

LONDON
SCHOOL of
HYGIENE
& TROPICAL
MEDICINE



Moss, S; Gray, A; Legood, R; Vessey, M; Patnick, J; Kitchener, H
(2006) Effect of testing for human papillomavirus as a triage during
screening for cervical cancer: observational before and after study.
BMJ, 332 (7533). pp. 83-85. ISSN 1468-5833 DOI: <https://doi.org/10.1136/bmj.38701.440961.7C>

Downloaded from: <http://researchonline.lshtm.ac.uk/9484/>

DOI: [10.1136/bmj.38701.440961.7C](https://doi.org/10.1136/bmj.38701.440961.7C)

Usage Guidelines

Please refer to usage guidelines at <http://researchonline.lshtm.ac.uk/policies.html> or alternatively contact researchonline@lshtm.ac.uk.

Available under license: Creative Commons Attribution Non-commercial
<http://creativecommons.org/licenses/by-nc/3.0/>

using human papillomavirus testing, and the negative implications for women of increased lifetime colposcopies (64-138%).

We thank those involved in the pilots, including the patients, and the laboratory and primary care staff at the pilot sites who assisted in the collection of workload and cost data; staff at the NHS Purchasing and Supplies Agency for providing indicative market prices of consumables and equipment; and the members of the steering and advisory groups. The views expressed are those of the authors and not necessarily those of the Department of Health.

Contributors: See bmj.com.

Funding: This study forms part of the independent evaluation of the liquid based cytology/human papillomavirus cervical screening pilot studies commissioned by the policy research programme, Department of Health.

Competing interests: None declared.

Ethical approval: Not required.

- Walboomers JMM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 1999;189:12-9.
- Wright TC, Cox JT, Massad LS, Twiggs LB, Wilkinson EJ. 2001 Consensus guidelines for the management of women with cervical cytological abnormalities. *JAMA* 2004;292:2120-9.
- Agence Nationale d'Accreditation et d'Evaluation en Sante. Management of a patient with an abnormal smear. Service recommendations et references professionnelles et service evaluation economique. Paris, France: ANAES, 2002:1-92.
- Moss S, Gray A, Legood R, Vessey M, Patnick J, Kitchener H. Effect of testing for human papillomavirus as a triage during screening for cervical cancer: observational before and after study. *BMJ* 2006;332:83-5.
- Myers ER, McCrory DC, Nanda K, Bastian L, Matchar DB. Mathematical model for the natural history of human papillomavirus infection and cervical carcinogenesis. *Am J Epidemiol* 2000;151(12):1158-71.
- West Midlands Cancer Intelligence Unit. *Invasive cervical cancer relative survival by stage in the West Midlands: tumours diagnosed 1995-1997 followed up to the end of 2002*. University of Birmingham: WMCIU, 2003.
- Quinn M, Babb P, Brock A, Kirby L, Jones J. *Cancer trends in England and Wales 1950-1999*. London: Stationery Office, 2001.
- Government Actuary's Department. *Life tables: females England and Wales*. London: GAD, 2003.
- Dickson RJ. Management of carcinoma in the cervix. *Practitioner* 1980;22:899-904.
- Department of Health. *Cervical screening programme. England: 2002-2003*. Statistical Bulletin 2003/24. London: DoH, 2003.
- Abryn M, Buntinx F, Van Ranst M, Paraskevaidas E, Martin-Hirsh P, Dillner J. Virologic versus cytologic triage of women with equivocal pap smears: a meta-analysis of the accuracy to detect high grade intraepithelial neoplasia. *J Natl Cancer Inst* 2004;96:280-93.
- Cuzick J, Szarewski A, Terry G, Ho L, Hanby A, Maddox P, et al. Human papillomavirus testing in primary cervical screening. *Lancet* 1995;345:1533-6.
- Noorani HZ, Brown AB, Skidmore B, Stuart GCE. *Liquid-Based Cytology and human papillomavirus testing in cervical screening*. Technology report No 40. Ottawa, ON: Canadian Coordinating Office for Health Technology Assessment, 2004.
- Netten A, Rees T, Harrison G. *Unit costs of health and social care*. Canterbury: University of Kent, 2001.
- Wolstenholme JL, Whynes DK. Stage-specific treatment costs for cervical cancer in the United Kingdom. *Eur J Cancer* 1998;34:1889-93.
- National Audit Office. *The performance of the NHS cervical screening programme*. London: Stationery Office, 1998.
- Great Britain HM Treasury. *Green book, appraisal and evaluation in central government*. London: Stationery Office, 2003.
- Nanda K, McCrory DC, Myers ER, Bastian LA, Hasselblad V, Hickey JD, et al. Accuracy of the Papanicolaou test in screening for and follow-up of cervical cytologic abnormalities: a systematic review. *Ann Intern Med* 2000;132:810-9.
- Briggs AH, Goeree R, Blackhouse G, O'Brien BJ. Probabilistic analysis of cost effectiveness models: choosing between treatment strategies for gastroesophageal reflux disease. *Med Decis Making* 2002;22:290-308.
- Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost effectiveness acceptability curves. *Health Econ* 2001;10:779-87.
- Cuzick J, Szarewski A, Cubie H, Kitchener H, Luesley D, McGoogan E, et al. Management of women who test positive for high-risk types of human papillomavirus: the HART study. *Lancet* 2003;362:1871-6.
- Kim JJ, Wright TC, Goldie SJ. Cost-effectiveness of alternative triage strategies for atypical cells of undetermined significance. *JAMA* 2002;287:2382-90.
- Sherlaw-Johnson C, Phillips Z. An evaluation of liquid-based cytology and human papillomavirus testing within the UK cervical cancer screening programme. *Brit J Cancer* 2004;91:84-91.

(Accepted 31 October 2005)

doi 10.1136/bmj.38698.458866.7C

Effect of testing for human papillomavirus as a triage during screening for cervical cancer: observational before and after study

Sue Moss, Alastair Gray, Rosa Legood, Martin Vessey, Julietta Patnick, Henry Kitchener on behalf of the Liquid Based Cytology/Human Papillomavirus Cervical Pilot Studies Group

Abstract

Objective To assess the effect of introducing testing for human papillomavirus combined with liquid based cytology in women with low grade cytological abnormalities.

Design Observational before and after study.

Setting Three cervical screening laboratories, England.

Participants 5654 women aged 20-64 with low grade cytological abnormalities found at routine cervical screening in a pilot; 5254 similar women in the period before the pilot.

Interventions Human papillomavirus testing combined with liquid based cytology in the management of women with borderline or mildly dyskaryotic cervical smear results compared with conventional smear tests, with immediate referral to

colposcopy of women positive for human papillomavirus.

Results 57.9% (3187/5506) of women tested in the pilot were positive for human papillomavirus. The rate of repeat smears fell by 74%, but the rate of referral to colposcopy for low grade cytological abnormalities more than doubled. The estimated negative predictive value of human papillomavirus testing varied between 93.8% and 99.7%.

Conclusion The addition of testing for human papillomavirus in women with low grade cytological abnormalities resulted in a reduction in the rate of repeat smears, but an increase in rates of referral to colposcopy.



Members of the pilot studies group are on bmj.com

This article was posted on bmj.com on 6 January 2006: <http://bmj.com/cgi/doi/10.1136/bmj.38701.440961.7C>

Editorial by Schiffman and Castle and p 79

Cancer Screening Evaluation Unit, Institute of Cancer Research, Sutton, Surrey SM2 5NG
Sue Moss
associate director

Health Economics Research Centre, Department of Public Health, University of Oxford, Oxford OX3 7LF

Alastair Gray
professor of health economics

Rosa Legood
senior researcher

continued over

BMJ 2006;332:83-5

Unit of Health Care Epidemiology, Department of Public Health, University of Oxford, Oxford OX3 7LF

Martin Vessey *emeritus professor of public health*

NHS Cancer Screening Programmes, Sheffield S10 3TH

Julietta Patnick *director*

University of Manchester, St Mary's Hospital, Manchester M13 0JH

Henry Kitcheener *professor of gynaecological oncology*

Correspondence to: S Moss sue.moss@icr.ac.uk

Introduction

Oncogenic human papillomavirus has been detected in almost all invasive cancers; its prevalence in precancerous lesions varies from about 80% to 95%. Triaging women with low grade cytological abnormalities on the basis of their human papillomavirus status would reduce requirements for repeat cytology and could improve utilisation of colposcopy¹; the introduction of liquid based cytology increases the feasibility of DNA testing for human papillomavirus.

Methods

The Department of Health commissioned pilot studies in which three cytopathology laboratories in England converted to using liquid based cytology combined with testing for human papillomavirus of women with borderline or mildly dyskaryotic cervical smear results for a 12 month period.

Results

A total of 5654 women aged 20-64 in the NHS cervical screening programme had borderline (n = 3797) or mildly dyskaryotic (n = 1857) smear results; 45.6% (1680/3681) and 82.6% (1507/1825) of those women tested, respectively, were positive for human papillomavirus. Respective results by age groups were 64.4% (1239) and 89.0% (1188) for women aged 20-34 years, 29.0% (353) and 69.4% (259) for those aged 35-49 years, and 16.2% (88) and 51.3% (60) for those aged 50-64 years.

Women who tested positive for human papillomavirus were referred for immediate colposcopy. Women who tested negative were referred for colposcopy if at six months cytology showed mild dyskaryosis or worse or they tested positive for human papillomavirus. As the protocol led to increased referral for colposcopy, two centres revised the protocol after six and eight months and referred younger women (20-34 years) positive for the virus only if at six months they remained positive or cytology showed mild dyskaryosis or worse. At six months, 64% (253/396) remained positive and 73.5% met the criteria for referral.

For comparison we collected data on 5245 women of a similar age distribution with borderline or mildly dyskaryotic smear results in the 12 months before the pilot, when policy would have been to refer for

colposcopy only after, respectively, two or one further abnormal smear results.

Estimated default rates for repeat smears for women negative for human papillomavirus were 19.4% (403/2075) compared with 15.7% for women with low grade abnormalities in the period before the pilot, whereas the estimated default rate for colposcopy in women positive for human papillomavirus and referred directly was 11.2% (264/2358).

In the initial protocol period the rate of repeat smears per woman fell by 70% for borderline smear results from 1.40 to 0.42 (rate ratio 0.30, 95% confidence interval 0.28 to 0.32) and by 87% for mildly dyskaryotic smear results, from 1.18 to 0.15 (0.13, 0.11 to 0.15). The rates of referral for colposcopy for these two categories increased from 15% to 44% (2.92, 2.64 to 3.24) and from 37% to 80% (2.15, 1.93 to 2.40), respectively (table).

Assuming that no high grade disease is present in those women who remained negative for human papillomavirus at six months (or were not retested) and were not referred for colposcopy, the negative predictive value of the human papillomavirus test for cervical intraepithelial neoplasia grade 2 or worse was estimated as 99.4% for women with borderline smear results and 96.5% for those with mildly dyskaryotic smear results.

Discussion

Although rates of repeat smears were reduced after triaging women on the basis of their human papillomavirus status, colposcopy referral rates were increased. Rates of referral to colposcopy after a borderline smear result may have been underestimated for the period before the pilot period. One study reported long term colposcopy and biopsy rates of 42% in a similar group of women.²

The estimated negative predictive value of testing for human papillomavirus was high and in line with other studies.³ Detection of cervical intraepithelial neoplasia (CIN) grades 2 and 3 increased during the initial protocol period, although this may simply represent more efficient diagnosis of prevalent disease. With the lower screening threshold raised to the age of 25, triage on the basis of human papillomavirus testing for borderline smear results may detect an increased amount of prevalent CIN-2 and CIN-3.

Results from other studies have been used to suggest different strategies for human papillomavirus testing or triage.^{4,5} The significant increase in referral rates for colposcopy observed in the present study means that if triage on the basis of human papillomavirus testing is to be implemented, appropriate management strategies need to be developed and introduced in a controlled manner.

This study forms part of the independent evaluation of the liquid based cytology/human papillomavirus cervical screening pilot studies commissioned by the Policy Research Programme at the Department of Health. The evaluation was carried out by research teams at the Cancer Screening Evaluation Unit, Institute of Cancer Research (SM, E Henstock), the Health Economics Research Centre, University of Oxford (AG, RL), and the Psychology and Genetics Research Group, King's College London (T Marteau, E Maissi). The views expressed are those of the authors and not necessarily those of the Department of Health.

Rates of repeat smears and referral to colposcopy for women with borderline or mildly dyskaryotic smear results according to age group

Smear results (age group)	Rate of repeat smears per woman				Rate of referral to colposcopy (%)			
	Before pilot	Pilot			Before pilot	Pilot		
		Initial protocol period	Revised protocol period	Both periods*		Initial protocol period	Revised protocol period	Both periods*
Borderline:								
20-34	1.28	0.26	0.71	—	19	59	32	—
35-64	1.50	0.61	0.62	0.61	12	27	26	27
Total	1.40	0.42	0.67		15	44	29	
Mildly dyskaryotic								
20-34	1.11	0.08	0.72	—	39	82	52	—
35-64	1.35	0.35	0.18	0.30	34	73	78	75
Total	1.18	0.15	0.55		37	80	60	

*For age group 35-64 when protocol remained unchanged.

What is already known on this topic

Testing for human papillomavirus could improve the management of women with borderline or mildly dyskaryotic smear results

Human papillomavirus testing for borderline cytology and colposcopy for women positive for human papillomavirus has greater sensitivity to detect cervical intraepithelial neoplasia grades 2 and 3 than repeat cytology

What this study adds

Triaging women on the basis of testing for human papillomavirus is feasible during cervical screening

Such testing in pilot studies in England led to reduced rates of repeat smears but increased referrals for colposcopy

Contributors: SM led the evaluation team and is the guarantor. AG and RL participated in the evaluation. MV and JP contributed to the design of the study. HK contributed to the design of the study and chaired the steering group for the pilot studies.

Funding: Department of Health Policy Research Programme.

Competing interests: None declared.

Ethical approval: Not required.

- 1 Cuzick J, Sasieni P, Davies P. A systematic review of the role of human papilloma virus testing (HPV) in the cervical screening programme. *Health Technol Assess* 1999;1:1-196.
- 2 Rana DN, Marshall J, Desai M, et al. Five-year follow-up of women with borderline and mildly dyskaryotic cervical smears. *Cytopathology* 2004;15:263-70.
- 3 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Human papillomaviruses. In: IARC monographs on the evaluation of carcinogenic risks to humans. Lyon: IARC Science Publications, 1995.
- 4 Cuzick J, Szarewski A, Cubie H, et al. Management of women who test positive for high-risk types of human papillomavirus: the HART study. *Lancet* 2003;362:1871-6.
- 5 Schiffman M, Solomon D. Findings to date from the ASCUS-LSIL triage study (ALTS). *Arch Pathol Lab Med* 2003;127:946-9.

(Accepted 14 December 2005)

doi 10.1136/bmj.38701.440961.7C

Risk factors for pulmonary tuberculosis in Russia: case-control study

Richard Coker, Martin McKee, Rifat Atun, Boika Dimitrova, Ekaterina Dodonova, Sergei Kuznetsov, Francis Drobniewski

Abstract

Objectives To determine risk factors for pulmonary tuberculosis in Russia.

Design Case-control study of exposure to a variety of risk factors before and during the development of pulmonary tuberculosis.

Setting Large city in Russia.

Participants Cases were 334 consecutive adults diagnosed as having culture confirmed pulmonary tuberculosis between 1 January 2003 and 31 December 2003. Controls were 334 individuals sampled from a validated population registry, matched for age and sex to the patients with tuberculosis. A questionnaire collected information on potential risk factors.

Main outcome measures Risk factors associated with the development of tuberculosis.

Results The main risk factors for tuberculosis were low accumulated wealth (univariate odds ratio 16.70), financial insecurity (5.67), consumption of unpasteurised milk (3.58), diabetes (2.66), living with a relative with tuberculosis (2.94), being unemployed (6.10), living in overcrowded conditions (2.99), illicit drug use (8.74), and a history of incarceration in both pretrial detention centres (5.70) and prison (12.50).

Conclusions When prevalence of exposure is taken into account the most important factors in the development of pulmonary tuberculosis in Russia are exposure to raw milk and unemployment.

Introduction

Rates of tuberculosis in Russia have increased since the break-up of the Soviet Union, but little is known about the risk factors for developing the disease. This case-control study aimed to determine the risk factors for pulmonary tuberculosis in adults in a region of Russia where changes in rates of tuberculosis have mirrored those for the country as a whole.

Methods

We undertook a case-control study in the city of Samara, 700 miles southeast of Moscow. All participants were residents of the city. We defined cases as all adults with culture confirmed pulmonary tuberculosis newly diagnosed at any of the city's specialist tuberculosis clinics between 1 January 2003 and 31 December 2003, and recruited to a WHO DOTS (directly observed treatment short course) programme. We estimated that 307 cases and an equal number of controls should be recruited to achieve 80% power to detect an odds ratio of 2.0 at the 5% significance level if 10% or more of the general population were exposed to the risk factor. Controls were sampled randomly from the general population of Samara city; they were matched for year of birth and sex, and they had no history of tuberculosis. A team of 22 trained interviewers administered a previously piloted questionnaire to

European Centre on Health of Societies in Transition, Department of Public Health and Policy, London School of Hygiene and Tropical Medicine, London WC1E 7HT

Richard Coker
reader

Martin McKee
professor

Boika Dimitrova
research fellow

Tanaka Business School, Imperial College London, London

Rifat Atun
reader

Samara Social Research Institute, Samara, Russia

Ekaterina Dodonova
research fellow

Samara Oblast Health Department, Samara

Sergei Kuznetsov
head of department of adult healthcare

continued over

This article was posted on *bmj.com* on 8 December 2005: <http://bmj.com/cgi/doi/10.1136/bmj.38684.687940.80>

BMJ 2006;332:85-7