

Short term persistence of human papillomavirus and risk of cervical precancer and cancer: population based cohort study

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EDITORIAL

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STUDY QUESTION What is the risk of cervical precancer and cancer after short term (one year) persistence of human papillomavirus (HPV)?

SUMMARY ANSWER About 20% of women with one year HPV persistence and 40% with one year HPV 16 persistence will develop cervical precancer or cancer in the subsequent three to five years.

Participants and setting

10 049 eligible consenting women living in Guanacaste, Costa Rica, were enrolled in a population based study of HPV and cervical neoplasia in 1993-4.

Design, size, and duration

The cumulative incidence of cervical intraepithelial neoplasia grade II or worse (II+) was assessed in a subcohort of 2282 women who had two measurements of HPV, one at enrolment and one 9-21 months later, and were actively followed every six to 12 months for five to seven years.

Main results and the role of chance

Women who had persistently positive test results (positive/positive) had a three year cumulative incidence of cervical intraepithelial neoplasia grade II+ of 17.0%, which was significantly higher than the cumulative incidence of those who tested negative/positive (3.4%), positive/negative (1.2%), and negative/negative (0.5%). There was little difference in the cumulative incidence of cervical intraepithelial neoplasia grade II+ between testing positive twice

for any carcinogenic HPV genotype (same genotype or different genotypes) versus testing positive twice for the same carcinogenic genotype (17.0% v 21.3%, respectively). Short term persistence of HPV 16 strongly predicted cervical intraepithelial neoplasia grade II+, with a three year cumulative incidence of 40.8%.

Bias, confounding, and other reasons for caution

Despite the size of the cohort and subcohort, there were few outcomes of precancer, resulting in unstable estimates of risk. Thus any losses to follow-up could influence the absolute estimates of cumulative incidence; however, as both HPV infection and cervical intraepithelial neoplasia grade II and III are asymptomatic, it is unlikely that there is a differential effect and the relative patterns are unlikely to change significantly. In addition, because of small numbers of outcomes, in most analyses we included grade II in our definition of cervical precancer and cancer. While histological cervical intraepithelial neoplasia grade II is the typical clinical threshold for treatment, there is an increasing awareness that it is an equivocal diagnosis of cervical precancer.

Generalisability to other populations

The cohort in Guanacaste was a true population sample, with high participation rates at enrolment and good rates of follow-up. The population risk of cervical precancer and cancer in Guanacaste, however, is higher than in most Western countries. This might have resulted in a higher absolute cumulative incidence than might be observed in other populations.

Study funding/potential competing interests

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THREE YEAR CUMULATIVE INCIDENCE RATES OF CERVICAL INTRAEPITHELIAL NEOPLASIA GRADE II OR MORE SEVERE AFTER REPEAT MEASUREMENTS OF CARCINOGENIC HUMAN PAPILLOMAVIRUS (HPV) AT ABOUT 1 YEAR INTERVAL (9-21 MONTHS)

Grade	No of women	No of cases	Rate (95% CI)	Rate ratio (95% CI)
Carcinogenic HPV persistence	260	38	17.04 (12.05 to 22.03)	14.53 (4.53 to 46.58)
Specific genotype persistence	209	38	21.26 (15.18 to 27.33)	18.12 (5.66 to 57.99)
Non-persistence	51	0	0.00	0.00
HPV 16 persistence	55	19	40.77 (26.40 to 55.13)	34.75 (10.66 to 113.26)
HPV 18 persistence	18	3	17.46 (-0.58 to 35.50)	14.88 (3.22 to 68.70)
Carcinogenic HPV persistence (not 16 and 18)	187	16	10.00 (5.32 to 14.68)	8.53 (2.51 to 28.91)
Acquisition	125	4	3.44 (0.10 to 6.78)	2.93 (0.66 to 12.98)
Clearance (reference)*	282	3	1.17 (-0.15 to 2.50)	1.00
HPV negative	1615	7	0.49 (0.13 to 0.85)	0.42 (0.11 to 1.61)

* Women who tested positive and then negative for carcinogenic HPV ("clearance")

p i c o

Effectiveness of cervical screening with age: population based case-control study of prospectively recorded data

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EDITORIAL
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STUDY QUESTION Does the association between cervical screening and a subsequent decrease in cervical cancer incidence vary with age?

SUMMARY ANSWER Cervical screening at ages 35-64 is effective at preventing cervical cancer. It is less effective at ages 25-34 and has no effect at ages 20-24.

Participants and setting

All women with invasive cervical cancer diagnosed aged 20-69 in participating UK centres; two controls per case individually matched on age and area of residence. Women registered with an NHS general practitioner were eligible as controls.

Design, size, and duration

Population based case-control study of prospectively recorded data, including 4012 cases (diagnosed 1990-2008) and 7889 controls. Dates and results of all screening tests (cervical cytology) were available from 1988 to 2007.

Primary outcome, risks, exposures

The odds ratio for strength of association between cervical screening (in a particular age band) and cervical cancer (in the subsequent five year age band). Odds ratios were estimated in overlapping age bands.

Main results and the role of chance

The odds ratio of having cervical cancer diagnosed at age 55-59 was 0.26 (95% confidence interval 0.19 to 0.36) in women screened at age 52-54 compared with women not screened between ages 50 and 54. These odds ratios vary from 0.18 to 0.36 between screening age bands 40-42 and 62-64, corresponding to screening being associated with a reduction in cervical cancer over the subsequent five to eight years of between 64% and 82%. In younger women these associations are substantially and significantly less. Screening between the ages of 30 and 37 is

associated with a reduction in cervical cancer over the next five years of between 43% and 60%. Despite over 350 cases in women aged 25-29, there is no indication of any benefit of screening at age 22-24 (compared with those not screened at age 20-24): 1.11 (0.83 to 1.50)

Bias, confounding, and other reasons for caution

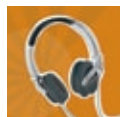
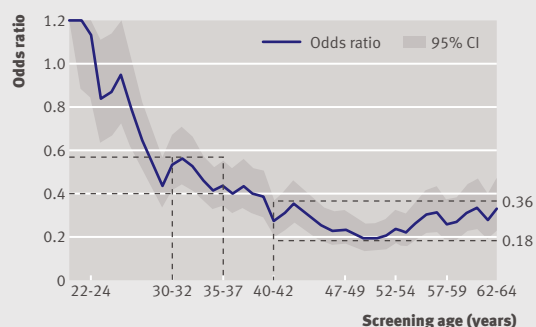
The prospectively recorded screening data and randomly selected controls eliminated recall bias and selection bias (data were obtained for all selected controls). As women who go for screening may differ from those who do not, the observed associations might not be causal. For the observed trends in odds ratios with age to be caused by confounding there would have to be differences in the way confounders affect the results at different ages. As this is unlikely, the differential benefits with age probably reflect the true effects of screening. Any decision on when to start screening women will have to weigh the benefits and harms and might depend on the local status quo. The underlying age specific rates of cervical cancer, the rate of positive screening test results, the morbidity caused by treatment of screen detected disease, and the benefits of having a cancer screen detected must be considered.

Generalisability to other populations

Because of the high quality of the UK screening programmes the findings are probably accurate and would apply to other countries.

Study funding/potential competing interests

This work was supported by Cancer Research UK (C8162/A6127 and C8162/A9481) and previously by the NHS cervical screening programme. Neither organisation had any input in the analysis or interpretation of the data or the writing of the paper. The authors have no competing interests.

RISK OF DEVELOPING INVASIVE CERVICAL CANCER BY AGE AT SCREENING

Lead author Peter Sasieni talks about this paper in the *BMJ* Podcast. Access it at podcasts.bmj.com/bmj/

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Cytological surveillance compared with immediate referral for colposcopy in management of women with low grade cervical abnormalities: multicentre randomised controlled trial

TOMBOLA Group

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STUDY QUESTION What is the effectiveness of cytological surveillance in primary care compared with immediate referral for colposcopic examination in women with low grade abnormal results on cervical cytology tests?

SUMMARY ANSWER Immediate referral for colposcopy detects more cervical intraepithelial neoplasia (CIN) grade II or worse at baseline, but there is little difference in its cumulative incidence by three years. Initial colposcopy leads to a large number of referrals where no CIN grade II or worse is found and to more problems with side effects than cytology. A policy of referral for colposcopy after low grade cervical abnormalities confers no clear benefit compared with cytological surveillance and causes more side effects.

Design

Multicentre individually randomised controlled trial. Randomisation to cytological surveillance or immediate colposcopy stratified by age group, index cytology result, human papillomavirus infection test result, and recruitment centre. Women were followed for three years, with colposcopic examination at an exit visit at which colposcopists were blinded to randomisation.

Participants and setting

In all, 4439 women, aged 20-59, with a cytology result showing borderline nuclear abnormalities or mild dyskaryosis, October 1999-October 2002, enrolled through the NHS cervical screening programmes in Grampian, Tayside, and Nottingham.

Primary outcomes

Cumulative incidence of CIN grade II or worse, grade III or worse, clinically significant anxiety and depression, other self reported after effects, and rates of non-attendance.

Main results and the role of chance

The cumulative incidence of CIN grade II or worse was 79/1000 person years in the colposcopy arm and

58/1000 person years in the cytological surveillance arm (relative risk 1.37, 95% confidence interval 1.19 to 1.57). This difference was less marked for CIN grade III or more severe disease, but the incidence was still higher in the colposcopy arm (relative risk 1.26, 1.04 to 1.53). The more marked difference between the arms in the occurrence of grade II or worse than in the occurrence of grade III or worse is probably because of spontaneous regression of some cases of grade II neoplasia.

Harms

More women in the colposcopy arm reported after effects, and these were of longer duration and more severe. Similar proportions of women were anxious or depressed in the two arms.

Bias, confounding, and other reasons for caution

The participation rate was 52%, and was higher in older women and in those living in the least deprived areas. As the distributions of these factors did not differ between the trial arms, incomplete participation will not have affected the randomised comparison. A third of participants did not attend the exit examination. As several of the factors associated with non-attendance for this examination are risk factors for CIN grade II/III and cervical cancer, the overall cumulative incidence of grade II or worse was probably underestimated, but the underestimation is probably small. The difference between the trial arms was attenuated when we restricted our analysis to women who had attended the exit examination.

Generalisability to other populations

This was a pragmatic trial set within the screening programmes in Scotland and England. It was population based, and its participation rate compares favourably with population based epidemiological studies and other trials involving women. Its results are generalisable to women with low grade cytological abnormalities identified in organised population based cervical screening programmes.

Study funding/potential competing interests

This study was supported by the Medical Research Council (grant No G9700808) and the NHS in England and Scotland. Various members of the TOMBOLA group have declared interests in GlaxoSmithKline and MSD Sanofi Pasteur (see online version for details).

Trial registration number

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CUMULATIVE INCIDENCE OF CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN) GRADE II, III, OR WORSE PER 1000 PERSON YEARS, BY TRIAL ARM

	CIN grade II, III, or worse		CIN III or worse	
	No of cases	Cumulative incidence	No of cases	Cumulative incidence
Cytological surveillance	350	58	193	32
Immediate colposcopy	468	79	238	40
Relative risk (95% CI)	1.37 (1.19 to 1.57)		1.26 (1.04 to 1.53)	

Biopsy and selective recall compared with immediate large loop excision in management of women with low grade abnormal cervical cytology referred for colposcopy: multicentre randomised controlled trial

TOMBOLA Group

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STUDY QUESTION What is the effectiveness of punch biopsy and selective recall for treatment compared with immediate large loop excision in the management of women with low grade abnormal cervical cytology referred for colposcopy?

SUMMARY ANSWER Punch biopsy and selective treatment detects as much cervical intraepithelial neoplasia (CIN) grade II or worse over three years as immediate large loop excision. Important disease is not missed. Immediate large loop excision results in overtreatment and more after effects.

Design

Multicentre individually randomised controlled trial. Randomisation to immediate large loop excision or targeted punch biopsies with recall for treatment (by large loop excision) if the biopsies showed CIN grade II or worse. Women with an abnormal transformation zone on colposcopic examination received the intervention. Colposcopists were not blinded to the randomisation. Women were followed for three years, concluding with an exit examination, including colposcopy.

Participants and setting

1983 women, aged 20-59, with a cytology result showing borderline nuclear abnormalities or mild dyskaryosis, October 1999-October 2002, enrolled through the NHS cervical screening programmes in Grampian, Tayside, and Nottingham.

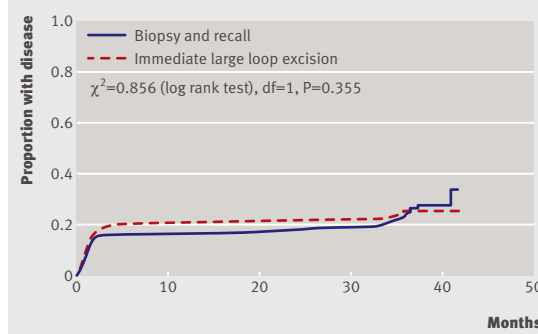
Primary outcomes

Cumulative incidence of CIN grade II or worse and grade III or worse; clinically significant anxiety and depression; and self reported after effects (pain, bleeding, discharge).

Main results and the role of chance

More women in the biopsy and recall arm were judged to have an abnormal transformation zone than in the immediate large loop excision arm (60% *v* 51%). In the biopsy and recall arm, 16% of women required a second clinic visit for treatment. Specimens from almost 60% of women in the immediate large loop excision arm showed no cervical intraepithelial neoplasia (31%) or grade I disease (28%). The cumulative incidence of CIN grade II or worse over three years follow-up was 79/1000 person years in the biopsy and recall arm and 84/1000 person years in the immediate large loop excision arm (relative risk 1.04, 95% confidence interval 0.86 to 1.25, *P*=0.687). For CIN grade III or worse the relative risk was 1.03 (0.79 to 1.34, *P*=0.841). There was

CUMULATIVE PROPORTION OF WOMEN DEVELOPING CIN GRADE II OR WORSE FROM TRIAL RECRUITMENT UP TO AND INCLUDING EXIT EXAMINATION, BY ARM



no significant difference between the arms in timing of detection of CIN grade II or worse (figure).

Harms

More women in the immediate large loop excision arm reported moderate or severe bleeding and discharge. The proportions of women reporting pain or who were anxious or depressed were similar in the two arms.

Bias, confounding, and other reasons for caution

The participation rate was 52% overall. The ratio of borderline nuclear abnormalities to mild dyskaryosis among participants was the same as in the NHS cervical screening programmes. A third of participants did not attend the exit examination, and their clinical outcomes were assessed from medical records and databases. The overall cumulative incidence of grade II or worse was probably slightly underestimated. The results were not changed when we restricted our analysis to women who had attended the exit examination.

Generalisability to other populations

The results are generalisable to women with low grade cytological abnormalities identified in population based cervical screening programmes who are referred for colposcopy.

Study funding/potential competing interests

This study was supported by the Medical Research Council (grant No G9700808) and the NHS in England and Scotland. Various members of the TOMBOLA group have declared interests in GlaxoSmithKline and MSD Sanofi Pasteur (see online version for details).

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Options for managing low grade cervical abnormalities detected at screening: cost effectiveness study

TOMBOLA Group

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STUDY QUESTION To estimate the cost effectiveness of three alternative methods of managing low grade cervical cytological abnormalities detected at routine screening: cytological surveillance v referral to colposcopy for biopsy and recall if necessary v referral to colposcopy with immediate treatment based on colposcopic appearance.

SUMMARY ANSWER Judged within the time frame of the evaluation, there is no compelling economic reason to favour any one follow-up method over either of the others.

Main results

The table displays the average costs of the alternative methods, each audited over three years. Also included are mean costs per case of cervical intraepithelial neoplasia (CIN) detected and mean quality adjusted life years (QALYs) experienced over 2.5 years.

Design

The economic evaluation was conducted in parallel with a randomised controlled trial.

Source(s) of effectiveness

Economic outcome was measured as QALYs. Participants completed an EQ-5D questionnaire immediately before initial randomisation and at 12, 18, 24, and 30 months after recruitment. We plotted index scores against time for each participant, with the area under the curve representing the total number of QALYs experienced by the participant between recruitment and 30 months thereafter. We excluded any woman whose initial or final questionnaire was incomplete and also any whose questionnaires at two or more adjacent time points were missing. When

a single utility value was missing within a woman's EQ-5D sequence, we used linear interpolation between the two known values.

Data sources

We collected data on use of resources for individual participants throughout the three year observation period (initial recruitment to exit). For cost discounting, we recorded the specific timing of every management event relative to the baseline. Events contributing to NHS screening costs were smear tests, colposcopies, and additional contemporaneous interventions, such as biopsies or large loop excisions. Resource use attributable to effects of management was captured in questionnaires returned by a subsample of trial participants. In addition to the costs of cervical screening and treatment borne by the NHS, we calculated costs borne by others in a questionnaire survey of a large subsample of participants. The unit costs of smear tests were estimated from two external studies and from a specific study at one of the trial centres. The unit costs of colposcopies and related procedures were derived from NHS reference costs and from published sources.

Results of uncertainty analysis

We estimated two sets of cost effectiveness ratios, one using the NICE convention and one based on social costs, using the Monte Carlo approach. The size of the confidence intervals for the cost and outcome distributions indicated that none of the three approaches were significantly more cost effective than the other two.

Limitations

Our results pertain to an economic evaluation within a trial and concern options for management of follow-up, rather than for cancer prevention. Judgments about long term cost effectiveness would require modelling to be undertaken, although such models would require information as yet unavailable—for example, the extent of spontaneous regression of neoplasia, future compliance with screening, and the impact of treatment on fertility.

Study funding/potential competing interests

This study was supported by the Medical Research Council (grant No G9700808) and the NHS in England and Scotland. One of the contributors has received fees from GlaxoSmithKline as a member of an independent data and safety monitoring committee for a trial of the efficacy of vaccination against HSV.

COSTS OF ALTERNATIVE METHODS OF MANAGING LOW GRADE CERVICAL ABNORMALITIES DETECTED AT SCREENING AND QUALITY ADJUSTED LIFE YEARS (QALYS) GAINED

	Cytological surveillance	Immediate treatment	Biopsy and recall
Mean discounted costs (£)			
NHS	150.20	240.30	241.10
Social	204.40	339.90	327.50
Mean discounted costs per CIN case detected (£)			
NHS perspective	1241	1073	1256
Social perspective	1689	1517	1706
Mean QALYs gained			
Overall	2.225	2.243	2.277

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