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Original Paper

High-risk HPV testing in women with borderline and mild dyskaryosis: long-term follow-up data and clinical relevance

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Abstract

In The Netherlands and most other European countries, women with two serial cervical smears with borderline or mild dyskaryosis (BMD) within 6 months are referred for colposcopy-directed biopsies. Only about 10% of these women have high-grade cervical intraepithelial neoplasia (CIN). This study therefore investigated whether human papillomavirus (HPV) testing could identify which women with smears read as BMD are most likely to have high-grade CIN, either at referral or during follow-up and the relationship was determined between clearance of high-risk HPV and regression of abnormal cytology. Women with smears read as BMD ($n=278$) were referred to the gynaecologist for colposcopy. They were subdivided into two groups; group A comprised women with a single smear ($n=172$) and group B women with two sequential smears ($n=106$) read as BMD before referral. High-risk HPV detection with Hybrid Capture II (HC II) was performed on a cervical scrape taken at the first visit before colposcopy (i.e. baseline smear) and during follow-up. Biopsies were taken when lesions suspected for CIN were seen at colposcopy. High-risk HPV DNA was present in the baseline smears of 126 (45.0%) women; 26 (20.6%) of them had histologically confirmed CIN 2/3 at the first visit and another 14 (11.1%) during follow-up. Only one of the 152 women (0.7%) with a negative high-risk HPV test had a CIN 2 lesion at the first visit and no CIN lesions were detected during follow-up of these women. After exclusion of women who were treated for prevalent high-grade CIN, the median follow-up times were 1.3 years (range 0.0–4.3 years) and 1.6 years (range 0.0–4.5 years) for women with HPV-negative and HPV-positive baseline smears, respectively. The sensitivity of a positive high-risk HPV test for CIN 2/3 at the first visit was 96.3%, the specificity 60.2%, the positive predictive value 20.6%, and the negative predictive value 99.3%. These values did not change markedly when stratified for group A or group B. Thus, a high-risk HPV positive test was strongly associated with the presence at the first visit and the development of CIN 2/3 lesions during follow-up. Moreover, regression of abnormal cytology in women with a positive high-risk HPV test at baseline was strongly associated with viral clearance and occurred 0.3 years (range −1.2 to 1.7 years) later than HPV clearance. This study establishes the value of a high-risk HPV positive test for women at risk of high-grade CIN, with virtually no risk for missing CIN 2/3. Addition of a test on high-risk HPV in women with BMD could prevent 55% of the referrals and/or repeat smears. Copyright © 2001 John Wiley & Sons, Ltd.

Keywords: HPV; Pap smears; borderline/mild dyskaryosis; referral policy; cervical cancer screening

Introduction

In cervical cancer screening in The Netherlands, about 4% of cervical smears are read as borderline or mild dyskaryosis (BMD) [1]. Since 1996, the policy for women with cervical smears read as BMD in The Netherlands and most other European countries has been to repeat cytology after 6 months [2]. If the repeat smear is read as BMD or worse, women are referred to the gynaecologist for colposcopy. However, the great majority (i.e. 90%) of these women do not have high-grade cervical intraepithelial neoplasia (CIN) and a marker that improved the prediction of high-grade CIN would considerably reduce the number of repeat smears and redundant referrals to the gynaecologist. Fewer repeat smears and referrals would not only benefit the efficiency of the cervical cancer screening programme, but also decrease the unnecessary anxiety among many of these women [3–8].

The role of high-risk human papillomavirus (HPV) infection in the pathogenesis of cervical cancer and its precursor lesions is well established [9–11]. Many studies have addressed the issue of HPV testing in triaging women with mild cytological abnormalities, to

select women at risk for high-grade CIN lesions [12–18]. Most of these studies have shown that prevalent high-grade CIN lesions occur mainly in women who reveal a positive high-risk HPV test. However, most of these studies do not provide information on long-term follow-up, especially of high-risk HPV-negative women and the occurrence of incident high-grade CIN. In this prospective study, we evaluated high-risk HPV testing in relation to the occurrence of high-grade CIN lesions at the first visit and during follow-up in women with cervical smears read as BMD. In addition, we studied clearance of high-risk HPV and its relationship to regression of abnormal cytology.

Materials and methods

Patient selection and study design

Patients were recruited either from general practitioners or from a gynaecological outpatient clinic from March 1996 until March 2000 in Walcheren, a municipality in The Netherlands. Women who were known to have a history of cervical pathology ($n=25$), or who presented with BMD of glandular epithelium ($n=49$), were excluded. An additional four women were excluded because of lack of follow-up. Ultimately, a total of 278 women with either a single smear or two sequential smears taken within an interval of 6 months, which were read as BMD, were included. For the purposes of this study, these women were subdivided into two groups; group A comprised women with a single smear ($n=172$) and group B women with two sequential smears ($n=106$). Details of the selected patients and study design are depicted schematically in Figure 1. All participants were referred to the gynaecologist within 3 months. During gynaecological examination, a cervical scrape was taken for HPV detection, after which colposcopy was performed. This smear is indicated as the baseline smear. Standard colposcopic assessment with acetic acid and iodine solutions was done by an expert gynaecologist (FdS). Colposcopically directed biopsies were taken when a lesion was visible.

Histologically confirmed high-grade CIN (CIN 2/3) was the end-point of the study and treatment was performed with LLETZ. After the first visit, women were kept under gynaecological surveillance by cytology and colposcopy every 6 months, as long as the previous smear was abnormal and/or positive for high-risk HPV DNA. Moreover, HPV testing was performed on the follow-up smears if the previous smear had been high-risk HPV-positive. The median follow-up time was 1.4 years (range 0.0–4.5 years).

Cytology

Cervical smears were read according to the KOPAC classification, the standard classification used in The Netherlands, and classified as normal (Pap 1), borderline dyskaryosis (Pap 2), mild dyskaryosis (Pap 3a1), moderate dyskaryosis (Pap 3a2), severe dyskaryosis (Pap 3b), suspected for carcinoma *in situ* (Pap 4), or suspected for at least invasive cancer (Pap 5) [19].

High-risk HPV DNA detection

The Hybrid Capture II (HC II; Digene) microplate method was used for the detection of high-risk HPV

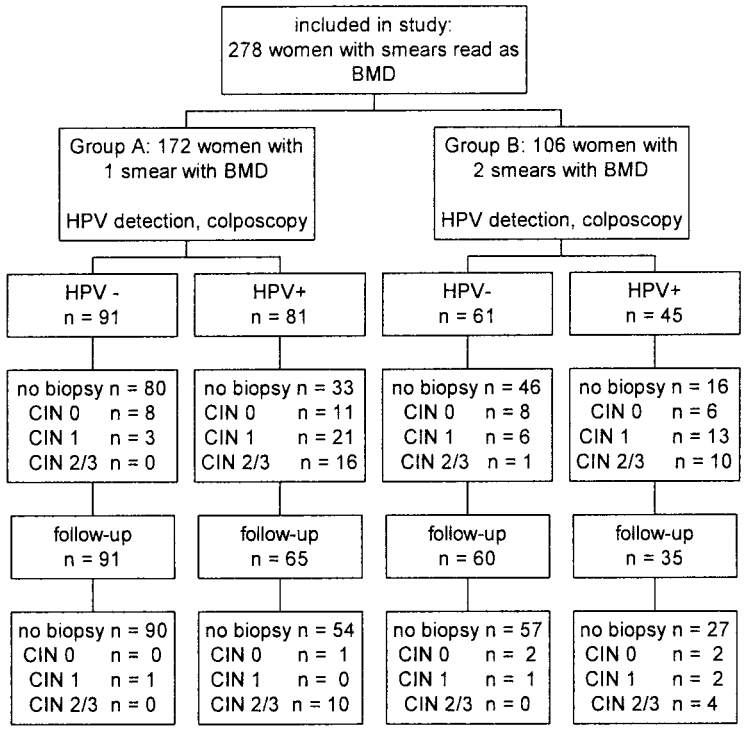

Figure 1. Flow chart of the study population

types 18, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68 as described by Lörincz [20]. Initially, the samples collected early in this study were analysed by Hybrid Capture I. From 1998 all these samples were blindly retested with HC II. Specimens were processed according to the manufacturer's instructions, and ultimately 5% of the samples were used for HPV testing. Triplicate assay controls representing 1.0 pg/ml of HPV DNA and negative control of carrier DNA in specimen transport medium were included. Specimens were scored positive for high-risk HPV DNA when their assay chemiluminescence was at least the average of three 1.0 pg/ml controls.

Definitions of HPV clearance and cytological regression

We considered women to have cleared the high-risk HPV infection when no high-risk HPV was detected at the next visit. High-risk HPV persistence was defined as the absence of viral clearance during follow-up. Regression of abnormal cervical cytology was defined as the presence of normal cytology in two consecutive cervical smears.

Statistical analyses

Differences between investigated categorical variables were tested using the chi-square test. The risk ratios (odds ratios, OR) and their confidence intervals were estimated from logistic regression analysis and adjusted for the age of the women, the number of smears (1 vs. 2), reason (screening programme vs. indication), site (outpatient clinic vs. general practitioner), and cytology (borderline vs. mild dyskaryosis).

Kaplan–Meier curves were used to analyse cytological regression and clearance of high-risk HPV. The time of cytological regression and HPV clearance was estimated using the mid-points between the last positive smear and the closest subsequent negative smear for abnormal cervical cytology and HPV DNA, respectively. Cytological regression was analysed for all 278 women and stratified for high-risk HPV status at the baseline [high-risk HPV-positive ($n=126$) vs. negative ($n=152$)]. Women with CIN 2/3 lesions were censored at the time of diagnosis.

High-risk HPV clearance was analysed for the women with a high-risk HPV positive test at the baseline ($n=126$) and stratified for cervical cytology. Women with CIN 2/3 lesions were censored at the time of diagnosis. Kaplan–Meier curves were compared using the log-rank test. In order to obtain insight into the sequence of high-risk HPV clearance and cytological regression, the follow-up times until cytological regression and HPV clearance were compared in women who reached both events ($n=111$), using the non-parametric signed rank test. A two-sided p value of less than 0.05 was considered significant.

Sensitivity, specificity, and positive and negative predictive values for cytology and HPV detection were computed using 2 by 2 tables.

Results

Patient characteristics

In this study, 278 women were placed into two groups depending on whether a single or two serial Pap smears read as BMD had been taken. Group A comprised women with a single smear ($n=172$; 61.9%) and group B women with two serial smears (106; 38.1%) (Figure 1 and Table 1). One to ten additional smears were taken from these women during a median follow-up time of 1.4 years (range 0.0–4.5 years).

The median age of women in group A was 40 years (range 20–76 years). In 135 (78.5%) of them, the smear was borderline dyskaryotic and in the remaining 37 (21.5%), the smear was classified as mild dyskaryosis (Table 1); 106 (61.6%) were included by the general practitioner and 66 (38.4%) by the gynaecologist.

The median age of group B women was 41 years (range 24–67 years); 78 (73.6%) of them had a second Pap smear classified as borderline dyskaryosis and 28 (26.4%) had this smear classified as mild dyskaryosis (Table 1). Of group B, 89 (84.0%) were included by the general practitioner and 17 (16.0%) by the gynaecologist.

Overall, 213 (76.6%) and 65 (23.4%) women had a borderline and mildly dyskaryotic smear, respectively, before referral.

Table 1. Baseline characteristics of all women with a single (group A) or two serial smears (group B) read as BMD

		Cytology group A		Cytology group B*		
		BD†	MD‡	BD	MD	Total
Population	Hospital	52	14	15	2	83
	GP	83	23	63	26	195
Indication	Screening	67	28	47	13	155
	Medical	68	9	31	15	123
Age distribution (years)	≤29	13	8	4	4	29
	30–39	40	20	23	9	92
	40–49	38	5	27	11	81
	≥50	44	4	24	4	76
HPV detection baseline smear	HPV+	50	31	24	21	126
	HPV−	85	6	54	7	152
Colposcopy or histology	No biopsy	104	9	54	8	175
	No CIN	13	6	12	2	33
	CIN 1	11	13	7	12	43
	CIN 2	5	6	3	5	19
	CIN 3	2	3	2	1	8
Total No. of patients		135	37	78	28	278

*Cytology of the second smear.
†Borderline dyskaryosis.
‡Mild dyskaryosis.
HPV = high-risk HPV.

Analysis at baseline

HPV detection

The overall high-risk HPV prevalence in the baseline smears was 45.3% (126/278). This was 47.0% (81/172) for group A and 42.5% (45/106) for group B. Women with smears read as mild dyskaryosis revealed the highest HPV prevalence, namely 80.0% (52/65), compared with 34.7% (74/213) of those with borderline dyskaryotic smears (Table 1, $p<0.01$). The HPV prevalence was 71.9% (87/121) in women younger than 40 years of age and 24.8% (39/157) in older women ($p<0.01$).

Histology at first visit

A histologically confirmed CIN 2/3 lesion at the first visit was present in 9.7% (27/278), including 9.3% (16/172) of group A and 10.4% (11/106) of group B (Figure 1 and Table 1). 5.6% (12/213) of the women with a borderline dyskaryotic smear and 23.1% (15/65) of those with mild dyskaryosis had a CIN 2/3 lesion (Table 1). The sensitivity of cytology (i.e. mild dyskaryosis) for CIN 2/3 at the first visit was 55.6%, and the specificity and positive and negative predictive values were 75.6%, 18.8% and 94.4%, respectively. CIN 3 lesions were present in 1.9% (4/213) of women with a borderline dyskaryotic smear and 6.2% (4/65) of women with a mildly dyskaryotic smear at referral ($p=0.09$). CIN 2 lesions were found in 3.8% (8/213) and 16.9% (11/65) of women with borderline and mild dyskaryosis, respectively ($p<0.001$).

After stratification for age, CIN 3 was found in 4.1% (5/121) of women younger than 40 years and in 1.9% (3/157) of those over 40 years of age ($p=0.27$). CIN 2 lesions were found in 14.9% (18/121) and 0.6% (1/157) of women younger and older than 40 years, respectively ($p<0.001$).

When stratified for high-risk HPV status, CIN 2/3 at the first visit was found in 0.7% (1/152) of the women with a negative HPV test, compared with 20.6% (26/126) of those with a positive HPV test ($p<0.00001$; Table 2).

Overall, the sensitivity of a positive HPV test at baseline for a CIN 2/3 lesion at the first visit was 96.3%; the specificity was 60.2%; and the positive and negative predictive values were 20.6% and 99.3%, respectively (Table 3). These values did not change markedly when stratified for group A or group B women. When stratified for age, the specificity and positive predictive value of a positive HPV test differed considerably between the two age categories of women, whereas the sensitivity and negative predictive value did not differ markedly (Table 3). In women younger than 40 years of age, the HPV test revealed a lower specificity (33.7% vs. 77.1%) but a higher positive predictive value (25.3% vs. 10.3%) than in older women.

The crude odds ratio for the presence of high-risk HPV at baseline to predict prevalent CIN 2/3 was 39 (95% CI 5.2–293). If the other variables were included in the model, only the presence of high-risk HPV (OR $_{\text{ADJUSTED}}$ 36, 95% CI 3.9–226) was significantly associated with a histologically confirmed CIN 2/3 lesion. The number of smears (single vs. two serial smears), cytology (borderline vs. mild dyskaryosis), age of women, indication for taking the smear (screening vs. medical), and population (hospital vs. general practitioner) did not significantly influence the risk for prevalent high-grade CIN lesions.

Table 2. Relationship between high-risk HPV presence in baseline smears and a CIN 2/3 lesion at the first visit stratified for cytology and age

		Histology/colposcopy		
Cytology or age (n)	**HPV (*n*)**	**CIN 3 (%)**	**CIN 2 (%)**	**No CIN 2/3* (%)**
Borderline dyskaryosis (213)	HPV + (74)	4 (5.4)	7 (9.5)	63 (85.1)
	HPV − (139)	–	1 (0.7)	138 (99.3)
Mild dyskaryosis (65)	HPV + (52)	4 (7.7)	11 (21.2)	37 (71.2)
	HPV − (13)	–	–	13 (100)
<40 years (121)	HPV + (87)	5 (5.7)	17 (20.0)	65 (74.3)
	HPV − (34)	–	1 (2.9)	33 (97.1)
≥40 years (157)	HPV + (39)	3 (7.6)	1 (2.6)	35 (89.8)
	HPV − (118)	–	–	118 (100)
All women (278)	HPV + (126)	8 (6.3)	18 (14.3)	100 (79.4)
	HPV − (152)	–	1 (0.7)	151 (99.3)
	All (278)	8 (2.9)	19 (6.8)	251 (90.3)

*Based on histology or colposcopy.
HPV = high-risk HPV.

Follow-up

Histology

After exclusion of women who were treated for prevalent high-grade CIN, the median follow-up times were 1.3 years (range 0.0–4.3 years) and 1.6 years (range 0.0–4.5 years) for women with HPV-negative and HPV-positive baseline smears, respectively.

Table 3. Performance of high-risk HPV test for prevalent CIN 2/3

Patient group	**Age (*n*)**	**Sensitivity**	**Specificity**	**PPV***	**NPV†**
Group A	<40 years (81)	100%	35.3%	22.8%	100%
	≥40 years (91)	100%	50.0%	12.5%	100%
	Both age groups (172)	100%	58.3%	19.8%	100%
Group B	<40 years (40)	90.0%	30.0%	30.0%	90.0%
	≥40 years (66)	100%	78.5%	6.7%	100%
	Both age groups (106)	90.0%	63.2%	22.2%	98.4%
All women	<40 years (121)	95.7%	33.7%	25.3%	97.1%
	≥40 years (157)	100%	77.1%	10.3%	100%
	Both age groups (278)	96.3%	60.2%	20.6%	99.3%

*PPV = positive predictive value.
†NPV = negative predictive value.

Table 4. High-grade CIN at the first visit and during follow-up in relation to high-risk HPV status at baseline

	CIN 2/3		
Follow-up time (years)	**HPV+/ No. of women**	**HPV−/ No. of women**	**Total No. of women**
First visit	26/29	1/7	36
>0 and ≤1	5/22	0/40	62
>1 and ≤2	5/33	0/66	99
>2 and ≤3	2/23	0/27	50
>3	2/19	0/12	31
Total	41/126	1/152	278

HPV = high-risk HPV.

Because of a colposcopic impression of a CIN lesion, biopsies were taken during follow-up in 3% (4/147) of the women with an HPV-negative test at baseline and in 23% (19/81) of those with a positive HPV test (Figure 1). High-grade CIN lesions were not detected during follow-up of up to 4.3 years in women who were negative for high-risk HPV at baseline (Table 4). However, two additional CIN 3 lesions and ten CIN 2 lesions were found within the same follow-up period amongst women with an HPV-positive baseline smear.

Cytological regression

The cumulative 1-year incidences of cytological regression were 26% (95% CI 17–35) and 53% (95% CI 45–62) for women with an HPV-positive and HPV-negative baseline smear, respectively (Figure 2). The median cytological regression times of women with an HPV-negative and HPV-positive baseline smear were 1.0 (95% CI 0.8–1.2) and 1.9 (95% CI 1.5–2.3) years, respectively.

Clearance of HPV

Overall, the cumulative 1-year incidence of HPV clearance was 45% (95% CI 34–56; Figure 3). The median duration of clearance of an infection with high-risk HPV was 1.7 years (95% CI 1.0–2.4).

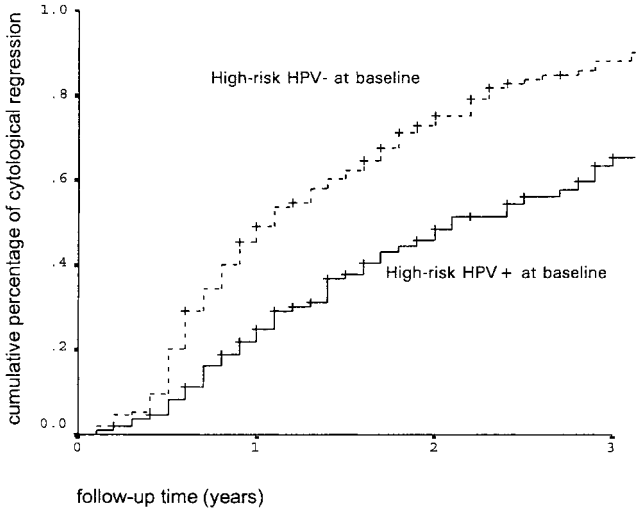

Figure 2. Cytological regression in women with BMD stratified for high-risk HPV status at baseline

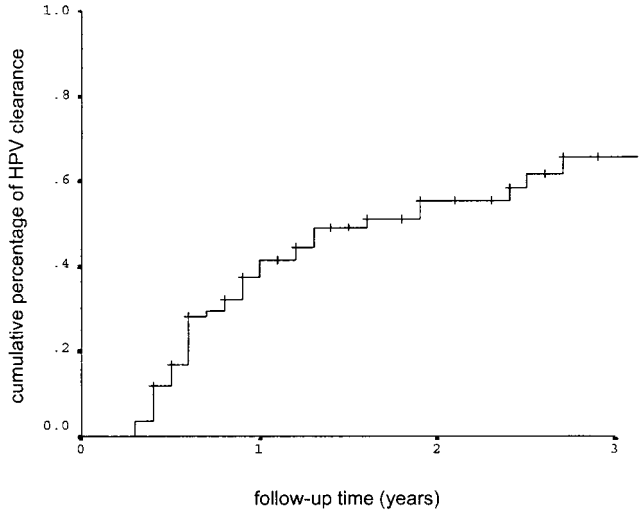

Figure 3. High-risk HPV clearance in women with smears read as BMD

Cytological regression in women with clearance versus persistence of HPV infection

Of the 126 women with a high-risk HPV-positive baseline test, 47 cleared the infection during follow-up and 79 revealed a persistent infection. The cumulative 1-year incidences of cytological regression in women showing HPV clearance and HPV persistence were 40% (95% CI 26–54) and 16% (95% CI 6–26), respectively. The median cytological regression time of women with clearance was 1.6 years (95% CI 1.2–2.0) and that of women with a persistent HPV infection was 3.2 years (95% CI 2.6–3.7).

Sequence of cytological regression and HPV clearance

A total of 43 women with a high-risk HPV-positive test at baseline reached both HPV clearance and cytological regression during follow-up. More than 50% of the women cleared high-risk HPV infection 0.3 years (range −1.2 to 1.7) earlier than the manifestation of cytological regression (Student *t*-test two-sided $p = 0.001$).

Discussion

This study provides information on the potential value of HPV testing to predict both prevalent and incident CIN 2/3 lesions in women with BMD. In particular, the sensitivity and negative predictive value of an HPV test to predict prevalent CIN 2/3 appeared superior to those of cytology (i.e. mild dyskaryosis). All except one of the CIN 2/3 lesions detected at the first visit occurred in women with an HPV-positive baseline smear. Consequently, HPV testing has the potential to identify the women, among those with BMD, who have the greatest likelihood of having prevalent high-grade CIN (OR $_{\text{ADJUSTED}}$ 36, 95% CI 3.9–226).

Although no follow-up was available due to treatment, the single exception (i.e. a woman belonging to group B with an HPV-negative baseline smear who had prevalent CIN 2) may represent a woman with a regressing lesion who already had cleared the virus. This impression is partly based on cytology, since the second smear of this woman was less abnormal (i.e. borderline dyskaryosis) than the first smear (i.e. mild dyskaryosis) taken 6 months earlier. Moreover, we found in this study that the median time of viral clearance was 3.6 months (0.3 years, range −1.2 to 1.7) earlier than the manifestation of cytological regression, which may explain the presence of a lesion in the absence of HPV DNA. However, the observed range also indicates that cytological regression apparently occurred before HPV clearance in a subset of women. One possible explanation for this phenomenon is that very small regressing lesions could have been missed by cytology, at the time that HPV DNA was still detectable. Alternatively, the lesion indeed could have disappeared completely, but the HPV DNA detected could represent a reinfection rather than a persistent infection underlying the regressed lesion. Similar data have recently been collected by PCR in a cohort of women with abnormal cytology previously described by Nobbenhuis *et al.* [21,22].

This study also showed that no high-grade CIN lesion developed within a median follow-up time of 1.3 years in women with BMD and a negative HPV test at baseline. Thus, high-risk HPV testing can detect women at high risk for high-grade CIN, both at the first visit and developing during follow-up, without virtually no risk of missing CIN 2/3.

There have been some disparate results reported, particularly with regard to specificity and the positive predictive value of the HPV tests performed in several studies on this topic [12–18]. Possible explanations may be differences in the methodology of HPV testing, differences in the severity of cytological abnormalities (borderline vs. mild dyskaryosis), and/or differences in the age distribution of women included. The fact that differences in the age distribution may effect these parameters became apparent from this study; in women younger than 40 year of age, the HPV test revealed a markedly lower specificity but a higher positive predictive value than in older women (Table 3). On the other hand, the negative predictive value of the HPV test in particular was largely unaffected by age variation and this value was generally also high in other studies on women with low-grade cytological abnormalities of the uterine cervix [12–18].

By inclusion of long-term follow-up, our data even reinforce the high negative predictive value for high-grade CIN of an HPV test for women with BMD. In particular, its high negative predictive value (99.3% in this study) makes the HPV test strongly recommended for the selection of women who should not be referred for colposcopy, independently of variables such as age. If, in our study population, only women with a positive test for high-risk HPV had been included in the referral policy, 53% (91/172) of the referrals of group A and 58% (61/106) of group B could have been prevented. In total, 55% (152/278) of referrals would have been prevented.

Taken together, our observations of a high negative predictive value of the HPV test, of no development of high-grade CIN during follow-up of women with a negative HPV test, and of the occurrence of regression of cytological abnormalities after clearance of the HPV infection support the notion that it is safe to keep women with a negative high-risk HPV test and BMD in the cervical cancer screening programme, instead of referring them to the gynaecologist. This could markedly decrease the current costs of follow-up.

We also observed that the prevalence of high-risk HPV in baseline smears of group A women (who had a single smear) was comparable to that of group B women (who had two serial smears read as BMD). One explanation may be that the duration of an infection with high-risk HPV is generally longer than 6 months [22,23]. In our study, in women with BMD, the median duration of clearance of an infection with high-risk HPV was 20.4 months (95% CI 12–29). If, therefore, an HPV test were to be included for the selection of women with BMD to be referred to the gynaecologist, a repeat smear after 6 months would be redundant. Hence, not only the number of referrals, but also the number of repeat smears could be decreased considerably by the inclusion of an HPV test.

In conclusion, this study has established the potential value of HPV testing for women with smears read as BMD. By inclusion of an HPV test, women with a smear classified as BMD but negative for high-risk HPV could be left in the screening programme, since they do not belong to the risk group of high-grade CIN. Instead, women with a positive HPV test should be referred for colposcopy-directed biopsy and kept in the follow-up because of their risk of developing high-grade CIN. Fewer repeat smears and referrals would not only benefit the efficiency of the cervical cancer screening programme, but also decrease unnecessary anxiety among the majority of these women.

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