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Screening with a primary human papillomavirus test does not increase detection of cervical cancer and intraepithelial neoplasia 3

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ABSTRACT

Aim: To determine cross-sectional validity of primary human papillomavirus (HPV) screening in comparison to cytological screening.
Methods: During 2003–2004, 61,149 women were individually randomised to screening with a test for oncogenic HPV DNA or to conventional cytological screening within the Finnish cervical screening programme.
Results: For HPV screening, cross-sectional relative sensitivity for cervical intraepithelial neoplasia (CIN) or cancer was 1.58 (95 % confidence interval 1.19–2.09) in comparison to cytology. At the level of CIN 3 or cancer no increase in relative sensitivity was observed. Cross-sectional specificity estimates for the screening arms were comparable, but the specificity of screening with sole HPV DNA test was clearly inferior.
Conclusions: Primary HPV screening with cytology triage finds more CIN lesions compared to conventional screening but mild lesions are overrepresented. This is likely to result in overdiagnosis since most mild lesions are regressive.

1. Introduction

For four decades cytological screening with the Papanicolaou (Pap) test has been the most effective method available for cervical cancer prevention. In most of the world, however, implementation of organised cytological screening programmes has not succeeded optimally.[1,2] Hence, alternative methods have been proposed for cervical cancer screening. Testing for the DNA of human papillomavirus (HPV) is one of the most intensively studied alternatives for cytology for many reasons. First, HPV DNA testing used as the sole test or in conjunction with cytology has higher cross-sectional sensitivity, although somewhat lower specificity, for cervical intraepithelial neoplasia (CIN) than cytological screening.[3–5] Second, HPV DNA test has been suggested to be more reproducible than cytology.[6,7] Third, costs of HPV DNA testing are not excessively much higher than the costs of cytological analysis and, thus, cervical screening with HPV DNA test might be more cost-effective than cytological screening – especially if the screening interval could be extended. For this, it is not surprising that numerous studies on HPV DNA testing in primary screening have been conducted and several

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are still ongoing.[8–12] In some studies a randomised trial protocol has been applied to allow reliable comparison of primary HPV screening to the predominant screening strategy or to other suggested screening strategies. Of the randomised trials, however, only a few have been designed for evaluation of long-term outcome of invasive cervical cancer incidence.

Specificity of the screening test is of high importance in population-based screening programmes for cervical cancer: it dictates the need for colposcopies and other further examinations as well as the need for intensified follow-up, which are all generally rather costly and limited in resources. Test specificity is also inversely related to the extent of screening-related adverse effects, such as anxiety and overtreatment. Due to this, assuming the HPV DNA test really has lower specificity compared to cytological test, using HPV DNA test as the sole primary screening test is unlikely to be the optimal strategy in countries with pre-existing cytological screening programmes. On the other hand, a cytological triage test offers means to improve the specificity of the HPV screening episode.

An experimental screening strategy has been applied into service screening in Finland in a randomised setting in 2003.[13,14] The aim of this screening trial is to study, whether the effectiveness of the cervical cancer screening programme in Finland can be further increased by primary HPV DNA testing; the trial is registered as an International Standard Randomised Controlled Trial, number ISRCTN23885553 (URL http://isrctn.org). In the current study we present 2-year results on cross-sectional validity (test positivity and detection rates, relative sensitivity, relative specificity and positive predictive values) of primary HPV screening with and without cytology triage protocol, in comparison to conventional cytological screening.

2. Materials and methods

In Finland, women between 30 and 60 years of age are invited for cervical cancer screening every 5 years.[15] In 2003–2004 one third of the women invited to organised cervical cancer screenings in nine municipalities in Finland were randomised to primary HPV DNA testing. Results of the HPV arm were compared to the results of conventional arm, which consisted of the women from the same municipalities randomised to cytological screening with the conventional Pap test. The current report includes screening data based on the 5-yearly invitations; findings from subsequent follow-up visits are not yet available. Study design, methods of randomisation and screening protocols have been previously described in more detail.[13]

Briefly, randomised screening with an HPV DNA test started in Finland in 2003 in seven municipalities served by one screening laboratory. In the beginning of 2004 two more municipalities and another screening laboratory joined the study. During 2003–2004, roughly two thirds of all women belonging to the target population of the organised cervical cancer screening within the participating municipalities (women aged 30, 35, 40, 45, 50, 55 and 60; in one municipality also those aged 25 and 65; no exclusion criteria) were individually randomised to screening with primary HPV DNA test or to screening with conventional cytology. One third was randomised to automation-assisted cytology (not described here).[16] Information on randomisations linked with personal identification codes was stored centrally and used to retain the individual random allocation at following screening episodes. The study was approved by the National Authority of Medicolegal Affairs, health boards of the participating municipalities, and the ethical committee of the local hospital district.

Screening samples were collected in regional health centres by registered nurses. For all women a cytological smear consisting of three sub-samples – vaginal, cervical and endocervical samples – was prepared on one glass slide. In women assigned to conventional screening the sub-samples were taken with standard equipment, two Ayre's spatulas and a cytobrush. In women assigned to HPV screening the endocervical sub-sample was collected using the special cervical sampler of the Hybrid Capture 2© test kit (Digene Corporation, Gaithersburg, MD, USA); after the smear was prepared, the same sampler was used to prepare the HPV DNA test sample, as the tip of the sampler was stored into Hybrid Capture 2© (also HC 2©) transport medium tube.

HPV DNA test samples were analysed for the 13 high-risk HPV types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68) included in the HC 2© high-risk probe. Result of high-risk HPV DNA measurement was reported as the ratio of relative light units (rlu ratio). Samples with rlu ratio less than 1.00 were classified negative for high-risk HPV DNA and samples with rlu ratio 1.00 or higher positive for high-risk HPV DNA. Training of the personnel, internal quality assurance, as well as selection of the test threshold, were done according to the recommendation of the manufacturer.

Smears from the conventional arm were analysed with manual light microscopy and classified according to the Papanicolaou classification system. Smears collected in the HPV arm were primarily stored – they were analysed only for the women who tested positive for HPV DNA (cytological triage test) and if, for any reason, HPV DNA test sample was not available (e.g. screenee refused from HPV DNA testing or sample taker forgot to prepare the HPV DNA test sample). In both screening arms women with cytology equal to low-grade squamous intraepithelial lesion (LSIL) or worse (Papanicolaou class III-V and a small proportion of class II) were referred for colposcopy and biopsies. This referral policy followed the Finnish Current Care guidelines. For quality control purposes a proportion (up to 10 %) of cytologically normal smears were re-read within each laboratory.

Colposcopies and other further examinations were performed in local hospitals, from which the information on histological confirmations was collected. In the analysis on histology we used the three-grade classification system for cervical intraepithelial neoplasia (CIN), in which mild dysplasia equals CIN 1, moderate dysplasia equals CIN 2, and severe dysplasia and carcinoma *in situ* are combined to the category CIN 3. Colposcopists and pathologists involved with histological confirmation procedures were aware of the screening test results.

2.1. *Statistical analysis*

We calculated the cross-sectional validity parameters of interest, i.e. relative sensitivity (measured by detection rates), relative specificity and positive predictive value (PPV) for screening visits in both arms by random allocation (or by intention to screen). Relative risks of colposcopy referral and histologically confirmed CIN were estimated in HPV screening arm with 95% confidence intervals (CI) using the conventional screening arm as the reference. Relative specificity was defined as the proportion of the screening test negatives among those with no histologically confirmed lesion (screening test negatives and false positives combined). For the HPV screening arm specificity was calculated with two definitions for test negativity: 1) cytology triage negative (i.e. no referral for colposcopy) and 2) primary screening test negative. Similarly, positive predictive values (PPVs) were calculated for the HPV screening arm with two different cut-offs for test positivity: 1) cytology triage positive (i.e. referral for colposcopy) and 2) primary screening test (HPV) positive. Relative risks of detection rates and differences in relative specificity and PPV were tested and 95% percent confidence intervals estimated by assuming the observations to follow a binomial test probability law.[17]

3. Results

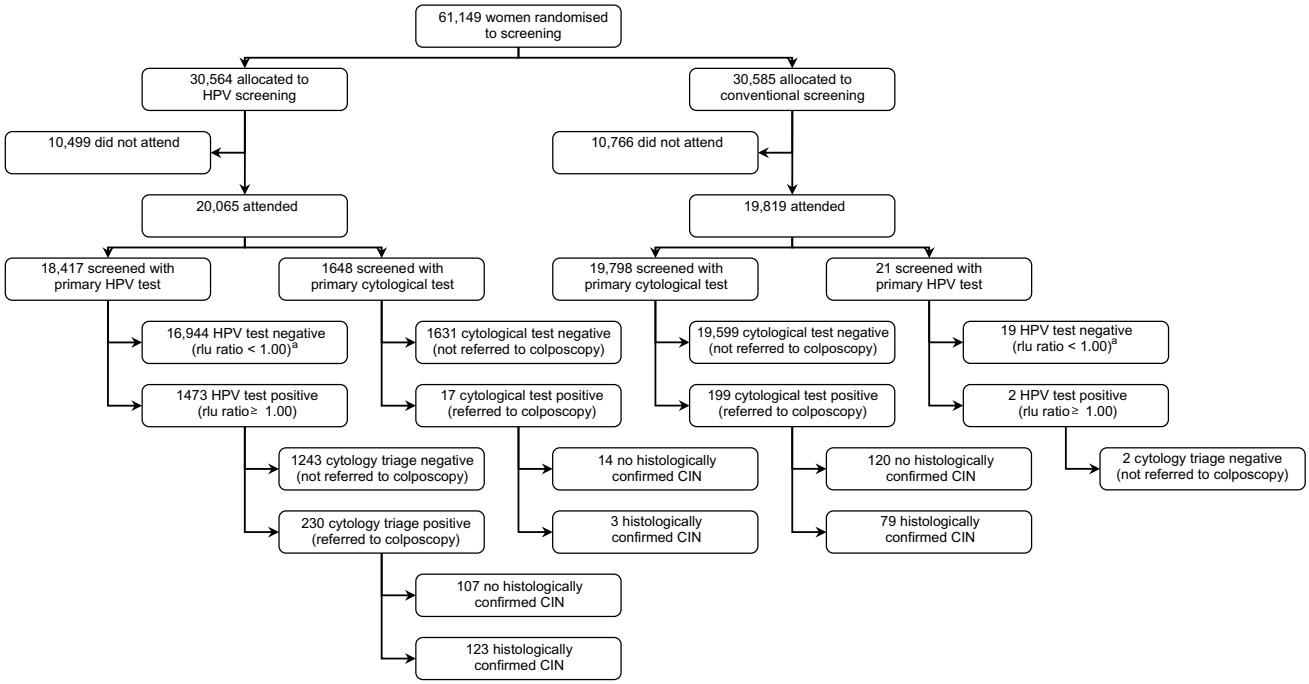
In 2003–2004, altogether 30,564 women were invited to screening in the HPV arm and a total of 20,065 screening visits were recorded. Of these, 18,417 women were screened with primary HPV DNA test (91.8%) and 1473 (8.0%) of them tested positive for high-risk HPV DNA and consequently had their smear analysed (i.e. cytology triage test performed). In addition, 1648 women were screened primarily with conventional cytology, resulting in a total of 3121 cytological tests in the HPV arm. Overall, 1490 women (7.4%) in the HPV arm had a positive primary screening test (1473 positive HPV DNA test and 17 positive cytology) and 247 (1.2%) were referred for colposcopy (230 after cytology triage and 17 after primary cytology) (Fig. 1).

In the conventional arm, 30,585 women were invited for screening and 19,819 attended. Of these, 99.9% were screened according to protocol, i.e. with conventional cytology. In this arm 201 women (1.0%) were primary test positives (199 cytology positives, 2 HPV test positives) and 199 of them were referred for colposcopy (all with primary cytological test) (Fig. 1).

In the HPV arm cytologically abnormal smears were detected in 22.1% of women with a cytological test. Of women with positive primary HPV DNA test 39.3% had abnormal cytology. Proportion of abnormal smears among women screened primarily with cytology was much lower, 6.7% in the HPV arm and 6.8% in the conventional arm (Table 1).

Compared to conventional screening, the relative risk (RR) of colposcopy referral in the HPV arm was 1.23 (95% CI 1.02–1.48). Cervical intraepithelial neoplasias were detected more often in the HPV arm than in the conventional arm: RR of any CIN or cancer (CIN 1+) was 1.58 (95% CI 1.19–2.09). For CIN 2 or more severe lesion (CIN 2+) RR was 1.44 (1.02–2.02). However, at the level of CIN 3 and invasive cancer there was no significant difference in detection rates between arms (Table 2).

Relative specificity of the HPV screening with cytology triage was close to that of cytological screening: the specificity estimate for CIN 1+ was 99.4% in the HPV arm, for CIN 2+ it was 99.1% and for CIN 3 or more severe lesion (CIN 3+)



[a]Of which 2067 also had a cytological test due to abnormal symptoms reported at screening visit (data not shown)

Fig. 1 – Screening flowchart for recruitment period of 2003–2004.

Table 1 – Cytological test results by screening arm and primary screening test

		HPV screening arm				Conventional screening arm			
		Primary HPV test[a]	Primary cytological test[b]	Total		Primary cytological test	Primary HPV test[a]	Total	
Papanicolaou	Bethesda 2001	*n*	*n*	*n*	%	*n*	*n*	*n*	%
I	Within normal limits	890	1536	2426	12.1	18,407	1	18,408	92.9
II	Reactive changes or ASC-US[c]	369	99	468	2.3	1180	1	1181	6.0
III	ASC-H[d], LSIL[e] or HSIL[f]	198	10	208	1.0	157	0	157	0.79
IV	HSIL[f]	11	1	12	0.06	16	0	16	0.08
V	Carcinoma	1	0	1	0.00	0	0	0	–
Unsatisfactory	Unsatisfactory	4	2	6	0.03	38	0	38	0.19
Not available, HPV DNA test only		16,944	0	16,944	84.4	0	19	19	0.10
Total		18,417	1648	20,065	100.0	19,798	21	19,819	100.0

a Cytology triage test performed for the HPV positive.
b HPV DNA test sample was not available.
c Atypical squamous cells of undetermined significance.
d Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion.
e Low-grade squamous intraepithelial lesion.
f High-grade squamous intraepithelial lesion.

98.8%; the respective estimates in the conventional arm were 99.4%, 99.3% and 99.1%. Relative specificity of sole HPV screening (without cytology triage) was significantly lower than that of HPV screening with cytology triage or of conventional cytological screening: specificity estimates for CIN 1+, CIN 2+ and CIN 3+ were 93.2%, 92.9% and 92.7%, respectively (Table 3).

The positive predictive value of HPV screening with cytology triage was 51.0% for CIN 1+, 32.4% for CIN 2+ and 8.9% for CIN 3+. For respective histological categories PPVs of cytological screening were 39.7%, 27.6% and 10.1%. PPV of screening with sole HPV test was, for all histological categories markedly lower than that of HPV screening with cytology triage or of cytological screening (Table 4).

4. Discussion

Compared to conventional screening, HPV screening with cytology triage resulted in 23% more referrals to colposcopy. Consequently, 58% more histologically confirmed CIN 1+ lesions were detected in the HPV arm than in the conventional arm. However, the observed difference in detection rates in favour of HPV screening was inversely related to the severity of the underlying lesion: it was highest at the level of CIN 1, more modest at the level of CIN 2 and non-existent at the level of CIN 3 and invasive cervical cancer. Due to limited statistical power, small differences in CIN 3 or cancer could not be ruled out. Correspondingly, the positive predictive value of HPV screening with cytology triage was higher than that of cytological screening at the level of CIN 1+ and CIN 2+, but lower at the level of CIN 3+. At all studied histological categories, relative specificity of HPV screening with cytology triage was almost as good as that of conventional cytological screening. Considering relative specificity and PPV estimates, the validity of sole HPV screening (without cytology triage) was clearly inferior to HPV screening with cytology triage or conventional cytological screening.

Current results on HPV screening confirm the finding from earlier studies, that primary HPV screening results in higher cross-sectional sensitivity than that of cytological screening.[3,13,18,19] However, contrary to previous experience the level of increase in the current study was highly dependent on the severity of the histological lesion: significant increase in detection was observed at the level of mild and moderate lesions, whereas the detection of CIN 3 lesions and cancers was not affected.[20,21] There are several alternative explanations for this observation. First, it is possible, that the knowledge of the HPV DNA test result as available in screening routine has affected cytological analysis, colposcopy performance and histological diagnostics and, as a result of changed criteria, more CIN diagnoses have been made. Also, the HPV DNA test itself may be more sensitive than conventional cytology to detect mild non-progressive CIN lesions. Furthermore, the sensitivity of conventional cytology for CIN 3+ lesions is probably so high, that only marginal increase can be achieved with an HPV DNA test. This hypothesis is supported by the fact that the effectiveness of the Finnish programme is among the highest in the world.[20] Differences in the sensitivity of cytology could

Table 2 – Relative risk (RR) of colposcopy referral and histologically confirmed lesions in the HPV screening arm versus conventional screening arm with 95% confidence interval (CI)

	HPV screening arm (n = 20,065)				Conventional screening arm (n = 19,819)		RR	95 % CI
	Primary HPV test	Primary cytological test[a]	Total		Primary cytological test			
	n	n	n	%	n	%		
Referred	230	17	247	1.23	199	1.00	1.23	1.02–1.48
Any CIN[b]	123	3	126	0.63	79	0.40	1.58	1.19–2.09
CIN 1[c]	46	0	46	0.23	24	0.12	1.89	1.16–3.10
CIN 2[d]	55	3	58	0.29	35	0.18	1.64	1.08–2.49
CIN 3[e]	19	0	19	0.10	17	0.09	1.10	0.57–2.12
Invasive cancer	3	0	3	0.02	3	0.02	0.99	0.20–4.89

a HPV DNA test sample was not available.
b Cervical intraepithelial neoplasia.
c Cervical intraepithelial neoplasia grade 1.
d Cervical intraepithelial neoplasia grade 2.
e Cervical intraepithelial neoplasia grade 3.

Table 3 – Specificity of the HPV screening for histologically confirmed CIN 1+, CIN 2+ and CIN 3+, in comparison to conventional screening

	No referral or no CIN[a] of given grade	Screening test negative	Specificity	
	n	n	%	95% CI
HPV screening, cytology triage				
CIN 1+[b]	19,938	19,809	99.4	99.2–99.5
CIN 2+[c]	19,985	19,809	99.1	99.0–99.2
CIN 3+[d]	20,043	19,809	98.8	98.7–99.0
HPV screening, sole HPV test[e]				
CIN 1+[a]	19,938	18,574	93.2	92.8–93.5
CIN 2+[c]	19,985	18,574	92.9	92.6–93.3
CIN 3+[d]	20,043	18,574	92.7	92.3–93.0
Conventional screening				
CIN 1+[b]	19,740	19,620	99.4	99.3–99.5
CIN 2+[c]	19,764	19,620	99.3	99.1–99.4
CIN 3+[d]	19,799	19,620	99.1	99.0–99.2

a CIN = cervical intraepithelial neoplasia.
b Cervical intraepithelial neoplasia grade 1 or more severe lesion.
c Cervical intraepithelial neoplasia grade 2 or more severe lesion.
d Cervical intraepithelial neoplasia grade 3 or more severe lesion.
e With rlu ratio cut-off 1.00.

partially account for the variation between different HPV trials.

Increased overall CIN detection may be beneficial, because if not treated, a considerable part of CIN lesions develop into cancers during the following decades.[22–24] An earlier study shows that after CIN treatment the risk of developing cervical cancer later is equally high for CIN 1, CIN 2 and CIN 3.[25] In the current study, however, the observed increase in detection, especially of CIN 1, is so marked when compared with the expected cervical cancer incidence rates, that it is likely to be at least partially due to overdiagnosis, leading to treatment of non-progressive lesions.

Possible overdiagnosis needs to be minimised in a well-organised screening programme, as it causes overtreatment and leads to increase in costs, patient anxiety and other adverse effects. There is growing evidence that CIN treatment can induce difficulties in reproductive health.[26,27] The majority of CIN lesions are harboured to fertile age women[20] and because the natural history for developing cervical cancer after HPV infection is known to be long,[28] mild lesions may not need active treatment but careful follow-up, e.g. within an organised screening programme, to allow for reproduction without the risk of developing cancer.

Nevertheless, the data used in our study is cross-sectional and on 5-yearly screening only, i.e. it does not contain information on smears, CIN diagnoses, and treatments from the follow-up period and/or from opportunistic screening. This kind of data will be required for truly reliable

Table 4 – Positive predictive value (PPV) of the HPV screening at the levels of histologically confirmed CIN 1+, CIN 2+ and CIN 3+, in comparison to conventional screening

	Screening test positive	CIN[a] of given grade	PPV	
	n	*n*	%	95% CI
HPV screening, cytology triage				
CIN 1+[b]	247	126	51.0	44.6–57.4
CIN 2+[c]	247	80	32.4	26.6–38.6
CIN 3+[d]	247	22	8.9	5.7–13.2
HPV screening, sole HPV test[e]				
CIN 1+[b]	1490	126	8.5	7.1–10.0
CIN 2+[c]	1490	80	5.4	4.3–6.6
CIN 3+[d]	1490	22	1.5	0.9–2.2
Conventional screening				
CIN 1+[b]	199	79	39.7	32.8–46.9
CIN 2+[c]	199	55	27.6	21.5–34.4
CIN 3+[d]	199	20	10.1	6.2–15.1

a CIN = cervical intraepithelial neoplasia.
b Cervical intraepithelial neoplasia grade 1 or more severe lesion.
c Cervical intraepithelial neoplasia grade 2 or more severe lesion.
d Cervical intraepithelial neoplasia grade 3 or more severe lesion.
e With rlu ratio cut-off 1.00.

estimation of benefits and potential adverse effects, such as overdiagnosis.

With the currently used protocol, HPV screening followed by cytology triage, the sensitivity of HPV screening can be utilised but the number of necessary colposcopies can be reduced almost to the level of conventional screening. However, as the HPV DNA positive but cytology negative women need to be followed up like the women with cytology equal to ASC-US (the majority of Papanicolaou class II) roughly equal resources are needed for follow-up procedures in both screening arms. Theoretically, HPV screening with or without cytology triage can also be applicable in a setting, where the resources for skilled cytological analysis are too limited to cover the need of an organised screening programme using a primary cytological test, but laboratory analysis can be performed in larger numbers. Validity of HPV screening without cytology triage was inferior compared to HPV with cytology triage or cytology. Nevertheless, without information on follow-up, the subsequent interval cancers and cancer related deaths, we cannot determine whether the outcome of HPV screening is inferior, equal, or superior compared to cytological screening. Also, other clinically relevant indicators, e.g. the number of screening tests during lifetime and treatments for CIN, are important. Further follow-up over at least one screening round will be needed to observe changes in incidence of severe lesions.

Essentially, primary HPV screening with cytology triage finds more CIN lesions compared to conventional screening but mild lesions are overrepresented, which results in overdiagnosis since most mild lesions are regressive.

Conflict of interest statement

PN has worked as a medical consultant for MSD Ltd and GSK Ltd. Other authors declare that they have no conflict of interest.

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