2 COMPARISON OF HPV AND CYTOLOGY TRIAGE ALGORITHMS FOR WOMEN WITH BORDERLINE OR MILD DYSKARYOSIS IN POPULATION-BASED SCREENING (VUSA-SCREEN TRIAL)

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ABSTRACT

Aim
We studied the effectiveness of high-risk human papillomavirus (hrHPV) triage for immediate colposcopy in women with borderline or mild dyskaryosis (BMD).

Methods
In the Utrecht province of the Netherlands, women aged 30–60 years who participated in the regular cervical screening programme were offered hrHPV testing and cytology (intervention group) or cytology only (control group). In the intervention group (n = 337), women with BMD were immediately referred for colposcopy only if the sample was hrHPV positive. Women with a hrHPV negative test were advised to repeat cytology at 6 and 18 months and were referred for colposcopy if and when the repeat test result was positive (BMD or worse). In the control group (n = 329), referral of women with BMD was delayed until cytology was repeatedly positive at 6 or 18 months.

Results
The CIN3 detection rates were 10.7% (36/337) in the intervention group and 6.4% (21/329) in the control group (p = 0.047). Moreover, hrHPV triaging resulted in shorter time to diagnosis (154 *vs*. 381 days). Although the number of colposcopy referrals was 51.5% higher in the intervention group than in the control group, the medical costs per detected CIN3 were slightly lower ([euro] 4781 *vs*. [euro] 6235). If, in addition, hrHPV negative women had been referred back to routine screening at baseline, the CIN3 rate would have been 10.1% (34/337) and colposcopy rate would only have been 30.4% higher than in the control group.

Conclusion
This study shows that hrHPV triaging of women with BMD is at least as effective for detecting CIN3 as repeat cytology, also when hrHPV negative women are referred back to routine screening.

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Introduction

In many European population-based screening programmes, women with borderline or mild dyskaryosis (BMD) are recalled for repeat cytology before being referred for colposcopy only if the cytological abnormality persists. This policy is used because only 5–15% of these women have or will develop high-grade cervical lesions.[1–3] A disadvantage of repeat testing is that women may become lost during follow-up.[4] Repeat cytology also induces a considerable amount of side effects in terms of psychological distress.[5,6] Several groups have studied the possible value of hrHPV testing and cytology for the detection of cervical lesions.[7,8] Most studies show that hrHPV testing is a sensitive instrument to triage women with BMD, but the optimal triaging strategy remains controversial.[9,10]

In the Netherlands, women with BMD are followed with cytology testing at 6 and 18 months. Since 2006, screening laboratories may choose to include a hrHPV test in the repeat cytology at 6 months.[11] This leads to a reduction in the number of repeat smears as it is considered safe to refer women with normal cytology and a negative hrHPV test back to the routine screening. A more substantial reduction in the number of repeat smears is expected when women with BMD are tested for hrHPV at baseline. However, population-based prospective evidence, in terms of the end-points CIN3 or cancer (CIN3+), colposcopy referrals and medical costs needed to support implementation of this strategy, is lacking.

To study the feasibility of hrHPV triage at baseline, we compared repeat cytology to direct referral of hrHPV-positive BMD women in a sub-study of the VUSA-Screen study (Vrije Universiteit Medical Centre SAltro laboratory population-based cervical SCREENing study). Outcome measures were CIN3+ and CIN2+ detection rates, number of colposcopy referrals, and medical costs.

Material and Methods

The present cohort study is part of the VUSA-Screen study. VUSA-Screen is an intervention study designed to evaluate the effectiveness of combined cervical cytology screening with hrHPV testing by Hybrid Capture 2 hybridization assay (HC2, Digene Corporation). The VUSA-Screen study has 2 aims. First, we evaluated the effectiveness of hrHPV triage in women with BMD by comparing current screening protocols using conventional cytology with a strategy where women with BMD were advised on the basis of hrHPV test result.

The second aim of the VUSA-Screen study was to evaluate the risk of developing high-grade CIN lesions in cytologically normal women with a hrHPV positive versus a hrHPV negative test result. Therefore, women with normal cytology and a positive hrHPV test were retested for cytology and hrHPV at 12 and 24 months. Women were referred if cytology was abnormal at 12 months and if cytology was abnormal and/or hrHPV positive at 24 months. Each hrHPV positive, cytologically normal woman was matched to 3 randomly chosen hrHPV negative, cytologically normal women of the same age, who were also rescreened at 24 months. In this article, we present the results of the BMD women only.

The study was carried out in the Utrecht province of the Netherlands in the setting of the regular Dutch screening programme. Women aged 30–60 years were advised

to visit their general practitioner (GP) for cytology screening every 5 years by means of a call and recall method. Between October 2003 and August 2005, GPs affiliated to the Saltro laboratory in Utrecht were asked to participate in the VUSA-Screen study. After education of 500 GPs, 254 agreed to participate and recruited women for both cytology and hrHPV testing. Women who agreed to receive cytology and hrHPV testing gave written consent and these women formed the intervention group. This group was compared with women visiting the GP for regular cytological screening who did not participate in the VUSA-Screen study, but were affiliated to the Saltro laboratory (control group). Women in the control group were screened according to the national guidelines[12,13] and data were analyzed anonymously.

Women were excluded from the analysis if they had a history of cervical intraepithelial neoplasia grade 2 or worse (CIN2+) or abnormal cytology in the preceding 2 years. All cytology and HC2 tests were performed in the Saltro laboratory in Utrecht under the supervision of a pathologist from the department of Pathology of the Vrije Universiteit Medical Center in Amsterdam. All study participants of the intervention group were given written information before screening regarding hrHPV infection and its role in carcinogenesis. A physician staffed telephone help desk was available throughout the study and follow-up period. The Ministry of Public Health obtained approval before the study started (advice nr 2002/02-WBO; ISBN-10: 90-5549-452-6), according to Dutch law. The study was registered in the trial register as NTR215, ISRCTN64621295.

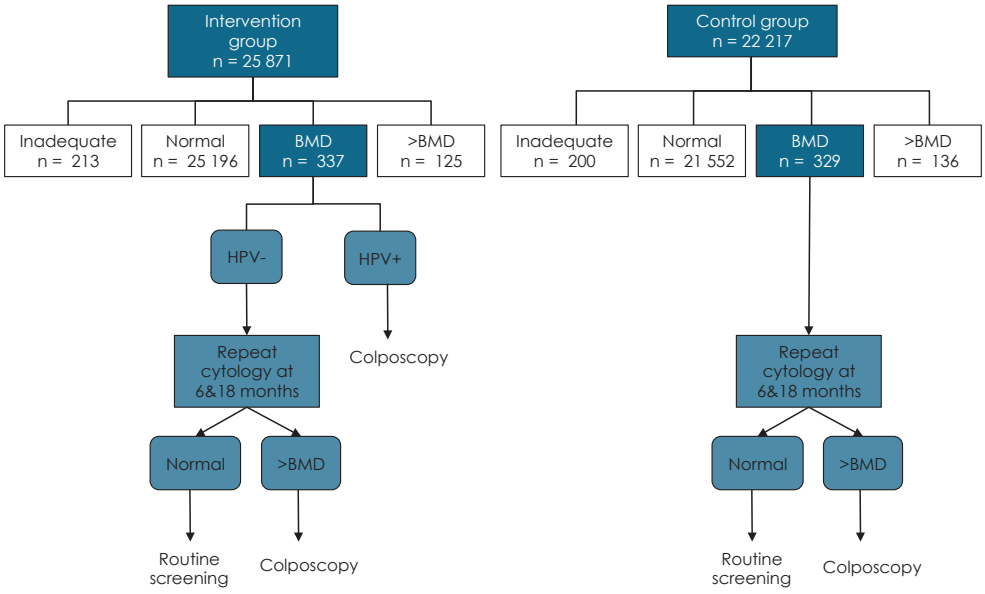

Figure 1 Flowchart study design. The baseline cytology results of the VUSA-Screen study and study design of women with BMD

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The triage design of the study and the baseline characteristics of women with minor cytological abnormalities are presented in Figure 1. Women in the intervention group were triaged according to both cytological testing and hrHPV DNA results. Women with BMD and a positive hrHPV test were directly referred to colposcopy. Women with BMD at baseline and a negative hrHPV test were tested for cytology at 6 and 18 months and referred if cytology was abnormal at one of these occasions. Women in the control group were tested with cytology according to the current guidelines for cervical screening in the Netherlands.[12] Women with BMD were advised to repeat the tests after 6 and 18 months. If one of the repeat tests was abnormal, women were referred to colposcopy.

A scrape was taken using a cytobrush (Rovers, Oss). After preparation of a conventional smear on a glass slide, the brush was placed in a vial containing 1 ml UCM (Universal Collection Medium, Dgene) for hrHPV testing. Cervical cytology results were reported, blinded to the hrHPV DNA testing results, according to the CISOE-A classification, which is routinely used in the Netherlands and can be easily converted into the BSCC classification.[14] Cytological results were grouped as normal, BMD and moderate dyskaryosis or worse (>BMD).

HrHPV testing was performed by the Hybrid Capture 2 (HC2) high-risk HPV DNA test in an automated format on a rapid capture system (RCS) according to the manufacturer's instructions (Qiagen, Gaithersburg, MD). This test uses a cocktail probe to detect 13 high-risk HPV types: 16, 18, 31,33, 35, 39, 45, 51, 52, 56, 58, 59 and 68. Positive controls containing 1 pg/ml of cloned HPV-16 DNA and negative controls (provided by the manufacturer) were included in each assay.[15] The results of the HC2 assay were expressed as relatively light units per cut-off value (RLU), representing the ratio between the emission from a sample to the average of 3 positive controls. Samples were considered positive if they attained or exceeded threshold of 1.0 RLU/CO (corresponding with 1 pg/ml HPV16 DNA).

Of the women that were referred to a gynaecologist for colposcopy, colposcopy-directed biopsies were taken from suspicious areas of the cervix, according to standard procedures in the Netherlands.[16] Histological examination of biopsies was done at local pathology laboratories and classified as normal, cervical intra-epithelial neoplasia grade 1, 2 or 3 or as invasive cancer, according to international criteria.[17,18] High-grade lesions were reviewed by 2 independent pathologists. Cytology and histology results of both the intervention and control group were retrieved from the nationwide network and registry of histopathology and cytopathology (PALGA; Bunnik, the Netherlands).

The primary outcome measure of the study was histologically confirmed CIN3+. Secondary outcome measures were histologically confirmed CIN2+, number of colposcopy referrals, and medical costs. The follow-up time was set at 3 years.

Baseline differences between the intervention and control group were examined for age (Mann-Whitney test), the prevalence of BMD in the screened population (Pearson Chisquare test), the percentage of women that attended the previous screening round (Chi-square test), and the socioeconomic status rank score (Mann-Whitney test). A woman was considered as a participant at the previous screening round if she had her last smear within 7 years. The socioeconomic status

score was postcode based and retrieved from the governemental ''Sociaal en Cultureel Planbureau'' (http://www.scp.nl/onderzoek/statusscores). The outcome measures, number of CIN3+, CIN2+ cases and colposcopy referrals were compared by Pearson's Chi-square test. Loss to follow-up was defined as no cytological or histological information obtained from women who were eligible for follow-up. The time to reach diagnosis was the time between baseline smear and histological diagnosis.

Women were referred to colposcopy on the basis of the study protocol. A woman could only be counted once for a referral to colposcopy. The colposcopy referral advices given by the gynaecologist after abnormal histology were not taken into account. Some women were referred for colposcopy despite the fact that the advice was repeat testing or return to routine screening programme. These cases were included in the calculation of the total number of colposcopy referrals. All calculations were repeated after omitting the follow-up of hrHPV-negative women in the intervention group. Clopper-Pearson confidence intervals were used for the detection rates, and normal intervals were used for the detection ratios and for the times to referral and diagnosis. The calculations were performed in STATA 10.0. Tests were two-sided and a test was significant if $p < 0.05$.

The number of screened women was targeted at 25,000 in both groups. Assuming a BMD prevalence of 2.5%, the sample size is sufficient to achieve 80% power to detect a 5% difference in CIN3+ yield.

The direct medical costs in euros per unit of health care resource utilization are included in the analysis and presented in Table 3. A health care perspective was taken and indirect costs and time and travel costs were not included. All costs were indexed at year 2006. The costs of screening and treatment were published previously and were updated to 2006 using the consumer price index.[9,19,20] The utilities for different health states (Table 3) were based on international publi-cations.[21,22] Following the Dutch guidelines, the discounting rate per year for costs and health effects were set at 4% and 1.5%, respectively.

Results

The patient characteristics of women with BMD are presented in Table 1. The intervention group and control group were comparable on all baseline characteristics.

Table 1 Characteristics of the women with BMD in the intervention and control group

Characteristics	Intervention group	Control group	p
Year of intake	2003-2005	2003-2005	
Region	Utrecht	Utrecht	
Median age	40.0	39.0	0.099
Prevalence of BMD in screening population	1.3%	1.5%	0.095
Borderline dyskaryosis	73.9%	72.0%	0.591
Mild dyskaryosis	26.1%	28.0%	0.591
Attendance at previous screening round[1]	82.5%	80.9%	0.637
Median socioeconomic status rank score[2]	0.43	0.47	0.677

[1] Computed for women who had received an invitation at a previous screening round (i.e. women ≥ 34 years of age). Attendance was defined as having a screening result within the last 7 years. [2] Ranks ranged from 0 to 1.

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Table 2. Follow-up results of women with BMD: 3-year cumulative colposcopy referrals and histology

	Number (% of total; 95 CI%)				Ratio, % (95% CI)	
Total	Control group n = 329	Intervention group n = 337	Intervention group, hrHPV+ n = 167	Intervention group, hrHPV- n = 170 hr	Intervention *vs* control group	Intervention (follow-up of hrHPV-negative women omitted) *vs* control group
No colposcopy referrals	204 (62.0; 56.5–67.2)	143 (42.4; 37.1-47.9)	0	143 (84.1; 77.7-89.3)	0.68 (0.59-0.80)	0
Colposcopy referrals[1]	125 (38.0; 32.7-43.5)	194 (57.6; 52.1-62.9)	167 (100)	27 (15.9; 10.7-22.3)	1.52 (1.28-1.79)	1.30 (1.10-1.55)
No biopsy	24 (7.3; 4.7-10.7)	40 (11.9; 8.6-15.8)	33 (19.8; 14.0-26.6)	7 (4.1; 1.7-8.3)	1.63 (1.00-2.64)	1.34 (0.81-2.22)
CIN0/1	40 (12.2; 8.8-16.2)	79 (23.4; 19.0-28.3)	64 (38.3; 30.9-46.2)	15 (8.8; 5.0-14.1)	1.93 (1.36-2.73)	1.56 (1.09-2.25)
CIN2+	61 (18.5; 14.5-23.2)	75 (22.3; 17.9-27.1)	70 (41.9; 34.3-49.8)	5 (2.9; 1.0-6.7)	1.20 (0.9-1.62)	1.12 (0.8-1.52)
CIN2	40 (12.2; 8.8-16.2)	39 (11.6; 8.4-15.5)	36 (21.6; 15.6-28.6)	3 (1.8; 0.4-5.1)	0.95 (0.63-1.44)	0.88 (0.58-1.34)
CIN3	21 (6.4; 4.0-9.6)	36 (10.7; 7.6-14.5)	34 (20.4; 14.5-27.3)	2 (1.2; 0.1-4.2)	1.67 (1.00-2.81)	1.58 (0.90-2.67)

hrHPV+= hrHPV positive; hrHPV-= hrHPV negative; CI= confidence interval; ≤CIN1= normal or CIN 1; CIN2+= CIN 2 or worse.[1]Criteria for referral to colposcopy: abnormal cytology or positive hrHPV test. Referrals include colposcopies that were performed despite the fact that the advise was repeat testing or return to routine screening programme.

Table 2 shows the histological results and the total number of gynaecological referrals for all women with BMD. The cumulative 3-year CIN3 detection rate was higher in the intervention group than in the control group (10.7% *vs.* 6.4%, $p = 0.047$). No cancers or adenocarcinoma in situ were detected. The CIN2+ rate was not statistically different between both groups (22.3% *vs.* 18.5%, $p = 0.235$), whereas the ≤CIN1 rate was higher in the intervention than in the control group (23.4% *vs.* 12.2%, $p < 0.001$). Of the 337 women with BMD in the intervention group, 167 (49.6%) were hrHPV positive. Of these, 34 (20.4%, 95%CI 14.5-27.3) had a CIN3 diagnosis. Of 170 hrHPV negative women with BMD, 2 (1.2%, 95%CI 0.1–4.2) had CIN3. Of the 329 women in the control group, 21 were diagnosed with CIN3 (6.4%, 95%CI 4.0–9.6). The colposcopy referral rate was higher in the intervention group than in the control group (57.6% *vs.* 38.0%, $p < 0.001$). However, the number of referrals per detected CIN3 was equal in both groups (5.4 *vs.* 6.0, $p = 0.689$). There was a marginal difference in the number of referrals per detected CIN2+ (2.6 *vs.* 2.0, $p = 0.074$).

Women with hrHPV negative test and women in the control group showed the same cytology follow-up at 6 and 18 months (75.3% *vs.* 76.9% $p = 0.690$ and 41.1% *vs.* 39.4% $p = 0.779$, respectively). The overall loss to follow-up was not statistically different between both groups (13.5% *vs.* 13.7%, $p = 0.935$).

Among women with a colposcopy referral, the mean time to referral was 39 (95%CI 22-55) days in the intervention group and 298 (95%CI 259-336) days in the control group. Among women with a histological diagnosis, the mean time to

diagnosis was 154 days (95%CI 124-184) in the intervention group and 381 days (95%CI 323-440) in the control group.

The medical costs of screening, diagnosis and treatment were €512 per woman in the intervention group and €398 per woman in the control group as shown in Table 3. Per detected CIN3, the medical costs were €4,781 in the intervention group and €6,235 in the control group. To study the impact of negative hrHPV triaging, we repeated the analyses while omitting follow-up after a hrHPV-negative test. In that case, the CIN3 detection ratio was 1.58 (95%CI 0.90–2.67%) compared with the control group and the colposcopy referral ratio was 1.30 (95% CI 1.10–1.55) compared with the control group. The medical costs per woman became €447 and the medical costs per detected CIN3 became €4,429 (Table 3).

Table 3 Medical procedure costs (screening, diagnosis, treatment): unit costs, costs per woman, costs per detected CIN2+ and CIN3

		Costs per woman with BMD (€)[2]		
		Intervention group		
	Unit costs (€)[1]		*Follow-up of hrHPV-negative women omitted*	Control group
First cytology[3]	57.0	57.0	57.0	57.0
Repeat cytology(s)[4]	55.0	43.2	11.6	57.8
		133.6	102.0	114.8
Colposcopy	158.4	91.2	79.2	60.2
Biopsy	68.1	31.1	27.1	20.9
Treatment and follow-up of:				
CIN 25	946.8	109.8	101.1	115.1
CIN 35	1362.4	145.8	137.5	87.0
Total costs per women		511.5	446.9	398.0
Costs per detected CIN2+		2298.3	2151.5	2146.6
Costs per detected CIN3		4781.3	4428.8	6235.4

[1]Unit cost of medical procedures, screening, diagnosis and treatment, based on recent Dutch data. [2]The costs of the average number of diagnostic. [3]Includes invitation organization, the visit at the GP and the collection of sample material and laboratory costs. [4]Includes the visit at the GP and the collection of sample material and laboratory costs. 5Treatment costs include the charge per type of treatment, preoperative diagnostics and cost of hospital days.

Discussion

HrHPV testing to triage women with borderline or mild dyskaryosis resulted in a much earlier diagnosis and was at least as effective for detection of CIN3 as repeat cytological testing. Although hrHPV triaging led to an increase in the number of colposcopies, this did not lead to an increase in the referral rate per CIN3. The medical costs per woman were similar for hrHPV triaging and repeat cytological testing and the costs per detected CIN3 were even slightly lower for hrHPV triaging.

The high CIN3/CIN2+ detection rate of the hrHPV triaging strategy is in line with a recent meta-analysis,[7] where it has been shown that hrHPV triaging has a higher sensitivity than repeat cytology (at the ASCUS threshold) for detection of CIN2+, without a marked specificity loss. We, therefore, evaluated the impact of ''negative triaging'' in which women with BMD and a negative hrHPV test are considered

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not to be at increased risk and thus able to return to the regular screening programme. This strategy has been suggested by several authors.[23–25] Therefore, we recal-culated the CIN3 yield after omitting the follow-up of hrHPV-negative women. This yield would still be at least as high as in the repeat cytology arm, indicating that hrHPV testing after BMD has a high-negative predictive value. This ensures that implementation of a protocol in which hrHPV-negative BMD women return to the regular screening programme does not lead to an increase in undetected lesions that are clinically meaningful.

We found higher colposcopy referral rates in the hrHPV triage arm than in the repeat cytology arm (57.6% *vs.* 38.0%). The ≤CIN1 rate was also higher in the hrHPV triage arm (23.4%) than in the repeat cytology arm (12.2%). This carries the potential risk of over-treatment in an additional 10% of cases. Our data did not allow us to analyze whether such was indeed the case. If women had been referred to the regular screening programme after a negative hrHPV test at baseline, the increase in colposcopy rate would have dropped from 51.5% to 30.4%. This increase in colposcopy rate, regardless whether it is implemented with or without negative hrHPV triaging, is not expected to lead to capacity problems in a country such as the Netherlands where the annual number of primary smears read as BMD is about 8,700.[26] On the basis of our study, introducing hrHPV triaging is expected to increase the number of colposcopies by about 1,700 without and 1,000 with a negative hrHPV triage scenario. The latter increase translates into an increase in the annual medical costs of 226,500 euros. In the Netherlands, the BMD prevalence is low and hrHPV positivity in BMD was 50% in our study. In countries where BMD rates are higher, hrHPV positivity in BMD may be lower in which case hrHPV triaging will be more efficient than in the Netherlands. This argument does not need to hold for a relatively young screening population in which hrHPV positivity and BMD rates are both high. A study by Moss et al.[10] in which most women were between 20–34 years old, showed higher colposcopy referral rates in the hrHPV triaging arm and lower colposcopy referral rates in the repeat cytology arm than our study.

Our study was a cohort study and not a randomized controlled trial. The study was performed in the setting of a private laboratory, a real life situation, and this made it difficult to organize randomization. Therefore, women may have different baseline characteristics, specifically as both groups were not recruited from the same GPs. To assess the possible effects of baseline differences, we compared the intervention and control group on the available characteristics; age, prevalence of BMD, screening history, and postcode-based socioeconomic status. We did not find any significant differences between the 2 groups, which strengthen the results in our study. In addition, the loss to follow-up was not statistically different between hrHPV negative women in the intervention group and the women in the control group.

The development of screening programme guidelines requires careful consideration of the benefits, burdens, and costs that are associated with the adaptation of new technologies. Our study clearly supports the evaluation of new guidelines for management of BMD, as early hrHPV triaging leads to equal or better CIN3 detection and can be implemented against low costs. The use of hrHPV triaging will lead to a faster diagnosis and less distress and is therefore an important step in improving the woman-friendliness of screening.

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