of the cost and activity of the cervical cytology programme in the NHS (Havelock, 1994) found that the major cost is of screening itself, that is, taking and processing the smear. The cost of inviting the women for testing and making a diagnosis using colposcopy and histology is relatively small by comparison. It is likely that this will also be true of HPV testing since the step-wise increase in cost will be where an increase in activity requires the addition of further laboratory staff or laboratory capacity with the purchase of new equipment.

The precise effect will, however, depend on the ability of HPV testing (as implemented within the screening programme) to reduce the incidence of and mortality from cervical cancer. The more effective the screening activity, the more disease is diagnosed and treated. When this results in

prevention of invasive cancer, the cost of its treatment including hospitalisation and surgery or radiotherapy will be saved. The more efficient the screening activity, the fewer women will be treated unnecessarily for disease that would not progress or would even regress in the absence of treatment. The balance between the rate of identifying and successfully treating preinvasive disease, and the appropriateness of the screening programme combined with the cost of the programme will determine its cost-effectiveness.

The value of such a programme within health services will depend on the relative cost-effectiveness when compared with alternative means for reducing mortality and morbidity from cervical cancer – such as by improving compliance in an existing programme.

Cost-effectiveness analysis has been performed by combining predictions for a number of parameters with estimates of the costs involved. For cervical screening, these parameters include the numbers of cases detected at each screening round, the sensitivity of the test, the period during which the cancer is non-symptomatic yet detectable through screening (the test-specific sojourn time) and the incidence of the disease in the community. (The incidence should be the incidence that would exist had there been no previous screening, unless one is only interested in the added benefit of an addition to the screening programme). As discussed above, an appropriate outcome measure is the cost per life gained. Once these parameters are known or estimated, an efficiency curve can be constructed. This assesses the relationship between the cost in currency or resources used against the gain in terms of life-years gained as the intensity of screening is increased.

A number of authors have shown that the curve for cervical screening rises slowly at first and then has a steep slope as the incremental costs of intensifying the screening programme rise faster than the health benefits accrue. This is explained by the relatively high sensitivity of the smear test and the long sojourn time of the disease, rendering frequent screening unnecessary. For cervical screening, the marginal or incremental costs rise rapidly after the screening interval is reduced beyond 4 years. The costs and benefits that will influence the impact of HPV testing on the shape of the efficiency curve are set out in *Box 1*. They could be applied to each of three possible approaches suggested in the literature for integrating HPV testing within cervical cancer screening. These are:

BOX 1 Costs and benefits affecting the efficiency of HPV testing

Costs
- Cost of collecting specimens and laboratory tests
- Costs of follow-up of HPV-positive non-symptomatic women
- Costs or earlier treatment for HPV-positive non-symptomatic women

Benefits
- Reduced morbidity and mortality from cervical cancer
- Less treatment of self-limiting and non-life-threatening disease
- Reduced costs of Pap smears and cytology

(1) addition of HPV testing to cytology to improve the sensitivity of the programme for detecting preinvasive cancer
(2) use of HPV testing as an alternative to cytology
(3) for managing minor cytological abnormalities and improving the specificity of the programme.

Psychological and social dimensions of the costs and benefits of HPV testing

An issue common to all screening programmes is the effect of information about risk and diseases status, especially for those who would not suffer any adverse effects (in the absence of screening). Since only a small minority of those found to have abnormal smears will develop significant disease, there will always be more 'worried well' than people who benefit. On the other hand, to an extent the benefit of screening is that it provides reassurance to those who test negative.

In the case of HPV testing there are some additional issues. Again, only a minority of those who test positive for HPV are likely to develop clinically significant disease, so that many well women will be 'labelled'. In addition, there is the problem that some stigma may be attached to testing positive for HPV since the virus is normally transmitted sexually. This could have important implications for the use of HPV in screening, since some people may be discouraged from undergoing screening, and those deterred may be at high risk. It is not clear how people would react to the information that they are infected with a virus thought to be associated with a potentially life-threatening disease, and how this compares to the reaction to knowledge that they have an abnormal result on a smear test.

The literature search found no studies addressing these questions in the context of HPV testing, although some literature exists in other settings dealing with broadly similar issues (e.g. the effects of being told that you have a sexually transmitted disease). Given the importance of understanding the positive or negative effects of these psychological and social issues on the uptake of screening, and the best ways to ensure that harm and distress within any programme are minimised, research on the effects of this information, and on ways of minimising harm, is needed before any overall assessment of the effects of HPV screening can be carried out.

The psychological impact of an HPV result, be it positive or negative, can only be fully evaluated in the context of HPV testing being an accepted routine screening procedure. Psychological studies conducted as part of trials can be informative, but will always reflect the artificial context of the trial where written informed consent to an experimental test can interfere with its perceived value.

Modelling studies of effectiveness and cost-effectiveness in cervical cancer screening

In cases where the available research provides evidence only of short-term outcomes and costs, modelling is used to derive the best estimates of the overall costs and benefits (Habbema *et al.,* 1985; Parkin 1985; Buxton *et al.,* 1997; van Ballegooijen *et al.,* 1997). Pidd (1996) defined a model as 'an external and explicit representation of part of reality as seen by the people who wish to use that model to understand, to change, to manage and to control that part of reality'. In cancer screening, mathematical modelling is used frequently, since the benefits and consequences for costs of care may occur many years after the screening takes place. Two major uses of mathematical models in cancer screening are for data analysis and evaluation. Data analysis models are used to test hypotheses about the natural history of the disease, screening tests and the association between early detection and risk of dying from the cancer. Evaluation modelling is used to estimate the effects and cost-effectiveness of screening and to identify optimal screening policies. The modelling articles reviewed in this study are restricted to the category of evaluation and prediction models. An overview of data analysis models is given by Prorok (1986).

Randomised controlled trials potentially give unbiased estimates of the effects of screening. They avoid the biases in case–control studies, and, where feasible, are the preferred type of study. However, it can take many years for the final differences between both groups become clear. Randomised controlled trials have never been conducted on cervical cancer screening, and would not now be considered ethical. The available evidence on mortality reduction from cervical cancer screening was obtained by less powerful methods. Furthermore, for optimisation of screening, randomised controlled trials are not suitable as a large number of strategies have to be compared with each other, not simply the two situations with and without screening. Using mathematical models can be an appropriate way to evaluate alternative strategies by extending the knowledge from empirical studies to other screening situations. Models combine information about natural history and screening tests obtained from a number of different sources with other relevant demographic and epidemiological characteristics of the population under study.

The modelling approach does have limitations. The natural history of cervical cancer is not completely understood, particularly concerning the asymptomatic, preclinical stage, which is the main focus of screening. There are several different hypothesised forms of the course of the disease which are plausible given the available data. This is an example of model uncertainty. Uncertainty about the true values of the demographic, epidemiological and screening characteristics is known as parameter uncertainty.

The papers relating to modelling are listed at the end of this chapter. The articles included in the review are discussed in terms of general modelling aspects, model structure and input, and model output.

Modelling aspects

Types of model

A possible classification of models used for evaluation and prediction is suggested by Bross *et al.* (1968). They distinguished two types: surface models and deep models. Surface models consider only events that can be directly observed, such as clinical incidence, prevalence and mortality. In deep models, assumptions about the natural history of the disease and the screening test are incorporated. In this case, explicit formulation of the model is often impossible, and only evaluation by simulation is possible.

The IARC working group on the evaluation of cervical cancer screening programmes compared

the effects of several screening policies by a relatively simple formula (a surface model). The cumulative incidence among unscreened women was related to incidence by time elapsed since the last negative smear for women with two or more previous negative smears (IARC, 1986). Other instances of surface models are the age-period multiplicative model used by Hristova and Hakema (1997) and the regression model used by Forsmo *et al.* (1997). Also, the articles of Chesebro and Everett (1996), Waugh and Robertson (1996), and Waugh *et al.* (1996) may be categorised as surface models, but these add some assumptions, for example the percentage of women with preclinical invasive disease who will develop invasive cervical cancer and the effects of screening.

A deep model including the mean duration of dysplasia and carcinoma *in situ* and a false-negative rate for the screening test was used by Knox (1976) to calculate the best ages for carrying out cervical cancer screening. This model gives an intuitive and transparent view on the influence of two highly important and uncertain parameters on the effects of screening. In the other studies, more detailed and comprehensive models have been designed, resulting in complex computations.

Study perspective

Studies differ in perspective: some studies concern a cohort of women, other studies use a population perspective. Population models, used by, among others, Habbema *et al.* (1985), Hristova and Hakema (1997), Koopmanschap *et al.* (1990a,b), Parkin (1985), and Parkin and Moss (1986), estimate the effects of screening in a calendar period. In this period, several birth cohorts with differing lifetime risks of getting cervical cancer will participate in (part of) the screening programme. Cohort model do not use a fixed calendar period, and most of them assume that all women are at the same risk of getting cervical cancer during their lifetime. Examples of studies using a cohort perspective are those of Bethwaite *et al.* (1986), Eddy (1990) and Fahs *et al.* (1992). Also, Gustafsson and Adami (1990) used a cohort model, but repeated their calculations for different cohorts with different lifetime risk of getting cervical cancer.

Results from cohort and population models can therefore not be compared directly.

Discounting

Time preferences for having money and material goods sooner rather than later can be accounted for by discounting future costs to present value. There has been some controversy over appropriate rates and application of discounting (Cairns, 1992; Parsonage and Neuberger, 1992; Sheldon, 1992), but it is now generally agreed that future costs and health effects should be discounted at the same rate. The importance of using a uniform discount rate for the comparability of cost-effectiveness analyses was illustrated by Koopmanschap (1990a). The recommended rate for public sector project in the UK is currently 6%, although it has been variously set at higher and lower rates in the past. Recently, the Panel on Cost-Effectiveness in Health and Medicine proposed a discount rate of 3% (Weinstein *et al.,* 1996). This percentage reflects the rate of return on riskless, long-term securities. Discount rates used in the literature vary from zero (no discounting) (Knox, 1973, 1976; Yu *et al.,* 1982; Parkin, 1985, 1986; Bethwaite *et al.,* 1986; IARC, 1986; Gustafsson and Adami, 1990, 1992; Sherlaw-Johnson *et al.,* 1994, 1997; van Oortmarssen *et al.,* 1992; Jenkins *et al.,* 1996; Forsmo *et al.,* 1997; Hristova and Hakema, 1997) to 7% (Waugh and Robertson, 1996; Waugh *et al.,* 1996).

Sensitivity/uncertainty analysis

The outcomes of predictive analyses of costs and effects are subject to uncertainty because of parameter uncertainty and model uncertainty as described above. Apart from computation of the outcomes under each alternative structural assumption, there is no appropriate way to deal with model uncertainty. To the best of our knowledge such computation of outcomes for different alternative structural assumptions has never been performed for evaluation of cervical cancer screening.

To deal with parameter uncertainty a sensitivity analysis or an uncertainty analysis can be performed. In an univariate sensitivity analysis the value of one of the parameters is successively changed to assess the impact of uncertainty on the model outcomes. In a multivariate sensitivity more parameters are involved. In this way the combined influence of changing these parameters can be investigated. The computation time increases, however, as a function of the number of uncertain parameters and the values considered for every parameter. For large numbers of parameters and values considered, uncertainty analysis may be more appropriate. In uncertainty analysis, draws are repeatedly taken from the multivariate probability distribution of the parameter values, and the model outcomes are calculated for that draw of parameter values. We do not know of any evaluation of cervical screening including an uncertainty analysis. However, sensitivity analyses

have often been carried out. Parameters frequently varied in sensitivity analyses are duration of disease states (Knox, 1976; Parkin, 1985, 1986; Parkin and Moss, 1986; Eddy, 1990; Gustafsson and Adami, 1992; Schechter, 1996; van Ballegooijen *et al.,* 1997), proportion regressing (Parkin, 1985, 1986; Fahs *et al.,* 1992; Gustafsson and Adami, 1992; Sherlaw-Johnson, 1994, 1997; Chesebro and Everett, 1996; Jenkins *et al.,* 1996; Waugh and Robertson, 1996), attendance rate (Parkin, 1985; Parkin and Moss, 1986; Koopmanschap *et al.,* 1990a; van Ballegooijen *et al.,* 1992; Sherlaw-Johnson *et al.,* 1994, 1997; Gyrd-Hansen *et al.,* 1995; Yu, 1982), sensitivity of screening test (Eddy, 1990; Fahs, 1992; Knox, 1976; Parkin, 1985; Sherlaw-Johnson, 1994, 1997; Jenkins, 1996; Schechter, 1996; Yu, 1982; van Ballegooijen *et al.,* 1997; Radensky, 1998), specificity of screening test (Parkin, 1985; Eddy, 1990; Fahs *et al.,* 1992; Sherlaw-Johnson *et al.,* 1994, 1997; Schechter, 1996; Radensky and Mango, 1998), and costs of screening and/or treatment (Parkin and Moss, 1986; Koopmanschap, 1990b; Schechter, 1996; Radensky and Mango, 1998; van Ballegooijen *et al.,* 1997).

The appendix to this chapter describes model inputs in more detail, including data on natural history, disease incidence and prevalence, performance of screening and costs.

Model output

Screening policies

The screening policies considered in evaluation and prediction studies vary. In evaluation studies the actual or currently recommended screening policy is usually studied and sometimes some alternative screening policies are included.

(Cost-)effectiveness measures

The effects of screening policies are usually measured in life-years gained or reduction in mortality. Reduction in incidence, which is supposed subsequently to lead to a reduction in mortality, is also frequently used. In their recommendations, the Panel on Cost-effectiveness in Health and Medicine advocate the use of QALYs for valuing the health consequences of a health intervention, to include also the negative side-effects of the intervention (Weinstein *et al.,* 1996). There are, however, no reports of such measurement and valuation in literature concerning health states produced or prevented by cervical cancer screening.

If costs are included, they are the result of expenditures of the screening programme (such as cost of screening tests, invitation costs and other organisation costs) and the savings induced by screening (savings in treatment costs and costs of terminal disease prevented).

Implicit in the calculation of costs and effects is a comparison between alternatives. In the case of cancer screening, the screening policy under study is compared with a suitably chosen alternative, which may be another screening policy or a situation without screening. The costs and effects ratio is then the incremental cost of obtaining a unit of health effect (e.g. life-year gained) from a given screening policy when compared with an alternative.

It is clear that, at least for some models of screening, screening provides health benefits at a lower cost than many other accepted preventive and treatment services. However, it is also clear that cost-effectiveness can vary significantly according to the details of the model of screening and follow-up, and there may be more cost-effective ways of reducing the burden of cervical disease.

Evaluation of cervical cancer models

Evaluation and prediction models reviewed in this study differ on many aspects. In this study, particular attention was focused on differences in types of models, study perspective, discounting, description of natural history, screening characteristics and costs. A wide diversity in existing models was displayed. This raises the question of which models are appropriate for evaluation and prediction of the (costs and) effects of cervical cancer screening. Eddy (1987) proposed four levels of validation of mathematical models. A first-order validation requires that the structure of the model makes sense to people who have a good knowledge of the problem. For cervical cancer models this means that important characteristics of the natural history of the disease and screening test known from literature should be incorporated in the model. Examples of these characteristics for cervical cancer are the possibility of regression of preinvasive stages, age-dependent incidence of preclinical lesions and differences in sensitivity according to disease stage. A considerable number of models used in this study accomplish this level of validation (see *Tables 19* and *20*).

The second-order validation examines how closely the model reproduces the data used to estimate the parameters for the model. The two other levels of validation compare predictions of

the model with empirical data that are available but not used for parameter estimation of the model at the time the model was built (third order), and the outcomes predicted by the model with empirical data that became available after the model was built (fourth order). These levels of validation are seldom fulfilled, or at least not described in the literature. Examples are, however, given by Eddy (1987), who compared the results of an independent analysis of empirical data from several large-scale cervical screening programs with the results of a mathematical model of cervical cancer calculated 10 years before (fourth-order validation), and Gustafsson and Adami (1990), who estimated the parameters of the model from population-based cancer and mortality statistics in Sweden (second-order validation).

The cervical cancer model used for prediction of cost and effects of cervical cancer screening fulfils all levels of validation at least to some extent. The MISCAN cervical cancer model incorporates all known characteristics of the natural history of the disease and the screening test such as regression, age-dependent incidence of cervical cancer and of its precursors, and differences in sensitivity according to disease state. Furthermore, comparison of model outcomes to empirical data sets are carried out. Parameter estimates of duration and sensitivity were derived from British Columbia (Canada) screening data (van Oortmarssen and Habbema, 1991 – second-order validation), and subsequently model outcomes were concluded to be compatible with data on interval cancers collected by the IARC (IARC, 1986; van Oortmarssen and Habbema, 1995 – third-order validation) and cervical cancer incidence and mortality data from The Netherlands (van Ballegooijen, 1998 – fourth-order validation). To our knowledge no other model has been validated as extensively as the MISCAN cervical cancer model.

The above-mentioned models of Eddy and Gustafsson and MISCAN have comparable structures. The model of Eddy, however, differs in quantification from the Gustafsson model and the MISCAN model, the latter two being very similar in quantification.

Cost-effectiveness of HPV testing

The background

An economic assessment of the introduction of HPV testing into the cervical screening programme can only be made following results from studies of its effectiveness in reducing incidence of and mortality from cervical cancer. Few empirical studies designed to test effectiveness were identified from the search strategy and none discussed cost or cost-effectiveness. Most studies concerned with cost base their conclusions on assumptions about the impact of HPV testing within existing cervical cytology programmes. In general, these assumptions relate to the likely value of HPV testing for improving the success of cervical screening. These are partial economic evaluations which identify costs and savings based on the likely impact of HPV testing on the numbers and relative proportions of Pap smears, colposcopies or histology procedures. They fail to compare costs in terms of the potential numbers of life-years gained or cancers prevented. Cost-effectiveness analysis by contrast, relies on studies relating costs to a single common effect which may differ in magnitude between different programmes.

The appropriate outcome measures for assessing the cost-effectiveness of HPV testing are the cost per year of life gained, of mortality prevented or of cancer prevented. Other outcome measures appropriate to a review of HPV testing might also include the cost per unit of improvement in quality of care such as in reducing the false-positive rate or in reducing hospitalisation from cervical cancer. Such studies might more properly be termed cost–benefit analysis, since both the costs and effects would be compared in terms of the use of resources – money. Other forms of economic studies such as cost minimisation or optimisation analysis might only apply once HPV testing had been introduced and the least-cost procedures were being sought in order to avoid wasted resources within the programme.

The literature

Only five papers were identified which contain analysis of direct relevance to assessing the cost-effectiveness of HPV testing in secondary prevention of cervical cancer (Jenkins *et al.,* 1996; Cuzick and Sasieni, 1997; Kaufman *et al.,* 1997; Sherlaw-Johnson *et al.,* 1997; van Ballegooijen *et al.,* 1997).

Cuzick and Sasieni (1997) costed the addition of an HPV test within the current English cervical cytology screening programme. The authors compare costs within different screening strategies. Fixed costs and costs to women are not considered, and the costs are not discounted. Grade II or III CIN is used as the end-point in this study, and no direct estimates of years of life gained are made, although they estimate that the improved detection rate would reduce morbidity and premature

deaths. Based on the assumption that the introduction of HPV testing would allow the screening frequency to be safely extended from once every 3 years to once every 5 years, they estimate savings of around £30 million per year. These savings arise from the need for 40% fewer Pap smears, for reduced follow-up and fewer inadequate smears. They estimate small increases in the cost of colposcopy and histology. Assumptions made about the management of abnormal smears or women with HPV-positive tests yet negative cytology are consistent with the current policy in one English district general hospital. Stringent criteria are also applied to positivity. The authors point out that the savings are dependent on strict quality control of HPV tests and adherence to protocols. Referral for women who are HPV-positive but have negative findings on cytology would be restricted to those with persistent high-grade lesions of high-risk HPV types. It is possible also that the population studied differs from reports from other authors, since patients were in high-risk categories and those treated for CIN within 2 years of referral were excluded. However, the study identifies several important issues, including the importance of the effects of HPV testing on cytology screening policies, protocols for treatment of those with lesions with or without the presence of high-risk HPV types and the need for strict quality control.

Van Ballegooijen *et al.* (1997) modelled the relationship between high-risk HPV and cervical cancer. Costs and cost-effectiveness were calculated for women at 3-yearly intervals comparing two screening tests (cytology plus HPV test and HPV test only) and three screening schedules (every 3 years, every 5 years and every 10 years). Costs included cytology, HPV testing, colposcopy, radiotherapy and other medical procedures.

Assuming a long duration of progressive HPV infection and a high sensitivity of the HPV test – model version A – makes HPV screening more effective in reducing mortality from cervical cancer than a relatively short duration of progressive HPV and a low sensitivity for HPV (model version B). The authors conclude, however, that no (longitudinal) data are available to falsify either model.

The alternative of replacing cervical cytology using a Pap smear with a HPV only test with a longer screening interval within the model version A gave the most favourable outcome for survival improvements, the lowest costs per life-year gained (3500 Dfl) and the lowest costs overall per woman screened (230 Dfl). These were 37 and 41% lower than 3-yearly Pap smears mainly because of the need for less-frequent screening. The highest costs were in model version B, which the authors point out does not favour replacing Pap smears with any form of HPV screening. Cost per life-year gained were up to six times higher in this version, with total costs up to five times higher compared with the results from model A. Negative side-effects increased, and there was no improvement in mortality.

The validity of the model depends very much on the assumptions made about sensitivity of the Pap smear for both CIN and in the preclinical phase. The model is based on the incidence of cervical cancer in The Netherlands, which is lower than the UK, though this should not greatly affect the results. The authors point to the importance of empirical HPV studies in women aged 30–60 years and not (as has been done in a large majority of the studies) only in young women, who have a high prevalence of HPV.

Costs are estimated from birth to death, and are not discounted. More details of the assumptions and results are contained in the section below on modelling studies. Sensitivity analysis of changes in frequency of follow-up and the costs of HPV testing did not alter the relative cost-effectiveness found in the model.

Jenkins *et al.* (1996) use a stochastic model to predict resource use for HPV testing, comparing three alternative screening policies. They express the results in terms of the numbers of diagnostic tests needed and the impact on mortality from and incidence of cervical cancer, and do not explicitly estimate costs. The present UK policy of repeating mild to borderline smears every 6 months is compared with a similar policy of introducing an HPV test during routine cytological screening with referral for colposcopy if high risk is found. The third strategy is routine screening by HPV testing with cytological follow-up for HPV-positive women. A complex decision about referral for colposcopy is based on a combination of HPV and Pap smear results.

The results for the first two screening strategies are broadly similar in terms of the numbers of smear tests and colposcopies performed as well as the proportion of colposcopies with negative findings performed (56 and 58%, respectively, compared with the baseline). The third screening strategy reduces by about 25% the numbers of Pap smears required, the numbers of HPV tests rise by around 40% over the second screening strategy and 100% over the first, and the total numbers of tests needed is increased by almost

a third. The proportion of colposcopies with negative findings is reduced slightly (49%).

The most effective strategy in terms of reducing mortality from cervical cancer appears to be a 10 year screening option for all three modalities with particular benefits from routine cytology and cytology with HPV follow-up. The authors conclude that the cost-effectiveness of HPV testing as a routine screening test will depend substantially on the proportion of HPV-negative cancers and the percentage of treatable cancers detected by cytology. HPV testing is likely to be cost-effective (lower cost and improved quality control and automation) in comparison with cytology, where HPV-negative precancers are less than 5%. It is clear that variations in the assumptions of this model particularly in relation to precancer progression will affect the outcome estimates. The model makes no attempt to cost resource use directly or to include treatment costs. The model is insufficiently detailed to derive estimates of cost per life-year gained or even of increased cancer detected. The authors conclude that the resource use depends on the frequency of screening, coverage, age range and age distribution of the target population, though no sensitivity analysis performed.

Sherlaw-Johnson *et al.* (1997) apply modelling techniques to the evaluation of cervical cancer screening programmes in developing countries. Some issues raised are more widely relevant, including the feasibility of particular HPV tests in field settings, the relationship between HPV infection and clinically significant disease, coverage of the screening programme and the quality of testing and follow-up management. Their results show that in countries with very scarce resources the priority is likely to be to ensure that every woman is screened at least once, and that there are diminishing returns from more frequent screening.

Kaufman *et al.* (1997) investigated the cost-effectiveness of HPV testing as a triage for women with abnormal cytology of unknown significance. Two triage algorithms are compared, one with repeat smears and colposcopy and the other additionally testing for HPV. Cost-effectiveness is compared mainly in terms of cases of high-grade CIN identified and the costs associated with colposcopy. The study does not make the costing methods very clear. The authors conclude that HPV testing in this context is unlikely to be considered cost-effective since few extra cases are detected and costs are significant. The study considers only a very specific use of HPV testing, and does not allow for the possibility that its use would affect more radically the approach to screening and follow-up. It offers limited guidance on future policy, but does draw attention to the fact that it is unlikely that HPV testing will be appropriately used if it is simply added to existing protocols for testing and follow-up.

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Appendix: model input and features

Natural history

The natural history of cervical cancer can be described by a succession of states, starting with a state without screen-detectable cancer, a screen-detectable preclinical state in which the tumour is only detectable by screening, and a clinical invasive state in which the tumour is detected because of symptoms. Often, regression of preclinical lesions, that is, the transition from the screen-detectable preclinical state back to the state without screen-detectable neoplasia, is assumed. The models categorised as deep models fit this outline, although the screen-detectable preclinical state is usually subdivided, except in the models of Knox (1976) and Yu (1982). In all studies using the MISCAN

model (Habbema *et al.,* 1985; Koopmanschap *et al.,* 1990a,b; van Ballegooijen *et al.,* 1997) and in Van Oortmarssen *et al.* (1992), the screen-detectable preclinical state is subdivided into a screen-detectable preinvasive state, corresponding with dysplasia and carcinoma *in situ*, and a preclinical invasive state. Also, Gustafsson and Adami (1990, 1992) used this subdivision but restricted the preinvasive state to cases of carcinoma *in situ*. Knox (1973), Parkin (1985), Parkin and Moss (1986), Gyrd-Hansen *et al.* (1995) and Bethwaite *et al.* (1986) made separate states for dysplasia and carcinoma *in situ*. Other subdivisions are mild, moderate and severe dysplasia (Chesebro and Everett, 1996), LSIL and HSIL (Schechter, 1996) or CIN I, CIN II and CIN III (Sherlaw-Johnson *et al.,* 1994, 1997; Jenkins, 1996). Sometimes the invasive state was also subdivided, for example into local, regional and distant invasive (Eddy, 1987, 1990), early and late invasive (Fahs, 1992), occult and clinical invasive (Parkin, 1985; Parkin and Moss, 1986), and occult, early clinical and late clinical invasive (Knox, 1973).

Most deep models use a Markovian approach, the states representing the different stages of the natural history of cervical cancer as described above. Only Eddy (1987, 1990) used stages of diagnosis (no diagnosis of cervical cancer and diagnosed cancer in various states as states of the Markov model) instead of natural history stages. Models use (prevented) death or life-years gained as the measure of effect. Some models use only 'death from cervical cancer' while others use 'death from other causes' in defining the end state.

Other differences between models result from differences in duration of the disease states and transition probabilities between these states. Both the duration and transition probabilities are important parameters determining the effects of screening. Long preclinical duration and a high onset rate, that is, the transition probability from the state without cancer to a preinvasive state ultimately progressing to clinical cancer, increase the effects of screening. Conversely, high regression rates contribute to the adverse effects of screening, because of overtreatment of screen-detected cases that would have regressed. The onset rate of progressive preclinical cancer corresponds with the clinical incidence rates in the situation without screening. Considerable differences exist in these incidence rates between countries. These must be taken into account if comparing (costs and) effects of screening between different studies.

In three studies a relationship between high-risk HPV and cervical cancer was included in the model (Jenkins *et al.,* 1996; Sherlaw-Johnson *et al.,* 1997; van Ballegooijen *et al.,* 1997). Part of the preclinical lesions were assumed to be preceded by and to be associated with a HPV infection. Jenkins *et al.* (1996) and Sherlaw-Johnson *et al.* (1997) also included low-risk HPV infections.

In *Table 19a* incidences in a situation without screening, duration of disease stages and regression rates, if included, are presented. For some models, transition rates per time unit were presented instead of duration; the characteristics of these models are presented in *Table 19b*.

Screening characteristics

In most models the screening test was a Pap smear. Some studies investigated the use of an HPV test in addition to or instead of the Pap smear (Jenkins *et al.,* 1996; van Ballegooijen *et al.,* 1997; Sherlaw-Johnson *et al.,* 1997). Other studies determined the costs and effects of automated rescreening of Pap smears (Schechter, 1996; Radensky and Mango, 1998).

The sensitivity of the screening test directly influences the effectiveness of screening. The higher the sensitivity of the screening test, the greater the effects of screening.

Another important parameter affecting the (cost-)effectiveness of screening is the attendance rate. An attendance of 100% is never attained; attendance rates of 70–90% are more realistic. Women not attending screening have been found to have a higher than average risk of getting cervical cancer, as reported by Berget (1979), Boyes *et al.* (1982) and Magnus *et al.* (1987). In some studies this relationship is modelled (Knox, 1973; Koopmanschap *et al.,* 1990b; Gustafsson and Adami, 1992). The estimates used for the sensitivity of the screening test and the attendance rates are shown in *Table 20*.

The effects of screening in the first years of the predictions will be influenced by the amount of previous (spontaneous) screening. The prevalence of cancer precursors, and thus the risk of developing cervical cancer, is lower in a screened than in an unscreened population. Some studies included historical screening and did not attribute its effect to the screening policy under study (e.g. Habbema *et al.,* 1985; Fahs *et al.,* 1992).

Costs

An overview is given of the costs of screening and treatment for the studies that included costs in *Table 21*.

TABLE 19a *Incidences in a situation without screening, duration of disease stages and regression rates*

Study	Mean duration (years)		Regression rate	
	Category	***n***	**Category**	**Percentage**
van Ballegooijen *et al.* (1992)	CIN III	15	CIN III	60
van Ballegooijen *et al.* (1997)	HPV CIN Preclinical invasive	1–10 11.8 3.9	CIN	72 (< 35 years) 40 (35–54 years)
Chesebro and Everett (1993)			Severe dysplasia	52
Eddy (1987)	Preinvasive	8 (95%) 1 (5%)	No regression	
Eddy (1990) Radensky and Mango (1998)	Preinvasive	8 (95%) 1 (5%)	Dysplasia Carcinoma *in situ*	Not specified Not specified
Gustafsson and Adami (1990, 1992)	Carcinoma *in situ* Preclinical invasive	11.8–17.8[a] 1.7–7.8[a]	Carcinoma *in situ*	85.3–89.2[a]
Gyrd-Hansen *et al.* (1995)	Preclinical	NA	Dysplasia Carcinoma *in situ*	80 50
Habbema *et al.* (1985)	Preclinical	18	Preinvasive	50
Knox (1976)	Preclinical	6 (3, 4, 10, 15)[b]	No regression	
Koopmanschap *et al.* (1990[a,b])	Progressive CIN III	10.1–14.8[c]	CIN III	0–93
van Oortmarssen *et al.* (1992)	Preinvasive Preclinical invasive	12.3 5		
Parkin (1985, 1986)				
Natural history 1	Dysplasia, all (progressive) Carcinoma *in situ*, all (progressive)	2.1 (2.2) 9.8 (10.2)	Dysplasia Carcinoma *in situ*	75–80 15
Natural history 2	Dysplasia, all (progressive) Carcinoma *in situ*, all (progressive)	2.0 (2.6) 6.1 (6.5)	Dysplasia Carcinoma *in situ*	Not specified Not specified
Natural history 3	Dysplasia, all (progressive) Carcinoma *in situ*, all (progressive)	2.0 (2.6) 9.3 (12.2)	Dysplasia Carcinoma *in situ*	75–80 50
Schechter (1996)	SIL	11	SIL	50
Yu (1982)	Carcinoma *in situ* or worse	Not specified	Carcinoma *in situ* or worse	Not specified

[a] *Depending on birth cohort, data from Gustafsson* et al. *(1989)*
[b] *Sensitivity analysis*
[c] *Depending on age, data from Habbema* et al. *(1988)*

TABLE 19b *Incidences in a situation without screening and transition rates for different transitions per time unit*

Study	Background incidence per 100,000 women	Time unit	From disease state to disease state	Transition rate (%)
Bethwaite *et al.* (1986)	30	Year	Normal to dysplasia	0.147
			Normal to carcinoma *in situ*	0.05
			Normal to invasive	0.01
			Dysplasia to carcinoma *in situ*	5.0
			Dysplasia to invasive	0.4
			Dysplasia to normal	32
			Carcinoma *in situ* to invasive	5.0
Fahs *et al.* (1992)	33	Year	Normal to CIN	0.33 (0.09, 0.54)[a]
			CIN to carcinoma *in situ*	17.80 (7.36, 26.70)[a]
			CIN to normal	3.81 (0.54, 26.5)[a]
			Carcinoma *in situ* to EICC	26.10 (18.10, 63.20)[a]
			Carcinoma *in situ* to normal	0.00 (20.0)[a]
			EICC to LICC	39.00 (22.00, 86.00)[a]
Jenkins *et al.* (1996) Sherlaw-Johnson *et al.* (1997)		6 months	No CIN/no HPV to CIN I	0.01
			No CIN/low-grade HPV to CIN I	0.5
			No CIN/high-grade HPV to CIN I	1.00
			No CIN/high-grade HPV to CIN II	0.40
			No CIN/high-grade HPV to CIN III	0.02
			CIN I to no CIN	2.0
			CIN I to CIN II	6.0
			CIN I to CIN III	2.5
			CIN II to CIN III	15
			CIN III to invasive cancer	1
		Year	HPV to no HPV	40
Knox (1973)			Normal to dysplasia	Not specified
		Year	Normal to carcinoma *in situ*	0–0.05[b]
Progressive natural history			Dysplasia to normal	2.7–6.7[b]
			Dysplasia to carcinoma *in situ*	1.3–3.3[b]
			Carcinoma *in situ* to occult invasive disease	0–16[b]
			Carcinoma *in situ* to clinical invasive disease	0–10[b]
Dynamic natural history			Normal to dysplasia regressive type, dysplasia progressive type, carcinoma *in situ* young type, carcinoma *in situ* older type, occult invasive disease, early clinical invasive or late clinical invasive	Not specified
			Dysplasia regressive type to normal, dysplasia regressive type to carcinoma *in situ*, dysplasia progressive type to normal, dysplasia progressive type to carcinoma *in situ*	10–30[b]
			Carcinoma *in situ* young type to normal	0–10[b]
			Carcinoma *in situ* young type to occult invasive	Not specified
			Carcinoma *in situ* older type to normal	0–10[b]
			Carcinoma *in situ* older type to occult invasive	0–20[b]
Sherlaw-Johnson *et al.* (1994)	5.9	6 months	Normal to CIN I	0.12
			CIN I to CIN II	6
			CIN I to CIN III	2.5
			CIN I to normal	2
			CIN II to CIN III	15
			CIN III to invasive cancer	1

EICC, early invasive cervical cancer; LICC, late invasive cervical cancer
[a] *Sensitivity analysis*
[b] *Depending on duration initial state*

TABLE 20 *Sensitivity of screening test by disease state and attendance rate used in the modelling studies*

Study	Screening test	Sensitivity of screening test		Attendance (%)
		Category	**Percentage**	
van Ballegooijen *et al.* (1992)	Pap smear	CIN III	70	65
van Ballegooijen *et al.* (1997)	Pap smear HPV test	CIN Invasive High-grade HPV	80 87.5 50, 100[a]	100
Bethwaite *et al.* (1986)	Pap smear	Not specified	80	Not specified
Chesebro and Everett (1996)	Pap smear		Not specified	Not specified
Eddy (1987, 1990)	Pap smear	Preinvasive	97	
Fahs *et al.* (1992)	Pap smear	CIN Carcinoma *in situ*	75 (50, 80)[a] 75 (50, 82)[a]	Not specified
Forsmo *et al.* (1997)	Pap smear		NA	NA
Gustafsson and Adami (1990)	Pap smear		Not specified	Not specified
Gustafsson and Adami (1992)	Pap smear	Modelled differently[b]		
Gyrd-Hansen *et al.* (1995)	Pap smear	All states	Not specified	80 (70, 90)[a]
Habbema *et al.* (1985)	Pap smear	Preinvasive	70%	70.6 (first screen)[c] 65 (subsequent screen)[c]
Hristova and Hakuma (1997)	Pap smear		NA	NA
IARC (1986)	Pap smear		NA	NA
Jenkins *et al.* (1996)	Pap smear HPV test	CIN I CIN II CIN III Invasive Low grade High grade	66 41 74 100 Not specified Not specified	80
Knox (1973)	Pap smear	Dysplasia Carcinoma *in situ* Occult invasive Early clinical invasive Late clinical invasive	60 75 80 90 70	70–90[d]
Knox (1976)	Pap smear	Pre-clinical	80 (70, 90)[a]	100

[a] *Sensitivity analysis*

[b] *Modelled differently: effects of screening depend on screening efficiency which has three major determinants, namely attendance pattern (including the possible self-selection bias among non-participants), sensitivity of screening test, and the completeness of the diagnostic work-up and treatment of positive findings. The screening efficiency was fixed at 0.75. Values investigated in sensitivity analysis are 1.0, 0.90, 0.50, 0.25, 0.10, and close to 0*

[c] *Averages; attendance rates depend on age and on response to the previous invitation*

[d] *Depending on pathological type to enable the association between women with high risk and low attendance, and vice versa*

TABLE 20 contd *Sensitivity of screening test by disease state and attendance rate used in the modelling studies*

Study	Screening test	Sensitivity of screening test		Attendance (%)
		Category	Percentage	
Koopmanschap *et al.* (1990a,b)	Pap smear	Severe dysplasia Carcinoma *in situ* Invasive IA Invasive IB Invasive II+	60 (50)[e] 70 (60)[e] 85 (75)[e] 85 (75)[e] 90 (80)[e]	40–65[f]
van Oortmarssen *et al.* (1992)	Pap smear	Preclinical	80	NA
Parkin (1985) Parkin and Moss (1986)	Pap smear	All grades of preclinical disease	70	50, 80
Radensky and Mango (1998)	Pap smear INNA rescreening	Not specified	85 (60–95)[a] 89–100	Not specified
Schechter (1996)	Pap smear Papnet rescreening	LSIL HSIL	75 85 Increase of sensitivity with 30%	Not specified
Sherlaw-Johnson *et al.* (1994)	Pap smear	CIN I CIN II CIN III Invasive cancer	43 37 100 100	70 (50, 90)[a]
Sherlaw-Johnson *et al.* (1997)	Pap smear HPV test	CIN I CIN II CIN III Invasive Low-grade HPV High-grade HPV	66 41 74 100 Not specified Not specified	50, 80[a]
Waugh *et al.* (1996)	Pap smear		Not specified	83
Yu (1982)	Pap smear	Not specified	75 (55, 95)[a]	80 (50, 90)[a]

[a] *Sensitivity analysis*
[e] *Values for sensitivity of organised (spontaneous) screening from Habbema* et al. *(1988)*
[f] *Attendance decreasing gradually from 65% up to age 50 years to 40% at age 70 years*

TABLE 21 *Costs of screening test, treatment costs and other costs as used in the modelling studies*

	Costs of screening test		Treatment costs		Other costs specified	
Study	**Test**	**Cost**	**Category**	**Cost**	**Category**	**Cost**
Bethwaite *et al.* (1986)			Dysplasia CIS Cervical cancer	$337.11 $2182.61 $11,733.91		
Chesebro and Everett (1996)	Pap smear	$50	Mild dysplasia Moderate dysplasia Severe dysplasia	$199 $359 $543		
Eddy (1987)	Pap smear	$20				
Eddy (1987, 1990)	Pap smear	$75	Carcinoma *in situ* Stage I Stage II/III Stage IV	$5641 $11,600 $16,891 $18,587	False positives Regressive lesion Terminal disease	$150 $5641 $22,150
Fahs *et al.* (1992)			CIN Carcinoma *in situ* EICC LICC	$1102.36 $4358.67 $9215.76 $13,358.76	False positives	$575.51
Gyrd-Hansen *et al.* (1995)	Costs not specified					
Hristova and Hakuma (1997)	Pap smear	$10	*In situ* Localised Non-localised	$4000 $20,000 $32,000		
Koopmanschap *et al.* (1990a,b)	Costs not specified					
Parkin and Moss (1986)	Pap smear	1 unit[a]	Dysplasia Carcinoma *in situ*, microinvasive Clinical invasive	30 units[a] 75 units[a] 400 units[a]		
Radenksky and Mango (1997)	Pap smear Pap smear and interactive neural network-assisted rescreening	$35.60 $46.01	Regressive lesion Carcinoma *in situ* Stage I Stage II Stage III Stage IV	$9156 $9156 $18,828 $27,416 $27,416 $30,168	Follow-up for positive findings Terminal care Care of patients dying of other causes	$204 $35,951 $40,577
Schechter (1996)	Pap smear PAPNET rescreening	$23 $30	LSIL HSIL EICC LICC	$1944 $9528 $23,015 $34,270	Colposcopy	$311
Waugh and Robertson (1996) Waugh *et al.* (1996)	Pap smear	£22.70			Colposcopy clinic visit	£30

[a] *Arbitrary units are used as cost measure. Sensitivity analysis done with half the treatment costs*

Chapter 8

Modelling the use of HPV testing in the prevention of cervical cancer

Introduction

The range within which the cost-effectiveness of HPV testing in screening and follow-up lies is identified, given the present knowledge. This is done using estimates derived from the review section of this report (e.g. prevalence of the HPV virus for different cytological stages, the sensitivity of the HPV test) and by making assumptions about HPV screening parameters that are not available from literature. A cervical cancer-screening model was constructed in the microsimulation programme MISCAN and adapted to English demographic, epidemiological and screening characteristics. This modelling exercise focuses on whether recommendations about HPV screening can already be made on the basis of the available data and what type of data will be required to decrease uncertainty. This section starts with a brief introduction to the model. This is followed by the modelling results. A discussion of the implications of these findings and their sensitivity to the assumptions made will be discussed.

Methods

Description of the model

The disease model is defined by the states in which the disease process has been subdivided (*Figure 7*), by the dwelling times in the states (assumed to be Weibull random variables with shape parameter set to 1.9, see *Table 22*), and by the probabilities of transitions between states

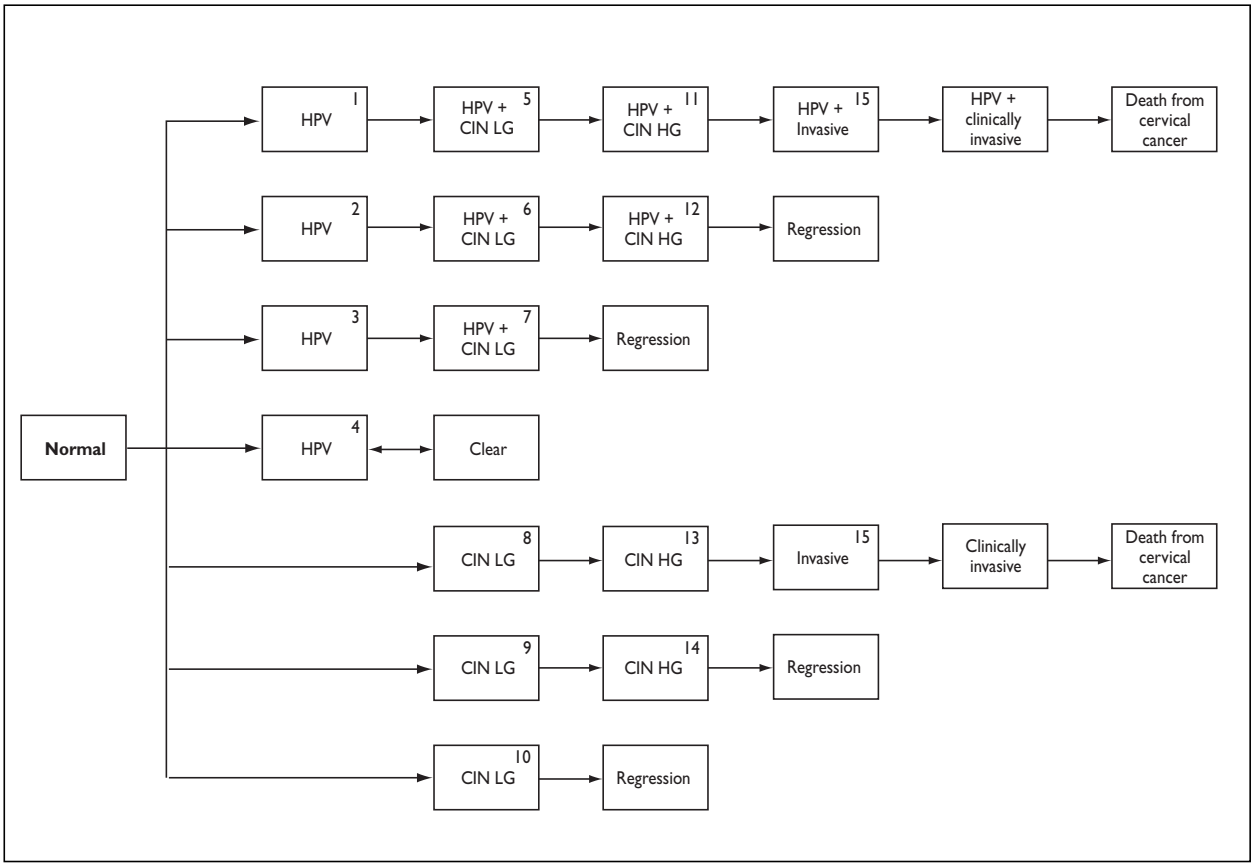

FIGURE 7 *The stages and possible transitions in the HPV cervical cancer model. The state 'death due to causes other than cervical cancer' is not included but can be reached from each state in the figure (HG, high grade; LG, low grade)*

(determined by the dwelling time distributions, except for the first transition from the normal state). Both the transition probabilities and the dwelling times in the states can be assumed to be age dependent. Values of transition to each of the seven arms in the disease model and the dwelling time distributions were chosen to obtain the overall marginal disease characteristics assumed below. (Further details of parameter values actually used are available from the authors.)

As shown in *Figure 7*, the model is based on the hypothesis that HPV infections found in invasive cervical cancer and in CIN preceding the neoplastic stages. Women who develop an HPV infection either clear if spontaneous or develop HPV-related CIN. This CIN plus HPV either regresses, or progresses into HPV-positive invasive cervical cancer. Women can also develop CIN without an HPV infection, and this CIN again can regress or (perhaps only rarely) progress into invasive cancer. Allowing for the possibility that women can develop CIN (with or without HPV) after having cleared an HPV infection would cause a shift between the different arms in the model without affecting the model outcomes presented in this study. Therefore, we did not complicate the model in this way. This semi-Markov model is an extension of a cervical cancer screening Pap smear model (Koopmanschap *et al.,* 1990a,b; van Ballegooijen *et al.,* 1992) validated on screening data from British Columbia (van Oortmarssen and Habbema, 1991), data on interval cancers collected by the IARC (van Oortmarssen and Habbema, 1995) and cervical cancer incidence and mortality data in The Netherlands (van Ballegooijen, 1998), accomplishing respectively the second, third and fourth orders of validation (see chapter 7). A comparable extension has been carried out by van Ballegooijen *et al.* (1997). According to this model, the average duration of CIN is 11.8 years and that of preclinical invasive cancer is 3.9 years (*Table 22*).

In the original model the sensitivity of the Pap smear was 80% in CIN, and 87.5% in preclinical invasive carcinoma. The estimates of duration and sensitivity were derived from the Canadian (British Columbia) screening data (van Oortmarssen and Habbema, 1991), and were compatible with data on interval cancers collected by the IARC (IARC, 1986; van Oortmarssen and Habbema, 1995). However, the sensitivity of the Pap smear estimated from English data is lower (*Table 23*).

The incidence of progressive CIN and mortality after clinical diagnosis of cervical cancer (i.e. transition from clinical invasive to death due to cervical cancer, see *Figure 7*) were chosen to reproduce cervical cancer incidence and mortality in England and Wales for the birth cohort 1955. These were estimated by modelling mortality rates between 1950 and 1996 and incidence rates between 1971 and 1992.

Two model versions

Since no adequate longitudinal HPV data were available for quantification of the model, there was a problem in identifying the parameters describing HPV infections. Test-positive rates in women screened for the first time depend on incidence, duration and sensitivity from cross-sectional data alone. Moreover, a broad range was found in the literature for HPV positivity for different cytological stages, and for estimates of the sensitivity of the HPV test. In view of this non-identifiability and uncertainty, two models with contrasting HPV screening outcomes were constructed, a model favourable for the use of the HPV test (model A) and an unfavourable model (model B). We varied duration and sensitivity and adjusted the incidence level in the different arms of the model (*Figure 7*), so that both models correspond with the observed incidence and mortality rates for cervical cancer and the assumed HPV prevalences.

The longer the duration of progressive (to CIN) HPV infections (disease stages 1–3 in *Figure 7*) and the higher the sensitivity of the HPV test, the more effective HPV screening will be in reducing cervical cancer mortality. In order to minimise the negative side-effects (i.e. follow-up of HPV-positive women who will not develop cervical neoplasia), it is favourable to assume a short duration of harmless (non-progressive) HPV infections (disease state 4 in *Figure 7*) and low HPV positiveness in cytologically negative women.

In model A (*Table 24*), the extra duration of the detectable preclinical phase resulting from HPV detection was assumed to be 10 years. The assumed sensitivity for HPV was 90% at all stages. The positiveness of HPV in cytologically negative women was fixed at 15% between the ages of 20–25 years, decreasing to 5 and 3% at 30 and 40 years of age, respectively. A long duration of progressive HPV and high sensitivity made model A very favourable for HPV screening. In model B, the detectable preclinical phase was only 1 year longer than in Pap smear screening, and the sensitivity for high-risk HPV types was considerably lower than in model A: in HPV infected neoplasia, the sensitivity of the HPV test was equal to the sensitivity of the Pap smear (50% in HPV-positive low-grade CIN, 60% in

HPV-positive high-grade CIN and 70% in HPV-positive invasive cancer), and the sensitivity was only 50% in HPV infections without neoplasia (*Table 24*). Twenty per cent of the cytologically negative women aged between 20 and 25 years were assumed to be HPV-positive, decreasing to respectively 8 and 6% at the ages of 30 and 40 years. Compared to model A, model B was very unfavourable for HPV screening.

The estimated percentage of invasive cancers that are HPV infected was kept constant at 95%, and the lifetime risk of contracting low-grade CIN and high-grade CIN of 15 and 5%, respectively, was the same in both models.

Costs and effects of screening

In order to assess the costs and savings of early detection, the costs of all aspects of disease control, including screening, follow-up, diagnosis and treatment, were considered (*Table 25*). Costs of cervical screening use the method of Havelock, and are taken directly from the 1988 annual report on cervical screening from Watford General Hospital, a unit processing 60,000 smears a year. The management of low- and high-grade CIN is taken from the NHS price tariff for healthcare resource groups. The cost of curative primary treatment are estimated from the literature (van Ballegooijen *et al.*, 1997) and data published by the Thames Cancer Registry (1997) to estimate the proportion of women undergoing hysterectomy, radiotherapy and chemotherapy for each of the alternative approaches available. The cost of care for advanced disease is based on the proportion of women expected to undergo further treatment and an average cost for palliative care.

Life-years gained and deaths prevented are used as effect measures of screening. The effects of a screening programme are calculated by comparing the life-years lost and the mortality due to cervical cancer in a scenario with screening to a scenario without screening, both scenarios being simulated.

Screening strategies

In both versions of the model, the effects and costs have been calculated for both 3-yearly and 5-yearly screening between 20 and 64 years of age. Predictions were made for three different tests or test combinations: cytology, cytology plus HPV testing, and HPV testing only. For screening with both cytology and HPV testing we assumed the sensitivity of the tests to be independent. The resulting sensitivities for each disease state can be calculated from the sensitivities of both screening tests separately as displayed in *Tables 23* and *24* (see the results of these calculations in the appendix to this chapter).

Women with relatively minor abnormalities receive the current surveillance of 6 monthly smears, while women with more severe abnormalities are referred for treatment. In *Table 26* an overview is given of the costs of dealing with the minor and more severe abnormalities for the different tests and test combinations. Surveillance ends after two consecutive negative smears (after which women go back to screening) or after three smears with borderline dysplasia, two smears with mild dysplasia, one smear with borderline and one smear with mild dysplasia, or one smear with moderate or severe dysplasia. The last group of women is referred for treatment.

Surveillance strategies

The cost-effectiveness of adding HPV testing to the follow-up of women with a positive test result was also studied by comparing the costs and effects of a 3-yearly screening programme between the ages of 20 and 64 years with the current surveillance strategy and surveillance with both cytological and HPV testing. In the case of combined cytological and HPV testing, women go back to routine screening when both the HPV and cytological test are negative. Women are referred directly after HPV positiveness and borderline or worse abnormalities on cytology, or otherwise after two HPV-positive results together with normal cytology, or in the case of HPV negativeness after three smears with borderline dysplasia, two smears with mild dysplasia, one smear with borderline and one smear with mild dysplasia, or one smear with moderate or severe dysplasia.

Cost-effectiveness calculations

Calculations were made for women born in 1955. The attendance rate at screening was assumed to be 85% with a 10 year coverage of 95%. Outcomes have not been discounted.

Results

Primary screening

The model predictions of the effects and costs of the different combinations of frequency and screening tests for both model versions are summarised in *Table 27*. For both model versions, more intensive Pap smear screening (every 3 years instead of every 5 years) would prevent more deaths, 8.3 per 1000 women instead of 7.0 per 1000 women (in a situation where the lifetime risk of dying from cervical cancer without screening is 10.9 per 1000 women), but was less cost-effective. This is caused by a considerable decrease in screening and surveillance costs if women are screened less often, which outweighs

the decrease in effects and the higher cost for invasive and advanced cancer.

According to model version A, which was favourable for HPV screening, the combined test performed once every 5 years reduced mortality more than did 3-yearly Pap smears. The costs will be only slightly higher. For screening with the HPV test only the effects of 5-yearly screening are lower than for 3-yearly Pap smears (70 versus 76%), but the costs are reduced by 75%, resulting in a substantially lower cost-effectiveness ratio (£100 per life-year gained compared with £390 per life-year gained). The lower costs of the HPV-only screening programme were mainly the result of lower screening costs and less (over)treatment of women referred without cervical neoplasia.

For model version B, which was unfavourable for HPV screening, the use of HPV testing to supplement or replace cytology based screening resulted in worse cost-effectiveness rates than cytology screening. Combined screening yielded a higher mortality reduction, but this was not proportional to the increase in costs if an HPV test would be added to the Pap smear. For screening with HPV alone, both the effects were lower (the 1 year extra detectable phase for which sensitivity is 50% is outbalanced by the 5% of progressive lesions that are in women who are HPV-negative) and the costs were higher. The higher costs were mainly the result of increased surveillance costs and lower savings in diagnosis and treatment costs.

Screening only at the ages of 25, 30, 40 and 50 years leads to lower costs per life-year gained than a 3-yearly cytology-based programme. For model version A, savings per life-year gained were expected if HPV is used for testing, but the percentage of mortality prevented decreased considerably and varied between 28 and 53% for the different model versions and screening test combinations.

An alternative screening policy of adding HPV screening after 35 years of age to 3-yearly cytology screening between 20 and 64 years of age yielded lower cost-effectiveness estimates for both model versions. The improvements in effectiveness do not outweigh the higher costs of screening.

Based on the model A version calculations, a decision might be made to introduce a screening programme with 5-yearly screening by Pap smear and HPV testing, to improve the prevention of mortality at slightly lower costs, or to substitute cytology based screening by 5-yearly HPV screening, to obtain almost the same mortality reduction at 75% lower costs.

However, the model B calculations suggest that Pap smear screening should not be replaced by any of the studied strategies.

HPV in surveillance

The expected effects and costs of a surveillance strategy with combined cytological and HPV testing are compared with the effects and cost of the prevailing surveillance strategy for 3-yearly screening between the ages of 20 and 64 years in *Table 28*.

Adding HPV testing only in the follow-up of mild to borderline smears will improve the mortality reduction in both model versions. Due to the higher savings in diagnosis and treatment of invasive and advanced cancer the costs are also lower for surveillance with both cytology and HPV testing, resulting in lower estimates of the cost per life-year gained. These favourable results must, however, be interpreted with caution. The effectiveness of the use of HPV testing in surveillance and of surveillance in general is dependent on the proportion of women in surveillance that already have (or are on the way to develop) invasive cervical cancer. For both models A and B, the risk for cancer associated with borderline and mild dyskaryosis has been assessed from cross-sectional data on the observed distribution of cytological results (from negative to high-grade dyskaryosis or higher) in different grades of disease (histologically confirmed low- and high-grade neoplasia). However, this presumes that the progressive potential of high-grade disease is independent of whether the smear is negative or positive, and independent of whether the HPV test is negative or positive. This may be a plausible assumption, but it has to be confirmed by prospective studies.

One possible study design would be to randomise women with borderline or mild smears to different intervention arms: one in which only repeat smears are made, and one in which HPV tests are also performed. The detection rates for high-grade neoplasia in the next screening round of women returned to routine screening should be included in the study. In this way, results will show both sides of the coin: how many women are treated and how well protected are those who are not treated.

In conclusion, although our model versions A and B represent two extremes regarding the effects of different primary screening strategies, they are not extremes concerning the effects of different surveillance strategies. This uncertainty about these

effects is not only influenced by the uncertainty about the natural history of HPV and the characteristics of the HPV test but is also strongly related to the uncertainty about cytology and the natural history of histologically proven preinvasive neoplasia. The latter uncertainty is not included in the calculations presented in *Table 28*.

Discussion

We have constructed a model that reproduces the estimated age-specific incidence and mortality in the situation without screening as assessed for UK women born in 1955. This was done by adjusting the age-specific incidence of progressive disease, accounting for the average duration and variation in the duration of preclinical disease, and by adjusting the age-specific and stage-specific survival to the mortality/incidence ratio by age. The regressive disease was adjusted to the assumed cumulative risk for women of this cohort (based on observed detection rates in the UK) to develop low-grade (15%) and high-grade (5%) CIN, respectively. The incidence of HPV (high-risk)-positive CIN was adjusted to the HPV positivity observed in women with low-grade and high-grade CIN, taking into account the assumed sensitivity for HPV in women with HPV-positive CIN. The age-specific incidence of HPV infections in women without cervical neoplasia was adjusted to the assumed HPV positivity in women with normal cytology, taking into account the assumed sensitivity for HPV infections in the cytology of women without neoplasia, and taking into account the duration of HPV infections in cases that progress to CIN and in cases that do not progress to CIN. It is assumed that 95% of the invasive cervical cancers are preceded and develop in the presence of an HPV infection. The sensitivity of the Pap smear for low- and high-grade neoplasia was adjusted to the observations from Cuzick *et al.* (1995), accounting for the other parameters (sensitivity of the HPV test on cytological material for CIN). The specificity of the Pap smear was adjusted to the percentage of women having borderline and mild dyskaryosis (who are offered cytological surveillance every 6 months) and the percentage of women referred in whom no CIN is detected at colposcopy follow-up (50%).

Since there is uncertainty about a number of key parameters in the disease and screening model just described, we constructed two models that produce contrasting estimates of the (cost-)effectiveness of HPV screening. In model A we chose the most favourable combination of estimates for the uncertain parameters. In model B, we did the opposite. In model A, progressive HPV infections have a long duration, and the sensitivity of the HPV test is high, and the HPV prevalence in women without cervical neoplasia is relatively low. In model B, it is the other way around.

We simulated several alternative screening strategies with both models. This was done in a cohort model, and the costs were not discounted. We varied both the primary screening strategy, and the strategy of surveillance following borderline and mildly dyskaryotic smears. For primary screening we considered (1) adding HPV to the Pap smear, and (2) replacing the Pap smear by the HPV test. We considered 3- and 5-yearly screening. For surveillance, we considered conventional surveillance with Pap smears only, and surveillance with both Pap smears and HPV testing every 6 months.

The uncertainty, as expressed by the differences between models, is so large, that results are inconclusive. Adding HPV testing to cervical cancer screening may or may not improve the (cost-) effectiveness of screening. There are relatively few longitudinal HPV screening studies with enough time lapse between measurement points to decrease uncertainty. More studies are needed.

It is important to ensure that we have used all available data on prevalence and natural history of HPV and its association with cervical neoplasia, as found by reviewing the literature. To do this, one should validate the model used for the predictions with these data, by simulating the studies. For instance, consider the study of Rozendaal *et al.* (1996) on the detection of high-grade CIN several years after negative Pap smears and stratified by the HPV test result at the time of the negative smear. If we trust the empirical data from this study, simulation of the study should reproduce its results, or at least results that are not statistically significantly different. Using model A, the detection rates of high-grade CIN in the years following a negative Pap smear and a negative HPV test will be considerably lower than in model B, probably even much lower than observed in the study. However, the limited numbers in the study allow for a large confidence interval in this respect. The other question is how to interpret the differences in results between the Dutch natural history studies, using GP5+/6+ and studies using other PCR systems. The same holds for differences between reproducibility studies and studies on archival studies: the studies are relatively small and results differ considerably. Validation studies were not in the scope of this review project. In addition to collecting further data, a next step in research

should be to analyse existing data more thoroughly using models.

The adjustment of the model to the Pap smear screening practice in the UK was not completed in detail. For instance, the model for conventional 3- or 5-yearly Pap smear screening predicts a detection rate for low-grade CIN that is higher than that for high-grade CIN, which is not what is observed. However, we do not expect that further adjustment will change the comparison between HPV screening and Pap smear screening, and concluded that available data are inconclusive regarding the outcomes of HPV screening. More importantly, the model used for Pap smear screening differs from the validated MISCAN cervix model reported in the literature. The sensitivity of the Pap smear in the validated model is higher, which is favourable for Pap smear screening. As a result, the mortality reduction of 3-yearly cytology in the model used in the present study was only 76%, as compared with 79% in the model used by van Ballegooijen *et al.* (1997). This difference was introduced because of the relatively high detection rate of CIN in women with negative cytology and a positive HPV test (Cuzick *et al.,* 1995). If it is assumed that these extra CIN cases have the same risk of developing into invasive cancer as the CIN cases with a positive Pap smear, these results give an upper limit to the sensitivity of the Pap smears as described in the model. However, we should bear in mind that there are data (although far from ideal) on the effect of Pap smear screening on incidence and mortality but not on the effect of HPV screening. In general, underestimation of the effectiveness of Pap smear screening will overestimate the favourable impact of introducing HPV screening and vice versa. Consequently, the range of confidence/uncertainty for the usefulness of HPV screening becomes larger if we account for the uncertainty about the effectiveness of Pap smear screening. However, investigation of the criticality of the assumptions (e.g. the sensitivity of Pap smear screening) for decisions on introducing HPV testing in cervical cancer screening will only be possible when more knowledge of the outcomes of HPV screening (i.e. more longitudinal data from HPV screening) becomes available. The same goes for the estimates on the costs of an HPV test in mass screening relative to those of the Pap smear.

The results of the modelling work show that for plausible values of prevalence, screening sensitivities and progression, HPV testing may be effective and cost-effective. For plausible assumptions about the model parameters, there are uses of HPV testing that would provide benefits at a lower cost than many existing healthcare programmes. However, the wide range of results that come from using high and low estimates for these parameters show that more work is needed to allow modelling using more robust estimates.

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Appendix

The sensitivity of combining cytology and HPV testing was calculated from the sensitivity of the Pap smear (see *Table 23*) and the sensitivity of HPV testing (see the section 'Two model versions' in this chapter) under the assumption that the sensitivities of the two tests are independent. The resulting sensitivities for combined testing are presented in *Table 29*.

TABLE 22 *Parameter values of the duration of detectable preclinical stages*

Disease stage	Duration: mean (5th percentile) (years)
Low-grade CIN (with or without HPV) [5–10][a]	4.0 (0.9)
High-grade CIN (with or without HPV) [11–14][a]	7.8 (1.8)
Invasive cancer (with or without HPV) [15, 16][a]	3.9 (0.9)

[ ] refers to the numbering of the disease stages in Figure 7
[a] *Mean of Weibull distribution, shape parameter 1.9*

TABLE 23 *Sensitivity of Pap smear and HPV testing by disease state*

Disease state	Pap smear result (%)				HPV + model A	HPV + model B
	Normal	Borderline	Mild	Moderate or more severe		
Normal	98	1	0.5	0.5	0	0
Low-grade CIN [8–10]	50	20	10	20	0	0
High-grade CIN [13,14]	40	15	20	25	0	0
Invasive cancer [16]	30	15	20	35	0	0
Normal + HPV [1–4]	98	1	0.5	0.5	90	50
Low-grade CIN + HPV [5–7]	50	20	10	20	90	50
High-grade CIN + HPV [11,12]	40	15	20	25	90	60
Invasive cancer + HPV [15]	30	15	20	35	90	70

[ ] refers to the numbering of the disease stages in Figure 7

TABLE 24 *Duration and sensitivity of HPV test for HPV disease stages in model versions A and B*

Disease stage	Model A		Model B	
	Duration (years)	Sensitivity of HPV test (%)	Duration (years)	Sensitivity of HPV test (%)
HPV that will develop into CIN + HPV [1–3]	10	90	1	50
HPV that will be cleared [4]	1	90	10	50

[ ] refers to the numbering of the disease stages in Figure 7

TABLE 25 *Estimates of costs by type of procedure*

Procedure	Cost (£)
Screening Pap smear[a]	16
Repeat Pap smear in surveillance[b]	20
HPV test[c]	17
Pap smear and HPV test in one screening session[d]	28
Repeat Pap smear and HPV test in surveillance[e]	33
Diagnostic work-up of the referral when no neoplasia is found[f]	190
Management of low-grade CIN	790
Management of high-grade CIN	1150
Curative primary treatment	
Microinvasive carcinoma	2970
IB invasive carcinoma	6000
II+ invasive carcinoma	6000
Care for advanced disease	9590

[a] *Includes the clinical staffing costs, laboratory costs and the cost of the call/recall system*
[b] *Includes the cost of an additional Cytoscreener® and of recall*
[c] *Includes the cost of the kit, though excludes the cost of the operator or laboratory costs*
[d] *Includes the cost of taking the HPV test*
[e] *Includes the cost of call and recall*
[f] *Colposcopy including the cost of the operator and the laboratory costs*

TABLE 26 *Categorisation of minor and more severe abnormalities for different test (combination)s*

Type of follow-up	Test (combination)		
	Cytology	HPV test	Cytology and HPV test
Surveillance	Borderline or mild dysplasia	HPV-positive	HPV-positive and normal cytology HPV-negative and borderline or mild dysplasia
Referral	Moderate or severe dysplasia		HPV-positive and borderline or worse on cytology

TABLE 27 *Effects and costs of different screening policies compared with the situation without screening in women between 20 and 65 years of age, two model versions. All figures are per 1000 women*

	Any model version		Model version A				Model version B			
	3-yearly cytology	5-yearly cytology	3-yearly cytology + HPV	5-yearly cytology + HPV	3-yearly HPV	5-yearly HPV	3-yearly cytology + HPV	5-yearly cytology + HPV	3-yearly HPV	5-yearly HPV
Favourable effects										
Mortality reduction, *n* (%)	8.3 (76)	7.0 (64)	9.6 (88)	9.0 (83)	8.6 (79)	7.7 (70)	9.3 (85)	8.4 (77)	7.4 (68)	6.0 (55)
Life-years gained (%)	80	67	93	87	84	74	89	81	72	58
Unfavourable effects										
Years in follow-up	220	145	700	465	600	400	1200	790	1135	735
Costs in £ (thousands)										
Screening	176	113	301	193	194	122	299	193	194	122
Surveillance	9	6	28	19	24	16	48	32	45	29
Follow-up of normal cytology with HPV+/–	11	7	12	8	1	0.5	15	10	2	1
Diagnosis and treatment										
Low-grade CIN	34	23	53	40	31	22	49	35	22	15
High-grade CIN	20	18	16	18	14	15	19	20	17	15
Invasive and advanced cancer	–170	–140	–200	–186	–179	–156	–191	–172	–150	–120
Total costs	80	26	210	92	85	19	238	117	131	63
Costs per life-year gained	390	155	900	420	400	100	1050	570	715	425

TABLE 28 *Effects and costs of different surveillance strategies compared with the situation without screening in case of 3-yearly screening between the ages of 20–65 years, two model versions. All figures are per 1000 women*

	Prevailing surveillance: any model version	Surveillance with combined cytological and HPV testing	
		Model version A	Model version B
Favourable effects			
Mortality reduction, *n* (%)	8.3 (76)	8.9 (82)	8.7 (80)
Life-years gained (%)	80	86	84
Unfavourable effects			
Years in follow-up	220	205	215
Costs in £			
Screening	176	174	174
Follow-up of normal cytology with HPV+/–	9	14	14
Diagnosis and treatment	11	12	13
Low-grade CIN	34	39	39
High-grade CIN	20	19	20
Invasive and advanced cancer	–170	–188	–183
Total costs	80	70	77
Costs per life-year gained	390	325	360

TABLE 29 *Sensitivity of combined Pap smear and HPV testing by disease state*

Disease state	Result of Pap smear and HPV test							
	Normal HPV–	Borderline HPV–	Mild HPV–	Moderate or more severe HPV–	Normal HPV+	Borderline HPV+	Mild HPV+	Moderate or more severe HPV+
Model A								
Normal	98	1	0.5	0.5	0	0	0	0
Low-grade CIN [8–10]	50	20	10	20	0	0	0	0
High-grade CIN [13, 14]	40	15	20	25	0	0	0	0
Invasive cancer [16]	30	15	20	35	0	0	0	0
Normal + HPV [1–4]	9.8	0.1	0.05	0.05	88.2	0.9	0.45	0.45
Low-grade CIN + HPV [5–7]	5	2	1	2	45	18	9	18
High-grade CIN + HPV [11, 12]	4	1.5	2	2.5	36	13.5	18	22.5
Invasive cancer + HPV [15]	3	1.5	2	3.5	27	13.5	18	31.5
Model B								
Normal	98	1	0.5	0.5	0	0	0	0
Low-grade CIN [8–10]	50	20	10	20	0	0	0	0
High-grade CIN [13, 14]	40	15	20	25	0	0	0	0
Invasive cancer [16]	30	15	20	35	0	0	0	0
Normal + HPV [1–4]	49	0.5	0.25	0.25	49	0.5	0.25	0.25
Low-grade CIN + HPV [5–7]	25	10	5	10	25	10	5	10
High-grade CIN + HPV [11, 12]	16	6	8	10	24	9	12	15
Invasive cancer + HPV [15]	9	4.5	6	10.5	21	10.5	14	24.5

[ ] refers to the numbering of the disease stages in Figure 7

Chapter 9
Discussion

Completeness

We have searched the major indexes for any mention of HPV and cervical neoplasia, checked the references of books on the subject and also the references of the major papers that were identified. This has turned up over 2100 references, and we are confident that most of the relevant papers published in peer-reviewed journals or well-known books and conference proceedings have been identified.

However, this is a very active area of research, and we are aware of a number of major ongoing or recently completed studies which are not published but for which, in some cases, initial data have been presented at scientific meetings. Inevitably this refers to the most recently developed assays and most relevant studies, which are more related to screening. Where possible we have tried to indicate preliminary results, but much of this is confidential until published. Awareness of these studies and their results will have a major impact on the choice of future studies. Known ongoing studies are listed in *Table 17*.

HPV testing methodology

Radical improvements have taken place in the methods for detecting HPV, and this is continuing. Detection of HPV in primary screening is currently best performed by one of two consensus PCR systems – MY09/11 or GP5+/6+, or by the HC-II system. The latter is commercially available and shows good reproducibility between laboratories and in retesting studies. In the future, more specific tests may be available, possibly for use as second-line procedures to refine indications for immediate referral, but it is not possible to review them at this stage. Research into a more sensitive *in situ* test shows early promise, but *in situ* techniques are currently inadequate for mass screening.

A range of collection devices have also been used to gather the sample. Most appear adequate, and published data suggest that there is little to differentiate between swabs, brushings, scrapes or lavage, although opinion generally favours use of a cervical brush sample and suggests that lavage may be less effective because of the large number of non-cervical (vaginal) cells that are collected.

Natural history

HPV infection of the cervix occurs after the beginning of sexual activity, and is affected by the number of sexual partners, their sexual history, and the age of first intercourse. HPV is clearly a venerally transmitted infection. Incidence rises rapidly in late adolescence, peaks in the mid-twenties and then declines steadily until the mid-forties, when it stabilises and then may begin to gradually rise again. Persistent infection is most clearly related to high-grade CIN, and most infections are transient with a mean time to clearance of less than a year. Serological studies have indicated that infection typically precedes the development of cancer by at least 5 years and can be apparent more than 20 years before the diagnosis of cancer. Women with borderline changes or mild dyskaryosis on their smears who test positive for a high-risk HPV are much more likely to have or progress to high-grade CIN than those who test negative.

Prevalence

The prevalence of HPV infection is clearly related to disease status. There is a wide range of positivity levels in women who are cytologically and colposcopically normal. This reflects different age distributions and different baseline risk characteristics in terms of sexual behaviour and previous disease. All but one HC-II study were carried out in young women where the (high-risk HPV) positivity rates were high (~20%). However, recent studies in normal women above the age of 35 years (most using PCR) indicate that a prevalence of about 5–7% can be expected in such a population.

There is more agreement about the positivity rate for women with high-grade CIN or cancer, especially in the more recent studies. Studies on cancer biopsies show positivity rates in excess of 95%, and the wide-spectrum tests for high-risk types indicate positivities in the 80–95% range for smears from women

with CIN II/III. In comparative studies, sensitivities of HPV testing for the detection of high-grade CIN are generally better than those of cytology.

Potential uses of HPV testing

HPV has three potential uses within the screening programme.

Management of borderline and low-grade cervical smears

Here the goal is to more efficiently manage women with minor cytological abnormalities. HPV positivity for high-risk types in such smears greatly improves the specificity and positive predictive value and reduces the need for repeated testing. But the cost-effectiveness also depends critically on the safety of reducing surveillance in women with borderline smears who are HPV-negative, and this is an area in need of further research.

Primary screening

HPV testing is more sensitive for detecting CIN II/III than cytology as a primary screening test. However, in many studies the specificity is substantially lower. The incidence of cancer rises sharply until 35 years of age, whereas the peak for CIN III is about 30 years of age and for HPV around the age of 20–25 years. Thus, the positive predictive value of HPV testing can be expected to increase with age. Until reliable second-stage tests become available to distinguish transient from persistent infections, the evidence suggests that it should not be used in women under the age of 30 years and that it should only be considered as an adjunctive test to cytology in women aged above 30 or 35 years. The increased sensitivity may allow the screening interval in negative women to be extended. It cannot be excluded that, with more evidence, HPV testing may prove to be adequate when used alone as the initial screening test. Ongoing studies will provide good data on the sensitivity and specificity of HPV testing at different ages. However, much larger studies with follow-up for at least 5 years will be needed to determine the length of protection afforded by a negative HPV test in conjunction with negative cytology. Definitive studies will also require use of invasive cancer as an end-point, since CIN II/III is not an obligate precursor and will regress in a variable proportion of cases. It is possible that the additional CIN cases detected by HPV only will have a different invasive potential than those detected by cytology, and this question needs to be addressed.

Post-treatment surveillance

Studies in this area are few and are lacking in many respects. There is a clear potential to more rapidly detect incomplete excision and to reduce the length of surveillance, and initial reports support this role. There is a need for further studies in this important area.

Economic and psychosocial issues

The results of our initial modelling studies for this review suggest that adding HPV testing could be a cost-effective adjunct to cytology, if it allows the screening interval to be lengthened considerably. These results are based on a number of assumptions about the effectiveness of the test which cannot be validated for lack of data. In addition, issues of cost are not clearly resolved at this stage; the cost for the test would be substantially reduced if it were to be used at a very high volume. Ideally, HPV testing needs to be compared with other new approaches to screening, but even less is known about most of these, so a comprehensive analysis is not currently possible. Further modelling is needed to quantify the effect of perturbations of the key parameters.

Very little is known about the psychosocial issues involved in providing cervical screening in general and HPV testing in particular. There are important issues regarding acceptability of testing, likely effects on participation in screening, and possible problems of stigmatising in women who are at little risk of significant disease. This needs to be evaluated. HPV testing may be amenable to self-sampling at home (with major cost implications), and this raises a further range of questions that need to be addressed.

HPV testing and the prevention of cancer

The current screening programme has had a substantial effect in reducing the incidence of and mortality from cervical cancer. Its effectiveness is, however, limited by: (1) coverage – 15% of eligible women have not been screened within the last 5 years; (2) the sensitivity of cytology – studies evaluating other screening techniques find that (even classifying borderline changes as positive) cytology misses 20–40% of high-grade CIN; and (3) quality – the effectiveness of cytological screening is highly dependent on the quality of taking, preparing and reading of smears, and all of these are subject to human error.

Epidemiological evidence suggests that the majority of cervical cancer is caused by persistent infection with an oncogenic HPV, and that infections which lead to cancer typically occur before the age of 35 years. Published research shows that PCR and HC-based testing has the potential for detecting HPV infections in cervical scrapes. Further, HPV positivity remains high in archival smears taken up to 10 years prior to cancer diagnosis. It is suggested that, because of viral shedding, the necessity to sample from the whole of the transformation zone may be less when using the scrape to test for HPV DNA compared with when it is used to look for dyskaryotic cells. It has also been demonstrated that these HPV tests can detect a significant amount of high-grade CIN in cytologically normal women.

Overall there is good evidence that introduction of HPV testing would reduce the amount of untreated high-grade CIN. Only a proportion of untreated high-grade CIN will progress to cancer. Indeed, for study purposes, Dutch gynaecologists have followed women with high-grade CIN only treating those with evidence of CIN III in three or more quadrants of the cervix. It is unclear whether the additional cases of CIN detected by HPV testing have the same potential for progression to invasive cancer as those associated with abnormal cytology.

Thus, high-grade CIN is an unproven surrogate marker for the development of invasive cancer. Direct verification of a reduction in cancer incidence should be obtained before introducing a new test into the screening programme. This requires a study which is very large with at least a 5 year follow-up. However, when viewed as part of the UK screening programme, a study requiring the addition of HPV testing for perhaps 2% of women being screened over a 2 year period is small compared with the cost of the screening programme. If well conducted, it would definitively answer the question of whether (and if so how) HPV testing should be used within the cervical screening programme.

Chapter 10

Answers to research questions

The questions posed in chapter 2 of this review can now be answered.

(1) Does HPV testing have a role as part of the primary screening test for cervical neoplasia? In addressing this question we have considered a number of more detailed questions including:

(a) Would the use of HPV testing increase the amount of high-grade CIN detected?

Yes, HPV testing used in primary screening would increase the amount of high-grade CIN detected.

(b) What are the false-positive rates of the available HPV tests? A false-positive test is defined as one with a positive result in a woman who does not have, and will not shortly develop, high-grade CIN.

Overall the positivity rate of tests for high-risk HPV types in women not known to have CIN was 13%, ranging from 10% for PCR using GP5/6 primers to 20% using HC-II. Rates are about half these levels in women aged over 35 years. The rates for HPV type 16 are much lower, but the sensitivity for high-grade CIN substantially reduced it. However, judicious selection of a few HPV types might improve specificity without substantially affecting sensitivity.

(c) Can HPV testing be used to safely lengthen the screening interval?

There is insufficient data to answer this question. It is possible that the screening interval could be extended for women aged 35 years or older with one HPV-negative test and substantially extended for those with two or more consecutive negative tests.

(d) Can HPV testing be used to safely restrict the population undergoing screening (e.g. < 50 years of age)?

There is insufficient data to answer this question, which can be viewed as an extension of the previous question. The answer largely depends on the extent to which cancer diagnosed at the age of 50 years is preceded by a persistent HPV infection before that age. The epidemiological evidence suggests that this is quite plausible. Very high sensitivity for the HPV test is also required.

(e) Would HPV testing be most effective if applied only to a particular subpopulation (e.g. only in women over 30 years old)?

Primary HPV testing in women under 30 years of age is unlikely to be cost-effective because of the high rates of transitory HPV infections in such women.

(f) Would increased detection of high-grade CIN by HPV testing result in a reduction in subsequent cancer? What proportion of the additional high-grade CIN lesions detected by HPV would progress to cancer before being detected by subsequent cytological tests?

It is not possible to determine this from existing studies. Nevertheless, studies of retrospective HPV testing have demonstrated that HPV DNA is often present in cytologically negative smears in the years preceding diagnosis of invasive cancer.

(g) Could women with inadequate cytology, but a negative HPV test, be safely recalled at the standard interval?

There is minimal data regarding cytology following an inadequate smear together with an HPV test. However, the sensitivity of HPV testing (about 75% for high-grade CIN and over 90% in cancer biopsies) is probably sufficient to make it unnecessary to repeat an inadequate smear accompanied by a negative HPV.

(2) Can HPV testing be used to improve the management of low-grade cytological abnormalities?

HPV testing may improve the management of women with borderline or mildly dyskaryotic

abnormalities, and small studies have indicated the high sensitivity of HPV testing in this setting. Several large studies addressing this question are nearing completion and should help to resolve the issue. The safety of reduced surveillance of women with minor cytological abnormalities who test negative for HPV has yet to be demonstrated. Different strategies may be optimal at different ages and for different cytological results (borderline changes versus mild dyskaryosis). Limited introduction of HPV testing with careful monitoring may be justified but should await the assessment of results from the two studies in this area that have been submitted for publication (Meijers/Walboomers and Manos/Kinney).

Would use of HPV testing in this setting:

(a) Reduce or increase anxiety?

There are no published studies addressing this issue.

(b) Reduce the rate of invasive cancer?

HPV testing in this setting is unlikely to have a noticeable impact on the rate of invasive cancer in the population since the majority of cancers may arise in unscreened women or following negative cytology. It should, however, reduce the number of cancers in women who do not attend for repeat cytology.

(c) Affect the number of unnecessary invasive procedures?

Depending on how women are managed, the addition of HPV testing would almost certainly affect the number of unnecessary invasive procedures. If women with a negative HPV test were returned to routine screening, then the number of invasive procedures would be reduced. If, on the other hand, women testing positive were immediately referred for colposcopy, the number of invasive procedures would increase.

(d) Shorten the time taken to resolve the disease status in women with low-grade abnormalities?

Almost certainly introduction of HPV testing would shorten the time taken to resolve low-grade cytological abnormalities.

(3) Can HPV testing be used to improve the accuracy of follow-up after treatment for precancerous or cancerous lesions? Can women who have had a negative HPV test after treatment be safely returned to routine call and recall?

The limited published data support the use of HPV testing to reduce post-treatment surveillance. Additional studies should clarify the safety of returning women testing HPV-negative to routine recall.

(4) Would HPV testing be cost-effective in any of the three settings considered: (a) primary screening; (b) management of low-grade cytological abnormalities; and (c) post-treatment surveillance? To address this question we have considered:

(i) The likely cost of HPV testing.
(ii) The effect of introducing HPV testing on the number of smears taken, the number of colposcopy referrals and the number of women treated, and on the number of cancers prevented and lives saved.

(a) Additional HPV testing in primary screening will not be cost-effective unless (1) the cost of HPV testing can be substantially reduced, or (2) the screening interval could be substantially lengthened as a result, or (3) the age at which women are no longer invited for screening could be lowered following a series of negative HPV tests. It is plausible that the screening interval could be doubled as a result of HPV testing, but additional retrospective studies and studies with long-term follow-up are required to establish this point.

(b) HPV testing in women with minor cytological abnormalities is being studied in large cohorts by at least four groups. Two of these studies should be published by the end of 1999.

(c) If women testing negative for HPV after treatment could be safely removed from surveillance, there would be a cost saving.

(5) How might HPV testing be implemented in practice?

(a) What is the most effective technology for the detection of HPV?

The only commercially available HPV testing technology is HC. PCR-based tests are also highly effective, but would require the establishment of specialist centres to provide this service on a large scale.

(b) How will HPV testing be influenced by other developing technologies such as (semi)automated cytology and liquid cytology?

This is largely outside of the scope of this review. Liquid-based collection offers the advantage of providing aliquots that could be used both for thin-layer cytology and HPV testing. If HPV testing were to be introduced as a primary test, it is likely that one would wish to combine it with liquid cytology. Automated or semi-automated cytology then becomes an attractive option, if cost-effective, since the combined sensitivity of HPV testing plus automated cytology will be very high even if automated cytology is less sensitive than conventional cytology.

(c) Could HPV testing replace cytology as the primary screening test? If they are both to be used, how should one manage a woman who had a normal smear, but tested positive for HPV?

The potential exists for HPV testing using one of the newer assays to become the sole method of primary screening, especially for older women, but this will require consistent evidence of high sensitivity for high-grade lesions that are likely to progress to cancer. For younger women, cytology may only need to be performed in HPV-positive women. The cost-effectiveness of such an approach will depend largely on the relative cost of cytology and HPV testing and the screening interval employed.

Women positive for HPV but negative on cytology would be treated much like those whose smears are currently borderline – they would be offered repeat testing at 6 months or 1 year. The (cost-)effectiveness of such a policy has not been evaluated.

(d) What quality assurance measures would be needed for laboratories undertaking HPV testing for the cervical screening programme?

This is beyond the scope of this review.

(6) What future research is needed to provide more reliable answers to the questions posed?

See the conclusions to this review (chapter 11).

Chapter 11

Conclusions, implications and recommendations

(1) The clearest role for HPV testing at the moment is in the management of women with borderline or mildly dyskaryotic smears. In particular, those aged above 30 years who test positive for high-risk types could be referred immediately for colposcopy, while those younger than 30 years who test negative could receive less-intensive surveillance.

Implications for practice. The evidence would support limited introduction with careful monitoring in this context. This should be done in such a way that comparisons with conventional management can be made.

Recommendation for research.

(a) The safety of returning women with borderline/mild smears which are HPV-negative to routine screening requires further research.
(b) HPV testing could either be performed on material stored from the initial scrape or by inviting women back for collection of a second sample. If a second sample is used, it could either be taken shortly after the initial cytology result becomes available or at 6 months. The cost and psychological implications of these three alternatives requires careful evaluation.

(2) HPV testing with a consensus PCR method or HC-II has a high sensitivity for high-grade CIN, usually exceeding that of cytology and certainly identifying cases missed by cytology.

Implications for practice. Although this is not sufficient to recommend routine screening with HPV tests (see below), the evidence would appear to support limited use of the test in conjunction with cytology in certain situations (such as when women are likely not to return for further screening) when high sensitivity is important.

Recommendation for research. Studies should be carried out to examine the safety of extending the screening interval and/or stopping screening after a certain age (e.g. 50 years) in women with history of negative results for both HPV and cytology.

(3) HPV testing appears to be less specific than cytology (as used for referral in the UK screening programme) with false-positive rates ranging from 3 to 10% in 'normal' women aged over 30 years: false-positive rates are higher in younger women. It should be noted that, if borderline smears are considered positive, the specificity of cytology is also poor particularly in younger women.

Recommendation for research. Further work is needed to clarify the management of HPV-positive but cytology-negative women and/or to establish methods for determining persistence of HPV infection.

(4) The potential exists for HPV testing using one of the newer assays to become the sole method of primary screening, especially for older women, but this will require consistent evidence of high sensitivity for high-grade lesions that are likely to progress to cancer. For younger women, cytology may only need to be performed in HPV-positive women. The cost-effectiveness of such an approach will depend largely on the relative cost of cytology and HPV testing and the screening interval employed.

Recommendation for research. More studies are needed.

(5) A full evaluation of HPV testing should provide information on the length of protection of a negative result and ideally demonstrate a reduction in cancer incidence. Several trials in the 10,000 patient range of current HPV tests are ongoing and should resolve issues of sensitivity, specificity and reproducibility and shed some light on the long-term risk of high-grade CIN following a negative HPV test.

Recommendations for research.

(a) New studies should take into account these ongoing trials.
(b) All large ongoing and future studies of HPV testing should follow women for at least 5 years.
(c) Ongoing studies should be encouraged to collaborate internationally to maximise the accuracy with which incidence reduction can be estimated.
(d) Consideration should be given to a very large (100,000–200,000 participants to receive HPV testing) randomised clinical trial to evaluate the effect of HPV testing on cancer incidence, and the length of protection afforded by a negative HPV test in conjunction with negative cytology. This should be incorporated into the national screening programme to minimise costs.

(6) A role may exist for HPV testing in post-treatment surveillance of high-grade CIN and localised cancer to determine more quickly and accurately if treatment has completely eradicated local disease.

Recommendation for research. Focused trials in the area are needed.

(7) Modelling studies show that HPV testing may be a cost-effective screening modality either alone or in conjunction with cytology. These models are dependent on the input parameter, which are currently ill determined due to lack of data.

Implications for practice. In view of the lack of full evidence on the (cost-) effectiveness of HPV screening, it should not yet be implemented in routine primary screening.

Recommendation for research. Further field studies are needed to improve estimates of the key model parameters.

(8) HPV testing has the potential to be used on self-collected cervical samples. This could help to improve coverage by reaching those who do not participate in the current screening programme.

Recommendations for research.

(a) The sensitivity of self-sampling should be evaluated.
(b) Pilot work should investigate whether the option of self-sampling could improve coverage.

(9) HPV testing with HC appears to be a readily automatable procedure that can achieve high throughput with a low level of technical support. PCR methods using the MY09/11 or GP5+/6+ consensus primers provide good results, but are not yet commercially available.

Recommendation for research. More work is needed to evaluate the implementation of these assays in different laboratories.

(10) HPV testing needs to be viewed in the context of potential improvements in cytology using thin-layer smears taken from liquid samples and automated reading.

Recommendation for research. A large study should evaluate the best way of integrating these technologies and the most cost-effective strategy.

Acknowledgements

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The referees are thanked for their perseverance in reading the report and the quality of their comments.

Appendix 1

Search strategies

Two strategies were used to identify studies for the literature review.

Strategy 1

The first strategy was designed to be less restrictive and to exclude irrelevant papers later. This was done by using a limited number of very broad search headings:

- Human papillomavirus and diagnos*
- HPV and diagnos*
- Human papillomavirus and cervi* cancer
- HPV and cervi* cancer
- Cervi* cancer and diagnos*

The following electronic databases were searched:

- MEDLINE
- EMBASE
- Cochrane Database of Systematic Reviews

Strategy 2

The second strategy was to combine searches with ANDs and ORs so as to find mostly relevant papers. The following searches A–K were conducted, using the electronic database MEDLINE.

Searches A–C

(1) HPV OR Human papillomavirus
(2) cervi*
(3) cancer OR carcinoma OR neoplasia OR CIN OR SIL
(4) test* OR screening OR diagnos*
(5) DNA OR PCR OR molecular OR Hybrid Capture OR Southern OR assay
(6) cost* OR' economic
(7) natural history OR model* OR progression

Search A: (1) AND (2) AND (3) AND (4) AND (5) ((1) and (2) title words, (3)–(5) title, keywords or abstract)
Economic
Search B: (1) AND (2) AND {(4) OR (5)} AND (6) (title, keywords or abstract)
Natural history
Search C: [(1) OR {(2) AND (3)}] AND (7) (title words only)

All three searches were limited to the English language and human only.

Search D

The results of this search are the papers found by search (7).

(1) *Papillomavirus, Human (exploded + focused)
(2) hpv (title word search)
(3) 1 or 2
(4) *Vaginal Smears (exploded + focused)
(5) (cervi* or vagina*) and (smear* or test* or screen* or diagno* or swab* or scrap*)
(6) 4 or 5
(7) 3 and 6 (limited to english language and human only)

Searches E–K

The words are assumed to be in the title, keywords or abstract:

(1) (HPV or human papillomavirus)
(2) (cervix or cervical)
(3) (SUBJECTS: human)
(4) (sensitivity OR specificity OR false positive rate OR positive predictive value)
(5) (natural history OR progression OR screening interval OR screening frequency OR follow-up)
(6) (prevalence OR rates OR positivity)
(7) age AND (compared OR relative OR contrast)
(8) inadequate
(9) cytology OR smear OR smears
(10) (test OR tests OR testing)
(11) (anxiety OR psycholog* OR quality of life)
(12) (cost OR costing OR price)
(13) (model or modelling)
(14) (JOURNAL: Econom*)

Search E: 1 AND 2 AND 3 AND 4
Search F: 1 AND 2 AND 3 AND 5
Search G: 1 AND 2 AND 3 AND 6 AND 7
Search H: 1 AND 2 AND 3 AND 8 AND 9 AND 10
Search I: 1 AND 2 AND 3 AND 9 AND 10 AND 11
Search J: 2 AND 3 AND (9 OR (1 AND 10)) AND 12
Search K: 1 AND 2 AND 14

Results of the searches were merged into a common EndNote 2 database, and duplicate citations were deleted. The resulting database contained 2109 different articles that were abstract scanned by two team members for relevance to the questions posed in this study.

Appendix 2

Data extraction forms: methodology, prevalence, natural history and modelling

Methodology

Study Details:

Reviewer: Reference Number:

Relevant Background Information:
_____
_____
_____

Includes Information on:

Absolute Sensitivity ☐ Relative Sensitivity ☐ Specificity ☐ PPV ☐ NPV ☐ Sample Stability ☐

Population Type(s):

Enter population types at the head of each column (e.g. screening, STD, general outpatient, gynae outpatient, colposcopy referral, ASCUS/borderline, CIN I, CIN II, CIN III, CIS, invasive cancer, etc.). Enter population characteristics below each heading

Pop. Type					
Number					
Mean Age					
Age Range					
Ethnicity					

Sampling Type:

Cervical Scrape ☐ Cervical Brush ☐ Vaginal Lavage ☐ Vaginal Swab ☐ Urine ☐

Other (state) _____

Testing Methodology:

PCR: No. Cycles ☐

GP5/6 ☐ GP5+/6+ ☐ My09/11 ☐ Other consensus ☐ _____

Type Specific ☐ Types & primers _____

Detection method: Gel (Southern) ☐ Restriction ☐ ELISA ☐ Dot ☐ Other ☐ _____

Hybrid Capture: HC I ☐ H C II ☐
High risk only ☐ High & Low Risk ☐

Other ☐ *describe* _____

Gold Standard:
Other Relevant References:

If only one test is used put line through test 2 and fill out marginals. If two tests are used but 2x2 tables are not given fill out marginals. If results are given, no need to fill in marginal totals.

Population:

Test 1: ______________________ Test 2: ______________________

Test 2 \ Test 1	+	−	T
+			
−			
T			

Population:

Test 1: ______________________ Test 2: ______________________

Test 2 \ Test 1	+	−	T
+			
−			
T			

Population:

Test 1: ______________________ Test 2: ______________________

Test 2 \ Test 1	+	−	T
+			
−			
T			

Population:

Test 1: ______________________ Test 2: ______________________

Test 2 \ Test 1	+	−	T
+			
−			
T			

Population:

Test 1: ______________________ Test 2: ______________________

Test 2 \ Test 1	+	−	T
+			
−			
T			

Population:

Test 1: ______________________ Test 2: ______________________

Test 2 \ Test 1	+	−	T
+			
−			
T			

Population:

Test 1: ______________________ Test 2: ______________________

Test 2 \ Test 1	+	−	T
+			
−			
T			

Population:

Test 1: ______________________ Test 2: ______________________

Test 2 \ Test 1	+	−	T
+			
−			
T			

Other Comments:

Prevalence Studies

Study Details:

Reviewer _____ Reference Number:

Include ☐ Exclude ☐ _____ Transfer to: _____

Description of study population (STD, gynae, etc):

Number of subjects:

Subdivision of population (cytology, histology, age, etc):

Age: Mean _____ Range _____

Method(s) of Sample collection _____

Spatula ☐ Lavage ☐

Brush ☐ Urine ☐

Cervical Swab ☐ Other ☐ _____

Vaginal Swab ☐

DNA methodology(s)

	Primers	Probes	Cycles	Types	Detection Method
Primary/Secondary					
Consensus PCR ☐					
Type Specific PCR ☐					

PCR containment conditions (to prevent contamination) described ☐ Adequate ☐

Hybrid Capture I ☐ High Risk/Low Risk

Hybrid Capture II ☐ High Risk/Low Risk

Other: _____

Method Quality:

Replicated Samples Yes/No

Negative Controls Yes/No

Positive Controls Yes/No

Other Comments _____

_____

Estimated Sensitivity _____

Other relevant papers in references

.....

Other papers on same patients

If the population is subdivided i.e. women <30 & women >30, then fill in a separate sheet for each population.

Population(s)	HPV positivity (%)							
	Number	Type 16	Type 18	Type 31	Type 33	High Risk	Other _____	
Normal (Unselected)								
Cytology Negative								
Abnormal Cytology/ Histology Negative								
Borderline/CIN1								
Histology CIN2/CIN3								
Histology CIN3/CIS								
Cancer								
Other _____								
Other _____								
Other _____								

Reviewer _____ Reference No. _____ Page No. _____

Natural History Studies

Study Details

Reviewer: Reference Number:

Other papers on same cohort:

Type of study: Prospective ☐, Nested case-control ☐, Other ☐ (specify)

Description of cohort: (inclusion criteria, recruitment strategy/setting, country/ethnicity):

Initial Cohort
Size of cohort Age range Mean age
Tested by: Cytology ☐, Colposcopy ☐, Histology ☐, HPV (DNA) ☐, HPV antibodies ☐

Intermediate Examinations
Maximum Number (excluding first and last): Minimum: Frequency (No. per year):
Tested by: Cytology ☐, Colposcopy ☐, Histology ☐, HPV (DNA) ☐, HPV antibodies ☐
Completeness of Follow-up (proportion of planned visits completed):

Final Examination
Number having final examination
Tested by: Cytology ☐, Colposcopy ☐, Histology ☐, HPV (DNA) ☐, HPV antibodies ☐

Duration of Study: Maximum Follow-up Other relevant measure of follow-up
Women years of follow-up: Median Follow-up

Results (Include initial state as final state to show persistence)
Give cytology result, biopsy result and type specific HPV result if known.

Initial State (S1)	Final State (S2)	No. starting in S1	No. moving (S1 to S2)	Annual transition rate

DNA Assay: Tick all used. Comment if method changed during follow-up.
Consensus PCR ☐, Type specific PCR ☐, Hybrid Capture I ☐, Hybrid Capture II ☐, Southern ☐, FISH ☐, NISH ☐, ViraPap ☐, Other ☐ _____.

Details:

Antibody Assay: (Antigens, reference)

HPV test:

No. Tested: Once ☐ Twice ☐ 3 Times ☐ 4 or more ☐

Number: Always positive ☐ Positive to negative (staying negative) ☐ Fluctuating (+ve, –ve, +ve) ☐

Average positivity rate on tests following an initial positive (No. +ve/ Total No.)

Interventions (e.g. Biopsy, Treatment)

Summary of results

Other Comments

Additional references

Appendix 3

References: included papers

Prevalence

Agorastos T, Bontis J, Lambropoulos AF, *et al.* Epidemiology of human papillomavirus infection in Greek symptomatic women. *Eur J Cancer Prev* 1995;**4**(2):159–67. **PR1**

Anonymous. Polymerase chain reaction and direct DNA tests in detection of human papillomavirus (HPV) DNA in cytologically normal and abnormal cervical smears. Scandinavian Multicenter Study Group. *Acta Obstet Gynecol Scand* 1992;**71**(2):98–103. **PR3**

Aziz DC, Ferre F, Robitaille J, *et al.* Human papillomavirus testing in the clinical laboratory. Part I: squamous lesions of the cervix. *J Gynecol Surg* 1993;**9**(1):1–7. **PR4**

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Methodology exclusions

Reference number	Reason
ME1	Sample size too small
ME2	Insufficient data for valid evaluation of PCR
ME6	Non-cervical and biopsy
ME8	HPV copy number amplification – not PCR
ME11	Type-specific PCR versus ViraPap/ViraType but data does not allow one to distinguish broader spectrum for ViraPap
ME13	Nested PCR and HPV 16 only
ME14	No direct comparison uses sequential samples
ME16	No comparison
ME18	Comparison only possible for HPV 16
ME19	A detection system (EIA) for MY09/11 PCR products
ME20	Prevalence data only
ME21	Exclude
ME23	Cloning of HPV 16 in 1983
ME27	No technology comparison
ME29	No technology comparison
ME30	Morphological assessment of HPV type
ME33	HCA association with cervical cancer
ME35	Sample size to small (n = 30)
ME37	Type-specific PCR for HPV 16 only and no comparative data
ME38	Dot blot only on paired biopsy and scrape specimens
ME39	Not relevant to screening as superseded by EIAs
ME42	No technology comparison – a prevalence study
ME44	Impossible to work out basis for comparison accurately
ME46	No comparison of technologies – original paper for type-specific PCR (type 31)
ME48	Analysis of biopsies using type-specific PCR 16 and 18 only compared with SB and DB
ME50	Outdated technology with suspect sensitivity and specificity
ME54	No comparative data
ME56	Type-specific PCR for HPV 16 only compared with SB
ME57	Self-sampling with HPV – profile assay (ViraPap) outdated and results not comparable to more modern techniques
ME58	PCR versus ViraPap – too few samples for meaningful comparison
ME59	Type-specific PCR (HPV 16) to in-house slot blot technique
ME60	No comparative data and presented data suspect
ME63	In situ PCR on formation fixed tissues – not relevant to screening
ME69	PCR on formation-fixed biopsies
ME72	Interlaboratory comparison of the same test (another study)
ME73	Exclude from methods – include in prevalence
ME78	Taq-Man technology not available for routine diagnosis
ME80	Exclude
ME82	Exclude from technology comparison – modified MY09/11
ME83	Data difficult to interpret and sample size small
ME86	No comparative technology for HPV with/without prevalence

continued

Methodology exclusions *contd*

Reference number	Reason
ME87	Sampling method for SB analysis
ME88	HPV seropositivity in relation to HPV cervical infection
ME89	Sample size small (220+)
ME91	Outdated technology
ME94	Exclude from methods – direct comparison of HC-I versus HC-II not possible for data presented
ME95	Exclude
ME98	Sample too small
ME100	Sharp assay no longer available and was unsuitable anyway
ME101	No comparative data presented
PR7	Direct comparison not possible
PR11	Data presented not sufficient for comparison of technologies
PR17	No technology comparison data presented
PR51	No technology comparison
PR56	Sample size too small (n = 20)
PR57	No technology comparison
PR67	No methodology comparison
PR77	Relevant data originally reported in PR8 (Bauer *et al. JAMA* 1991;**265**(4):472–7)
PR80	No technology comparison
PR83	Data not suitable for direct comparison
PR87	Insufficient data for methods comparison
PR89	Data insufficient for a comparison of technologies

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This report was identified as a priority by the Population Screening Panel.

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Copies of this report can be obtained from:

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 1703 595 639 Email: hta@soton.ac.uk
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