Management of Abnormal Smears

23 November 2013
Dr TC Pun
Honorary Associate Professor
Dept of Obstetrics & Gynaecology
The University of Hong Kong
Management of Abnormal Smears

- Guidelines
- Endometrial cells
- Smear test specimen adequacy
- Infections in cervical smear
- Other issues
1 INTRODUCTION

The Guidelines on the Management of Abnormal Cervical Cytology was revised in 2002 because of the revision of the Bethesda System in 2001 and the introduction of HPV testing in the management of atypical squamous cells. This revision is based on new information being available, including the ASC-US/LSIL Triage Study (ALTS) and the use of HPV testing as an adjunct in cervical cytology. In this guideline, HPV testing refers to testing for high-risk HPV types (1,2,3).

In this revision, the recommendations for atypical squamous cells (ASC) and low-grade squamous intraepithelial lesion (LSIL) are essentially unchanged, except in special

when it forms part of an organized programme of screening (4).

2.3 The long latency which normally exists between the emergence of precursor lesions and occurrence of invasive, life threatening disease provides the foundation of the screening program for cervical cancer (5).

3 TARGET POPULATION AND SCREENING INTERVAL

3.1 The target population encompasses all women from age 25 or the time of commencing sexual activity (whichever is later) until they reach 65 years of age. In view of the rarity of
Welcome to The Hong Kong Society for Colposcopy and Cervical Pathology

A New Website is undergoing construction at the moment, due to be launched in September 2012.

Conference of Asia Oceania Research Organization Genital Infection and Neoplasia (AOGIN 2012)

New Scientific Data for Cervical Cancer Vaccines (6 July 2010)

List of HKCOG-HKSCCP Accredited Colposcopists

Training and Accreditation of Colposcopists, Smear Takers and Colposcopy Centres

List of HKSCCP Accredited Smear Takers

List of HKCOG-HKSCCP accredited colposcopy service centres
Colposcopy Service Provision and Standard

(1) All colposcopy should be performed by colposcopists or trainees under supervision.
(2) Colposcopists must have undergone training in colposcopy recognized by the HKCOG.
(3) The service should record the waiting times for both new patients and treatments.
   - for patients with cytology showing invasive lesion, patient should be offered an appointment to be seen within two weeks.
   - for patients with cytology showing high grade SIL, patient should be offered an appointment to be seen within 6 weeks
   - for patients with cytology showing ASCUS where high grade lesion cannot be excluded or AGUS favors neoplastic or two consecutive ASCUS/AGUS not otherwise specified or low grade SIL, patient should be seen within 12 weeks
(4) The service should adhere to local written protocols that should reflect published Guidelines in Hong Kong.
(5) The service should ensure adequate data collection for quality assurance at annual reviews.
   - At least 60% correlation between colposcopic diagnosis and histological diagnosis of high grade lesion is expected i.e. sensitivity. Data on the positive predictive value of colposcopic diagnosis should be provided as
2012 Updated Consensus Guidelines for the Management of Abnormal Cervical Cancer Screening Tests and Cancer Precursors

L. Stewart Massad, MD, Mark H. Einstein, MD, Warner K. Huh, MD, Hormuzd A. Katki, PhD, Walter K. Kinney, MD, Mark Schiffman, MD, Diane Solomon, MD, Nicolas Wentzensen, MD, and Herschel W. Lawson, MD, for the 2012 ASCCP Consensus Guidelines Conference

From Washington University School of Medicine, St. Louis, Missouri; Albert Einstein College of Medicine, New York, New York; University of Alabama School of Medicine, Birmingham, Alabama; Division of Cancer Epidemiology and Genetics and Division of Cancer Prevention, National Cancer Institute, Bethesda, Maryland; The Permanente Medical Group, Sacramento, California; and Emory University School of Medicine, Atlanta, Georgia

© 2013, American Society for Colposcopy and Cervical Pathology
Journal of Lower Genital Tract Disease, Volume 17, Number 5, 2013, S1–S27
ASC-US

- Reflex HPV DNA testing – refer for colposcopy if positive; if negative, repeat smear at 12 months
- Repeat smear at 4-6 months and refer for colposcopy if abnormality persists; return to routine screening after 2 repeat negative
- Colposcopy service standard: should be seen within 12 weeks
Box 1. Essential Changes From Prior Management Guidelines*

- Cytology reported as negative but lacking endocervical cells can be managed without early repeat.
- CIN 1 on endocervical curettage should be managed as CIN 1, not as a positive ECC.
- Cytology reported as unsatisfactory requires repeat even if HPV negative.
- Genotyping triages HPV-positive women with HPV type 16 or type 18 to earlier colposcopy only after negative cytology; colposcopy is indicated for all women with HPV and ASC-US, regardless of genotyping result.
- **For ASC-US cytology, immediate colposcopy is not an option. The serial cytology option for ASC-US incorporates cytology at 12 months, not 6 months and 12 months, and then if negative, cytology every 3 years.**
- HPV-negative and ASC-US results should be followed with co-testing at 3 years rather than 5 years.
- HPV-negative and ASC-US results are insufficient to allow exit from screening at age 65 years.
- The pathway to long-term follow-up of treated and untreated CIN 2+ is more clearly defined by incorporating co-testing.
- More strategies incorporate co-testing to reduce follow-up visits. Pap-only strategies are now limited to women younger than 30 years, but co-testing is expanded even to women younger than 30 years in some circumstances. Women aged 21-24 years are managed conservatively.
<table>
<thead>
<tr>
<th>Action</th>
<th>Action Description</th>
<th>Colposcopy Service Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASC-H, LSIL</td>
<td>Refer for colposcopy</td>
<td>Seen within 12 weeks</td>
</tr>
<tr>
<td>HSIL</td>
<td>Refer for colposcopy</td>
<td>Seen within 6 weeks</td>
</tr>
<tr>
<td>Invasive cancer</td>
<td>Biopsy if frank growth; otherwise early referral for colposcopy</td>
<td>Seen within 2 weeks</td>
</tr>
</tbody>
</table>
Abnormal glandular cells

• Can perform endocervical sampling
• Refer for colposcopy
• Colposcopy service standard: seen within 12 weeks
• AGC-endometrial cells – endometrial sampling first
• (AGC-favor neoplasia, AIS – early referral for colposcopy)
Management of Abnormal Smears

• Special circumstances – postmenopausal women, pregnant women, adolescents
• Endometrial cells
Management of Abnormal Smears

• Guidelines
• Endometrial cells
• Smear test specimen adequacy
• Infections in cervical smear
• Other issues
## Endometrial cells

<table>
<thead>
<tr>
<th>After menopause</th>
<th>Investigation recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;=40</td>
<td>Interpret the smear result together with the clinical findings to determine the management</td>
</tr>
<tr>
<td>&lt;40</td>
<td>Treat as normal</td>
</tr>
</tbody>
</table>
European guidelines for quality assurance in cervical cancer screening: recommendations for clinical management of abnormal cervical cytology, part 1


*Birmingham Women’s Hospital, Birmingham, UK, †Unit of Cancer Epidemiology, Scientific Institute of Public Health, Brussels, Belgium, ‡Department of Obstetrics and Gynaecology, Royal Preston Hospital, Preston, UK, §Technical University, Munich, Germany, ¶Department of Obstetrics and Gynaecology, Hôpitaux Universitaires de Strasbourg, Strasbourg, France, **Centro de Oncologica de Coimbra, Coimbra, Portugal, ††Mass Screening Registry, Finnish Cancer Registry, Helsinki, Finland, ‡‡Department of Obstetrics and Gynaecology, Helsinki University Central Hospital, Helsinki, Finland and §§Department of Obstetrics and Gynaecology, Coombe Women’s Hospital, Dublin, Ireland

Accepted for publication 10 September 2008


European guidelines for quality assurance in cervical cancer screening: recommendations for clinical management of abnormal cervical cytology, part 1

The current paper presents the first part of Chapter 6 of the second edition of the European Guidelines for Quality Assurance in Cervical Cancer Screening. It provides guidance on how to manage women with abnormal cervical cytology. Throughout this article the Bethesda system is used for cervical cytology terminology, as the European guidelines have recommended that all systems should at least be translated into that terminology while cervical intraepithelial neoplasia (CIN) is used for histological biopsies (Cytopathology 2007; 18:213–9). A woman with a high-grade cytological lesion, a repeated low-grade lesion or with an equivocal cytology result and a positive
Management of cervical smears showing endometrial cells

• Follow up by repeat cervical cytology is not appropriate
• Endometrial cells in keeping with the stage of the cycle – no need for further investigation
• Endometrial cells not in keeping with stage of the cycle – no need for further investigation in young women, but may require assessment in older women

Jordan et al 2008 Cytopathology 19:342-54
• Endometrial cells in women with an IUD – no need for further investigation

• Normal appearing endometrial cells in a postmenopausal woman – always warrant further assessment even if the woman is using oestrogen replacement therapy. The minimum assessment should be a vaginal ultrasound to assess the endometrial thickness

• Atypical endometrial cells or cytological findings suggestive of endometrial adenocarcinoma – ultrasound, hysteroscopy and biopsy or diagnostic curettage

Jordan et al 2008 Cytopathology 19:342-54
Other than during the first half of the menstrual cycle, the presence of spontaneously exfoliated endometrial cells in the Pap smear is abnormal. The preferred cutoff day for abnormal shedding ranges from day 10 to 14, according to different authorities.

DeMay 1996 The art & science of cytopathology Vol 1, p124. ASCP Press
Management of Abnormal Smears

- Guidelines
- Endometrial cells
- **Smear test specimen adequacy**
- Infections in cervical smear
- Other issues
ASCCP Patient Management Guidelines: Pap Test Specimen Adequacy and Quality Indicators

Diane D. Davey, MD, Chair,¹ R. Marshall Austin, MD, PhD,² George Birdsong, MD,³ Henry W. Buck, MD,⁴ J. Thomas Cox, MD,⁵ Teresa M. Darragh, MD,⁶ Paul A. Elgert, CT (ASCP),⁷ Vivien Hanson, MD,⁸ Michael R. Henry, MD,⁹ and Jeffrey Waldman, MD¹⁰

¹Department of Pathology and Laboratory Medicine, University of Kentucky, Lexington, KY; ²Coastal Pathology and Medical University of South Carolina, Charleston, SC; ³Department of Pathology, Emory University School of Medicine and Grady Health System, Atlanta, GA; ⁴Watkins Student Health Service, University of Kansas, Lawrence, KS; ⁵Gynecology Clinic Health Services, University of California, Santa Barbara, CA; ⁶Department of Pathology, University of California, San Francisco, CA; ⁷Department of Pathology, New York University School of Medicine at Bellevue Hospital Center, New York, NY; ⁸Reproductive Health Program, Bremerton-Kitsap County Health District, and University of Washington, Seattle, WA; ⁹Department of Pathology, University of Maryland Medical Center, Baltimore, MD; and ¹⁰Planned Parenthood Shasta-Diablo, Concord, CA
ASCCP Patient Management Guidelines

• Negative but lacking an endocervical/transformation zone component – repeat in 12 months; within 6 month may be beneficial for patients with previous squamous abnormality, previous unexplained glandular abnormality, positive high risk HPV within 12 months, inability to clearly visualise the cervix, immunosuppression, insufficient previous screening

• Negative but partially obscuring blood, inflammation, other partially obscuring factors, or partial air drying – same; also consider early repeat if similar obscuring factor in consecutive test
• Unsatisfactory – repeat within a short interval of 2-4 months; consider specific treatment if due to obscuring inflammation

• Repeatedly unsatisfactory because of obscuring blood, inflammation or necrosis – colposcopy or biopsies

(Davey 2002 J Lower Gen Tract Dis 195-199)
Diagnostic procedures for the evaluation of abnormal cytology

Repeat cytology

- The cervical epithelium needs time to regenerate after cytology. Repeat cytology should not be performed <3 months after a previous test.

Jordan et al 2008 Cytopathology 19:342-54
Box 1. Essential Changes From Prior Management Guidelines*

- Cytology reported as negative but lacking endocervical cells can be managed without early repeat.
- CIN 1 on endocervical curettage should be managed as CIN 1, not as a positive ECC.
- Cytology reported as unsatisfactory requires repeat even if HPV negative.
- Genotyping triages HPV-positive women with HPV type 16 or type 18 to earlier colposcopy only after negative cytology; colposcopy is indicated for all women with HPV and ASC-US, regardless of genotyping result.
- For ASC-US cytology, immediate colposcopy is not an option. The serial cytology option for ASC-US incorporates cytology at 12 months, not 6 months and 12 months, and then if negative, cytology every 3 years.
- HPV-negative and ASC-US results should be followed with co-testing at 3 years rather than 5 years.
- HPV-negative and ASC-US results are insufficient to allow exit from screening at age 65 years.
- The pathway to long-term follow-up of treated and untreated CIN 2+ is more clearly defined by incorporating co-testing.
- More strategies incorporate co-testing to reduce follow-up visits. Pap-only strategies are now limited to women younger than 30 years, but co-testing is expanded even to women younger than 30 years in some circumstances. Women aged 21-24 years are managed conservatively.
Unsatisfactory Cytology

- HPV unknown (any age)
  - Abnormal: Manage per ASCCP guideline
  - Negative: Routine screening (HPV-/unknown) or Cotesting @ 1 year (HPV+)

- HPV negative (age ≥ 30)
  - Repeat Cytology after 2-4 months
    - Negative: Colposcopy
    - Unsatisfactory: Either is acceptable

- HPV positive (age ≥ 30)
  - Abnormal: Manage per ASCCP guideline
Management of Abnormal Smears

- Guidelines
- Endometrial cells
- Smear test specimen adequacy
- Infections in cervical smear
- Other issues
Significance of a Diagnosis of Microorganisms on Pap Smear

Valerie A. Fitzhugh, MD and Debra S. Heller, MD
Department of Pathology and Laboratory Medicine, New Jersey Medical School, University of Medicine and Dentistry of New Jersey, Newark, NJ

Abstract: The Pap smear has been in use for more than half a century as the primary screening test for preinvasive and invasive lesions of the uterine cervix. Although not the primary use and an imperfect test, it can be extremely useful in the diagnosis of some microorganisms. This review focuses on the use of the Pap smear in the diagnosis of several microorganisms including Actinomyces, Chlamydia trachomatis, Candida, Trichomonas vaginalis, Leptothrix vaginalis, Herpes Simplex Virus, the causative agents of bacterial vaginosis, and other rarer organisms. The accuracy of diagnosis using the smear varies among the different organisms in question.

Actinomyces israelii is the most common pathogen in human infections [1]. Other members of the genus, such as Actinomyces naeslundii, Actinomyces viscosus, Actinomyces neuii, and Actinomyces eriksonii, cause similar infections in the clinical setting [1].

If patients do not have mucosal injury, Actinomyces cannot cross mucosal barriers. In a low-oxygen environment where mucosal injury has occurred, actinomycosis may result [1]. This genus grows grossly as colonies that breach anatomical boundaries, forming abscesses sur-

© 2007, American Society for Colposcopy and Cervical Pathology
Journal of Lower Genital Tract Disease, Volume 12, Number 1, 2008, 40–51
• Actinomyces can be identified and diagnosed confidently on Pap-prepared slides with high sensitivity and specificity
FSRH Guidance (November 2007)
Intrauterine Contraception
(Date of planned revision 2013)

Purpose and scope

This Guidance provides evidence-based recommendations and good practice points for clinicians on the use of intrauterine methods of contraception as a long-term option. Intrauterine methods include the copper-bearing intrauterine device (Cu-IUD), framed and unframed devices and the levonorgestrel-releasing intrauterine system (LNG-IUS). Recommendations on the use of a Cu-IUD as emergency contraception are covered in separate Faculty of Family Planning and Reproductive Health Care (FFPRHC) [now Faculty of Sexual and Reproductive Healthcare (FSRH)] Guidance.1 This document will focus primarily on the use of intrauterine methods as contraceptives but will briefly cover other uses. This Guidance updates and combines the two previous FFPRHC Guidance documents on intrauterine methods.2,3 Recommendations from the National Institute

1 Health professionals should be familiar with UK Medical Eligibility Criteria for Contraceptive Use recommendations for intrauterine contraceptive use (Good Practice Point).

What should clinicians assess when a woman is considering intrauterine contraception?

Clinical assessment

A clinical history (including sexual history) should be taken before providing intrauterine contraception (Box 1).7–9 An infection screen may be required for some women in advance of intrauterine contraceptive insertion. A sexual history should identify women at risk of sexually transmitted infections (STIs) for whom an infection screen should be obtained.
• Actinomyces Israeliii is a commensal of the female genital tract
• The role of ALO in infection in women using IUD is unclear
• There is no need to remove IUD in asymptomatic women with ALO
• If women using IUD, who have ALO identified by swabs, present with symptoms of pelvic pain, then removal of intrauterine contraception may be considered. Other more common causes of pain should be excluded.
• Chlamydia infection – lack of sensitivity and specificity
• Herpes simplex – ancillary studies should be considered
• Candida – inadequate as a screening test
• Trichomonas vaginalis – diagnostic among patients from high prevalence settings but is indeterminate in medium- to low-prevalence settings
Other specific infections

- Candida – treat only if symptomatic
- Trichomonas – treat even if asymptomatic, screen for other STDs
- Herpes – screen for other STDs; ?HSV-2-specific antibodies
- Chlamydia, gonococcus – needs confirmation
Management of Abnormal Smears

- Guidelines
- Endometrial cells
- Smear test specimen adequacy
- Infections in cervical smear
- Other issues
Liquid Compared With Conventional Cervical Cytology

A Systematic Review and Meta-analysis

Marc Arbyn, MD, MSc, Christine Bergeron, MD, PhD, Paul Klinkhamer, MD, Pierre Martin-Hirsch, MD, PhD, Albertus G. Siebers, MSc, and Johan Bulten, MD, PhD

OBJECTIVE: To compare test performance characteristics of conventional Pap tests and liquid-based cervical cytology samples.

DATA SOURCES: Eligible studies, published between 1991 and 2007, were retrieved through PubMed/EmBase searching and completed by consultation of other sources.

METHODS OF STUDY SELECTION: Studies were selected if a conventional and a liquid-based sample were prepared from the same woman or when one or the other type of sample was taken from a separate but similar cohort. The current systematic review and meta-analysis is restricted to studies where all subjects were submitted to gold standard verification, based on colposcopy and histology of colposcopy-targeted biopsies, allowing computation of absolute and relative test validity for cervical intraepithelial neoplasia grade 2 or worse. Randomized trials were selected as well if all test-positive cases were verified with the same gold standard, allowing computation of the relative sensitivity. Impact of study characteristics on accuracy was assessed by subgroup meta-analyses, meta-regression, and summary receiver operating characteristic curve regression.

TABULATION, INTEGRATION, AND RESULTS: The relative sensitivity, pooled from eight studies, with complete gold standard verification and from one randomized clinical trial, did not differ significantly from unity. Also, the specificity, considering high-grade and low-grade squamous intraepithelial lesions as cutoff, was similar in conventional and liquid cytology. However, a lower pooled specificity was found for liquid-based cytology when presence of atypical squamous cells of undetermined significance was the cutoff (ratio 0.91, 95% confidence interval 0.84–0.98). Differences in study characteristics did not explain interstudy heterogeneity.

CONCLUSION: Liquid-based cervical cytology is neither more sensitive nor more specific for detection of high-grade cervical intraepithelial neoplasia compared with the conventional Pap test.

(Obstet Gynecol 2008;111:167–77)
Evidence-based medicine versus liquid-based cytology

- Facilitate HPV testing – the reasoning that HPV triage of ASC-US unequivocally justifies use of liquid-based cytology is contestable
- Potential benefit of fewer unsatisfactory tests with liquid-based cytology is unlikely to justify its use, especially in light of concurrent false-positive testing
- Laboratory simply stopped reading conventional tests

(Sawaya 2008 Obstet Gynecol 111;2-3)
[Health technology assessment report. Use of liquid-based cytology for cervical cancer precursors screening].

Efficacy and undesired effects: LBC with manual interpretation: The estimates of cross-sectional accuracy for high-grade intraepithelial neoplasia (CIN2 or more severe and CIN3 or more severe) obtained by a systematic review and meta-analysis published in 2008 were used. This review considered only studies in which all women underwent colposcopy or randomised controlled trials (RCTs) with complete verification of test positives. A systematic search of RCTs published thereafter was performed. Three RCTs were identified. One of these studies was conducted in 6 Italian regions and was of large size (45,174 women randomised); a second one was conducted in another Italian region (Abruzzo) and was of smaller size (8,654 women randomised); a third RCT was conducted in the Netherlands and was of large size (89,784 women randomised). No longitudinal study was available. There is currently no clear evidence that LBC increases the sensitivity of cytology and even less that its introduction increases the efficacy of cervical screening in preventing invasive cancers. The Italian randomised study NTCC showed a decrease in specificity, which was not observed in the other two RCTs available. In addition, the 2008 meta-analysis observed a reduction - even if minimal - in specificity just at the ASC-US cytological cut-off, but also a remarkable heterogeneity between studies. These results suggest that the effect of LBC on specificity is variable and plausibly related to the local style of cytology interpretation. There is evidence that LBC reduces the proportion of unsatisfactory slides, although the size of this effect varies remarkably.
Liquid-based cytology (LBC) has replaced conventional cytology (CC) for cervical cancer screening in some countries. However, it remains unclear whether LBC is superior to CC. A randomized controlled trial was conducted between August 2007 and March 2009 in Germany to compare LBC, alone and in combination with computer-assisted imaging technology (CAS), to CC in the detection of histologically confirmed cervical intraepithelial neoplasia (CIN). The main outcome measures were detection rates, relative sensitivities, positive predictive values (PPVs) and relative PPVs comparing LBC without and with CAS to CC. Primary histological outcome was CIN2 or higher. Included were 20,627 women participating in opportunistic cervical cancer screening at 20 gynecologic practices. The practices were randomized weekly to use LBC (n = 11,331) or CC (n = 9,296). Patients with positive findings were invited to expert colposcopy. The relative sensitivity of LBC versus CC using the CIN2+ cut-off was 2.74 (95% confidence interval [CI] 1.66–4.53). The relative sensitivity of LBC/CAS versus CC for CIN2+ was 3.17 (95% CI 1.94–5.19). The PPV of LBC and CC for CIN2+ was 48% and 38%, respectively. The PPV ratio did not differ significantly from unity. Differences between LBC and CC were smaller in some sensitivity and subgroup analyses; however, relative sensitivity of LBC remained increased. LBC without and with CAS compared with CC under the field conditions of an opportunistic screening system had a significantly higher sensitivity for the detection of CIN without deterioration of PPVs. Additional use of CAS did not further improve sensitivity of LBC.
The revised BSCC terminology for abnormal cervical cytology

K. J. Denton*, A. Herbert†, L. S. Turnbull‡, C. Waddell§, M. S. Desai‖, D. N. Rana‖, N. Dudding+++ and J. H. F. Smith+++ on behalf of the British Society of Clinical Cytology

*Cellular Pathology Department, Southmead Hospital, Bristol, UK, †St Thomas’s Hospital – North Wing, London, UK, ‡Royal Liverpool University Hospital, Liverpool, UK, §Birmingham Maternity Hospital, Birmingham, UK, ‖Manchester Cytology Centre, Manchester, UK, +++Northern & Yorkshire Cytology Training School, Yorkshire, UK and +++Department of Histopathology and Cytology, Royal Hallamshire Hospital, Sheffield, UK

Accepted for publication 16 April 2008


The revised BSCC terminology for abnormal cervical cytology

The BSCC terminology was originally published in 1986 and although highly successful, requires revision. Through a process of professional consensus and literature review this has been undertaken by the BSCC. The revision takes account of recent developments and improvements in understanding of morphology and disease process and is compatible with other terminologies in use elsewhere, whilst still maintaining a focus on practice in the UK cervical screening programmes.
Achievable standards, Benchmarks for reporting, and Criteria for evaluating cervical cytopathology

Third edition including revised performance indicators
The last decade has witnessed major changes to the NHSCSP. These include the introduction and national implementation of liquid-based cytology (LBC) sampling, and the implementation of high-risk human papillomavirus (HR-HPV) testing for triage of borderline and low-grade abnormalities and test of cure. Consequently, the NHSCSP and the Royal College of Pathologists have agreed that an updated version of the ABC guidance is required. That revision is presented here.

The principal changes introduced in this document are as follows:

- The NHSCSP will adopt the revised British Society for Clinical Cytology (BSCC) terminology for reporting cervical cytology:
  - Division of the category ‘borderline change’ into ‘squamous’ and ‘endocervical’ categories.
  - Division of dyskaryosis into ‘low-grade’ and ‘high-grade’ categories (the latter encompassing moderate and severe dyskaryosis).
  - Division of glandular neoplasia into ‘endocervical’ and ‘non-cervical’ categories.
- Guidance on the management of abnormal cytology results has been linked to this terminology:
  - Management guidance has been updated in the light of HR-HPV testing for triage of low-grade cytological abnormality and test of cure.
  - Expanded codes have been developed for standard cytology results to take account of the changes outlined above.
  - Performance indicators for evaluating cervical cytopathology have been expanded. They now include the referral value, the mean cervical intraepithelial neoplasia (CIN) score (MCS), the abnormal predictive value (APV), and the HR-HPV-positive rate for borderline/low-grade samples.
Evidence Regarding Human Papillomavirus Testing in Secondary Prevention of Cervical Cancer

Marc Arbyn\textsuperscript{a,b,*}, Guglielmo Ronco\textsuperscript{c}, Ahti Anttila\textsuperscript{d}, Chris J.L.M. Meijer\textsuperscript{e}, Mario Poljak\textsuperscript{f}, Gina Ogilvie\textsuperscript{g}, George Koliopoulos\textsuperscript{h}, Pontus Naucler\textsuperscript{i}, Rengaswamy Sankaranarayanan\textsuperscript{j}, Julian Peto\textsuperscript{k}

\textsuperscript{a} Unit of Cancer Epidemiology, Scientific Institute of Public Health, Brussels, Belgium
\textsuperscript{b} European Cancer Network, IARC, Lyon, France
\textsuperscript{c} Unit of Cancer Epidemiology, Centro per la prevenzione Oncologica, Turin, Italy
\textsuperscript{d} Mass Screening Registry, Finnish Cancer Registry, Helsinki, Finland
\textsuperscript{e} Department of Pathology, VU University Medical Centre, Amsterdam, The Netherlands
\textsuperscript{f} Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia
\textsuperscript{g} Division of STI/HIV Prevention and Control, BC Centre for Disease Control, Vancouver, Canada
\textsuperscript{h} Department of Obstetrics and Gynecology, University Hospital of Ioannina, Ioannina, Greece
\textsuperscript{i} Department of Infectious Diseases; Department of Microbiology, Tumor & Cell Biology, Karolinska University Hospital, Stockholm, Sweden
\textsuperscript{j} Screening Group, International Agency for Research on Cancer, Lyon, France
\textsuperscript{k} London School of Hygiene and Tropical Medicine, London, UK

Primary screening for hrHPV generally detects more CIN2, CIN3 or cancer compared to cytology at cut-off atypical squamous cells of undetermined significance (ASC-US) or LSIL, but is less specific. Combined HPV and cytology screening provides a further small gain in sensitivity at the expense of a considerable loss in specificity if cytology is used at a high cut-off (ASC-H).
Cost-effectiveness of cervical cancer screening: cytology versus human papillomavirus DNA testing

J van Rosmalen, IMCM de Kok, M van Ballegooijen

Department of Public Health, Erasmus MC, University Medical Center, Rotterdam, the Netherlands
Correspondence: Dr J van Rosmalen, Department of Public Health, Erasmus MC, University Medical Center, PO Box 2040, 3000 CA, Rotterdam, the Netherlands. Email j.vanrosmalen@erasusmc.nl

Accepted 18 October 2011. Published Online 18 January 2012.

Objective To determine the most cost-effective screening programme for cervical cancer.

Design Cost-effectiveness analysis from a societal perspective.

Setting The Netherlands.

Population Dutch women who have not been invited for human papillomavirus (HPV) vaccination.

Methods We calibrated the microsimulation screening analysis (MISCAN) model to Dutch epidemiological data. We used this model to consider nine screening strategies that use: (i) cytological testing with cytology triage for borderline/mildly abnormal smears; (ii) HPV testing with cytology triage for HPV-positive smears; or (iii) cytological testing with HPV triage for borderline/mildly abnormal smears. For each strategy, we varied the number of screening rounds, the time interval, the age of the first screening, and the type of cytological testing (conventional or liquid-based cytology).

Main outcome measures Quality-adjusted life years (QALYs) gained and costs from a societal perspective.

Results Under the base-case assumptions, primary HPV testing with cytology triage is the most cost-effective strategy. Using cost-effectiveness thresholds of €20 000 and €50 000 per QALY gained yields optimal screening programmes with three and seven screening rounds, respectively. The results are sensitive to several uncertain model inputs, most importantly the costs of the HPV test. For women aged 32 years or younger, primary cytology screening is more cost-effective than primary HPV testing.

Conclusions Increasing the interval between screening rounds and changing the primary test from cytology to HPV testing can improve the effectiveness and decrease the costs of cervical cancer screening in the Netherlands.

Keywords Cervical cancer, cost-effectiveness analysis, HPV test, human papillomavirus, screening.
Management of Women ≥ Age 30, who are Cytology Negative, but HPV Positive

Repeat Cotesting
@ 1 year Acceptable

Cytology Negative and HPV Negative

≥ASC or HPV positive

Colposcopy

Manage per ASCCP Guideline

Repeat Cotesting @ 1 year

HPV DNA Typing Acceptable

HPV 16 or 18 Positive

HPV 16 and 18 Negative

Repeat Cotesting @ 1 year

Manage per ASCCP Guideline
Evaluation of 14 triage strategies for HPV DNA-positive women in population-based cervical screening

Dorien C. Rijken\textsuperscript{1}, Johannes Berkhof\textsuperscript{2}, Folkert J. van Kemenade\textsuperscript{1}, Veerle M.H. Coupe\textsuperscript{2}, Albertus T. Hesselink\textsuperscript{1}, Lawrence Rozendaal\textsuperscript{1}, Danielle A.M. Heideman\textsuperscript{1}, Ren H. Verheijen\textsuperscript{3}, Saskia Bulk\textsuperscript{4}, Wim M. Verweij\textsuperscript{5}, Peter J.F. Snijders\textsuperscript{1} and Chris J.L.M. Meijer\textsuperscript{1}

\textsuperscript{1} Department of Pathology, VU University Medical Center, Amsterdam, The Netherlands
\textsuperscript{2} Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, The Netherlands
\textsuperscript{3} Division of Woman and Baby, Gynaecological Oncology, University Medical Center, Utrecht, The Netherlands
\textsuperscript{4} Department of Medical Genetics, University Medical Center, Utrecht, The Netherlands
\textsuperscript{5} SALTRO, primary health care laboratory, Utrecht, The Netherlands

High-risk human papillomavirus (hrHPV) testing has a higher sensitivity but lower specificity than cytology for detection of high-grade intraepithelial neoplasia (CIN). To avoid over-referral to colposcopy and overtreatment, hrHPV-positive women require triage testing and/or followup. A total of 25,658 women (30–60 years) enrolled in a population-based cohort study had an adequate baseline Pap smear and hrHPV test. The end-point was cumulative two-year risk of CIN grade 3 or worse (CIN3+). In a post-hoc analysis, fourteen triage/followup strategies for hrHPV-positive women (n = 1,303) were evaluated for colposcopy referral rate, positive (PPV) and negative predictive value (NPV). Five strategies involved triage testing without a repeat test and nine strategies involved triage testing followed by one repeat testing. The tests were cytology, hrHPV, HPV16/18 genotyping and HPV16/18/31/33/45 genotyping. Results were adjusted for women in the cohort study who did not attend repeat testing. Of the strategies without repeat testing, combined cytology and HPV16/18/31/33/45 genotyping gave the highest NPV of 98.9% (95%CI 97.6–99.5%). The corresponding colposcopy referral rate was 58.1% (95%CI 55.4–60.8%). Eight of the nine strategies with retesting had an estimated NPV of at least 98%. Of those, \textit{cytology triage followed by cytology at 12 months} had a markedly lower colposcopy referral rate of 33.4% (95%CI 30.2–36.7%) than the other strategies. The NPV of the latter strategy was 99.3% (95%CI 98.1–99.8%). Triage hrHPV-positive women with cytology, followed by repeat cytology testing yielded a high NPV and modest colposcopy referral rate and appear to be the most feasible management strategy.
Summary

• 2008 revised HKCOG guidelines, HKSCCP standards, 2012 Updated Consensus

• In-phase endometrial cells in women >=40 or endometrial cells in patients with IUD inserted: no further action unless symptomatic

• No need to repeat cervical smear earlier if smear negative but lacking an endocervical/transformation zone component

• Repeat after 3 months if smear unsatisfactory
Summary

• Actinomycetes-like organisms: no need to remove IUD in asymptomatic women
• Other specific infections: diagnosis reliable for trichomonas and herpes; need confirmation for chlamydia and gonococcus
• No good evidence that liquid based cytology is better
• NHS has introduced significant changes to their screening program
• ?HPV test for primary screening
Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials

Guglielmo Ronco, Joakim Dillner, K Miriam Elfstrom, Sara Tunesi, Peter J F Snijders, Marc Arbyn, Henry Kitchener, Nereo Segnan, Clare Gilham, Paolo Giorgi-Rossi, Johannes Berkhof, Julian Peto, Chris J L M Meijer, and the International HPV screening working group*

Summary

Background  In four randomised trials, human papillomavirus (HPV)-based screening for cervical cancer was compared with cytology-based cervical screening, and precursors of cancer were the endpoint in every trial. However, direct estimates are missing of the relative efficacy of HPV-based versus cytology-based screening for prevention of invasive cancer in women who undergo regular screening, of modifiers (eg, age) of this relative efficacy, and of the duration of protection. We did a follow-up study of the four randomised trials to investigate these outcomes.

Methods  176464 women aged 20–64 years were randomly assigned to HPV-based (experimental arm) or cytology-based (control arm) screening in Sweden (Swedscreen), the Netherlands (POBASCAM), England (ARTISTIC), and Italy (NTCC). We followed up these women for a median of 6.5 years (1214415 person-years) and identified 107 invasive cervical carcinomas by linkage with screening, pathology, and cancer registries, by masked review of histological specimens, or from reports. Cumulative and study-adjusted rate ratios (experimental vs control) were calculated for incidence of invasive cervical carcinoma.

Findings  The rate ratio for invasive cervical carcinoma among all women from recruitment to end of follow-up was 0.60 (95% CI 0.40–0.89), with no heterogeneity between studies (p=0.52). Detection of invasive cervical carcinoma was similar between screening methods during the first 2.5 years of follow-up (0.79, 0.46–1.36) but was significantly lower in the experimental arm thereafter (0.45, 0.25–0.81). In women with a negative screening test at entry, the rate ratio was 0.30 (0.15–0.60). The cumulative incidence of invasive cervical carcinoma in women with negative entry tests was 4.6 per 105 (1.1–12.1) and 8.7 per 105 (3.3–18.6) at 3.5 and 5.5 years, respectively, in the experimental arm, and 15.4 per 105 (7.9–27.0) and 36.0 per 105 (23.2–53.5), respectively, in the control arm. Rate ratios did not differ by cancer stage, but were lower for adenocarcinoma (0.31, 0.14–0.69) than for squamous-cell carcinoma (0.78, 0.49–1.25). The rate ratio was lowest in women aged 30–34 years (0.36, 0.14–0.94).

Interpretation  HPV-based screening provides 60–70% greater protection against invasive cervical carcinomas compared with cytology. Data of large-scale randomised trials support initiation of HPV-based screening from age 30 years and extension of screening intervals to at least 5 years.
Thank you

Dr TC Pun
Honorary Associate Professor
Dept of Obstetrics & Gynaecology
The University of Hong Kong