GYNECOLOGY

Benefit and burden in the Dutch cytology-based vs high-risk human papillomavirus-based cervical cancer screening program

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BACKGROUND: In 2017, the Dutch cervical cancer screening program had replaced the primary cytology-based screening with primary high-risk human papillomavirus-based screening, including the opportunity to participate through self-sampling. Evaluation and balancing benefit (detection of high-grade cervical intraepithelial neoplasia) and burden of screening (unnecessary referrals, invasive diagnostics, and overtreatment) is needed.

OBJECTIVE: This study aimed to compare the referral rates, detection of high-grade cervical intraepithelial neoplasia, overdiagnosis, and overtreatment in the new high-risk human papillomavirus-based screening program, including physician-sampled and self-sampled material, with the previous cytology-based screening program in the Netherlands.

STUDY DESIGN: A retrospective cohort study was conducted within the Dutch population-based cervical cancer screening program. Screenees with referrals for colposcopy between 2014 and 2015 (cytology-based screening) and 2017 and 2018 (high-risk human papillomavirus-based screening) were included. Data were retrieved from the Dutch Pathology Registry (PALGA) and compared between the 2 screening programs. The main outcome measures were referral rate, detection of high-grade cervical intraepithelial neoplasia or worse, overdiagnosis (cervical intraepithelial neoplasia grade 1 or less in the histologic specimen), and overtreatment (cervical intraepithelial neoplasia grade 1 or less in the treatment specimen).

RESULTS: Of the women included in the study, 19,109 received cytology-based screening, and 26,171 received high-risk human papillomavirus-based screening. Referral rates increased from 2.5% in cytology-based screening to 4.2% in high-risk human papillomavirus-based screening (+70.2%). Detection rates increased to 46.2% for cervical intraepithelial neoplasia grade 2 or worse, 32.2% for cervical intraepithelial neoplasia grade 3 or worse, and 31.0% for cervical cancer, and overdiagnosis increased to 143.4% with high-risk human papillomavirus-based screening. Overtreatment rates were similar in both screening periods. The positive predictive value of referral for detection of cervical intraepithelial neoplasia grade 2 or worse in high-risk human papillomavirus-based screening was 34.6% compared with 40.2% in cytology-based screening. Women screened through self-sampling were at higher risk of cervical intraepithelial neoplasia grade 2 or worse detection (odds ratio, 1.38; 95% confidence interval, 1.20—1.59) and receiving treatment (odds ratio, 1.31; 95% confidence interval, 1.16—1.48) than those screened through physician-sampling.

CONCLUSION: Compared with cytology-based screening, high-risk human papillomavirus-based screening increases detection of high-grade cervical intraepithelial neoplasia, with 462 more cervical intraepithelial neoplasia grade 2 or worse cases per 100,000 women but at the expense of 850 more cases per 100,000 women with invasive diagnostics indicating cervical intraepithelial neoplasia grade 1 or less.

Key words: cervical intraepithelial neoplasia, cervical smear, colposcopy, population screening, overdiagnosis, overtreatment

Introduction

Organized population cervical cancer screening has resulted in the reduction of incidence and mortality of cervical cancer through early detection and treatment of cervical intraepithelial neoplasia (CIN).[1] Until the end of 2016, in the Netherlands, women aged 30 to 60 years were invited for primary cytology cervical cancer screening with 5-year intervals. Several studies have reported that high-risk human papillomavirus (hrHPV)-based screening has a higher detection rate for ≥CIN2 lesions than cytology-based screening.[2–4] In 2017, the Dutch screening program had replaced primary cytology-based screening with primary hrHPV-based screening.[5] In this new program, women aged 40 and 50 years who receive negative test results for hrHPV are screened with an extended 10-year interval. In addition, self-sampling hrHPV screening has been offered to women who otherwise might not participate in the screening.

With cytology-based screening, women with high-grade cytology (high-grade squamous intraepithelial lesion) or persistent low-grade cytology (atypical squamous cells of undetermined significance [ASC-US] or low-grade squamous intraepithelial lesion [LSIL]) were referred for colposcopy. In hrHPV-based screening, all women who are hrHPV positive with ≥ASC-US, in the first testing or retesting at 6 months in case of normal cytology at primary testing, are referred to colposcopy (Figure 1).[6] According to the Dutch National Institute for Public Health and the Environment (RIVM), this should result in an increase of 49% in ≥CIN2 detection, 186% in ≤CIN1 detection, and 65% in referrals.[7] Increasing referral rates could cause unnecessary invasive diagnostics or overtreatment, arguing

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AJOG at a Glance

Why was this study conducted?

Large randomized controlled trials have revealed that high-risk human papillomavirus (hrHPV)-based screening results in more high-grade cervical intraepithelial neoplasia (CIN) detection than cytology-based screening. The Netherlands was among the first countries who replaced cytology-based screening with hrHPV-based screening on a national level. Evaluation and balancing the benefit and burden of the screening is needed.

Key findings

Detection rates in hrHPV-based screening increased to 46.2% for ≥CIN2, 32.2% for ≥CIN3, and 31.0% for cervical cancer. Referral rates and overdiagnosis in hrHPV-based screening increased to 70% and 143%, respectively, whereas overtreatment rates were similar in both the screening methods. Women screened through self-sampling were at higher risk of ≥CIN2 and receiving treatment than those screened through physician sampling.

What does this add to what is known?

hrHPV-based screening increases detection of high-grade CIN but at the expense of more invasive diagnostics indicating ≤CIN1. hrHPV-based screening does not lead to more overtreatment.

for better and more specific triage of women who are hrHPV positive.

According to the Dutch guidelines on CIN treatment, updated in 2015, CIN1 should be treated conservatively with follow-up cytology, because the complications of the treatment do not outweigh the risk of progression.[8,9] In cases of CIN2, an individual decision should be made, taking into account the age and the potential wish of having children in the future, because treatment may cause obstetrical-related complications.[10] CIN3 should be treated to prevent progression to cervical cancer.[9]

Because the Netherlands is among the first countries with a fully implemented hrHPV-based screening program for 3 years now, this is a good moment to compare our data with the expectations of the RIVM.[7] Therefore, the aim of this study was to compare the changes in referral rate, detection of high-grade CIN, overdiagnosis, and overtreatment in the primary hrHPV-based screening program with the cytology-based screening program in the Netherlands.

Materials and Methods

This population-based cohort study included all screened women aged 29 to 64 years with a referral advice for colposcopy. Women with histologic results obtained only by hysterectomy, polypectomy, or endocervical or endometrial curettage were excluded.

Data were retrieved from the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA, Houten, Netherlands).[11] Outcomes were compared for women referred in the cytology-based screening program between January 1, 2014, and July 1, 2015, with women referred in the hrHPV-based screening program between January 1, 2017, and July 1, 2018. Follow-up data were collected on December 31, 2016 and July 31, 2019, respectively. Outcomes in the hrHPV-based screening program were also stratified in physician-collected and self-collected samples.

Samples were collected in ThinPrep liquid-based cytology media (PreservCyt, Hologic, Marlborough, MA), regardless of whether cytology or hrHPV was the primary test. hrHPV testing was performed with the cobas HPV test (Roche Diagnostics, Risch-Rotkreuz, Switzerland, or Roche Molecular Systems Inc, Branchburg, NJ).

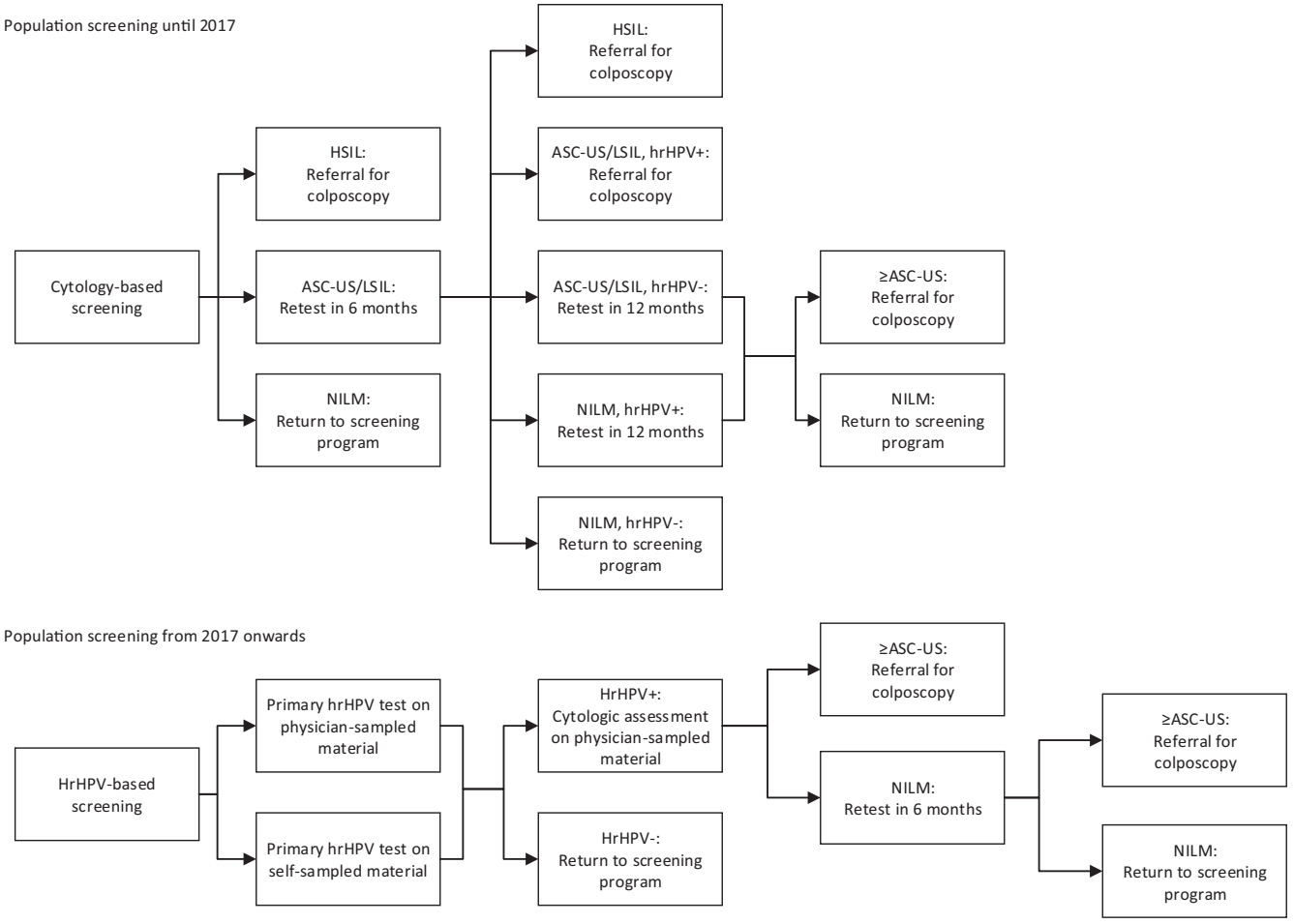
Cytology results were classified according to the CISOE-A framework, which can be easily converted to the 2001 Bethesda System.[12] The highest cytologic result within the screening moment, including repeat cytology during follow-up after 6 or 18 months, was used as the referral cytology. Histology was classified according to the CIN histologic grading system. Histologic outcome was based on the highest histologic diagnosis during follow-up.

Colposcopy was performed according to the latest Dutch national guidelines, and the decision for diagnostic biopsy or treatment was the responsibility of the individual colposcopist. The following 4 management strategies after referral were defined: conservative management with cytology only, conservative management with biopsy only, biopsy followed by loop electrosurgical excision procedure (LEEP) (2-step method) and immediate treatment with LEEP (see-and-treat method). Conservative management included patients with cytology and/or biopsy only within 6 months after referral cytology. The 2-step method was referred to as a biopsy within 6 months after referral cytology and a LEEP within 6 months after biopsy. The see-and-treat method was defined as LEEP within 6 months after referral cytology and without previous histology results.

The primary outcomes were referral rate; detection rate of ≥CIN2, ≥CIN3, and cervical cancer; overdiagnosis (defined as ≤CIN1 in histologic specimen); and overtreatment (defined as ≤CIN1 in treatment specimen). Secondary outcomes were the management of CIN lesions within different grades of abnormal cytology.

Baseline characteristics were summarized using descriptive statistics. To compare clinical features in the 2 different groups, the 1-sample *t* test was used for continuous variables and the chi-square test for categorical variables. Binary logistic regression, with and without adjustment for age, was used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for the main outcomes between the 2 different screening programs and between physician-sampled and self-sampled materials in the hrHPV-based screening program. Statistical analysis was done with the Statistical Analysis Software

FIGURE 1
Cytology-based vs hrHPV-based screening program in the Netherlands



ASC-US, atypical squamous cells of undetermined significance; *hrHPV*, high-risk human papillomavirus; *HSIL*, high-grade squamous intraepithelial lesion; *LSIL*, low-grade squamous intraepithelial lesion; *NILM*, negative for intraepithelial lesion or malignancy.

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(version 9.4; SAS Institute, Cary, NC) and Statistical Package for the Social Sciences Statistics (version 25; International Business Machines Corporation, Armonk, NY).

Results

We identified 95,607 patients with abnormal cytology, from which 45,280 referrals were included in the study as follows: 19,109 (42.2%) from the cytology-based screening and 26,171 (57.8%) from the hrHPV-based screening. Duplicates in the database (n=1003), women with abnormal cytology but without referral advice (n=47,815), and women with histology only available from other techniques than biopsy and LEEP, such as hysterectomy, polypectomy, and endocervical or endometrial curettage (n=1509), were excluded.

Table 1 lists the demographic characteristics of the 2 different screening methods. The referral rate increased from 2.5% in cytology-based screening to 4.2% in hrHPV-based screening (+70.2%). Therefore, in cytology-based screening, 40.9% of all referrals were direct referrals, whereas in hrHPV-based screening, 72.2% of all referrals were direct referrals. The median age was 40 years in both groups (range, 29−64), but more women aged ≥50 years were screened with hrHPV testing than with cytology testing (22.6% vs 15.5%, respectively). Women were referred on the basis of low-grade cytology more frequently in the hrHPV-based screening program than in the cytology-based screening program (68.8% vs 55.0%, respectively). Furthermore, relative more biopsies without following treatment were performed in women primary screened with hrHPV testing compared with women primary screened with cytology testing (41.3% vs 28.0%, respectively). This means that with hrHPV-based screening, there were 1048 more women who received conservative management after biopsy per 100,000 screened women.

Compared with physician sampling, women who are hrHPV positive and

TABLE 1
Demographic characteristics of women referred for colposcopy after participation in the Dutch cervical screening program: primary cytology-based screening vs primary hrHPV-based screening

		Primary hrHPV-based screening		
	Primary cytology-based screening	Total	Through physician sampling	Through self-sampling
Variable	N (%)	N (%)	n (%)	n (%)
Total number of screened patients	769,442	619,253	575,922	43,331
Number of referrals	19,109 (2.5)	26,171 (4.2)	24,974 (4.3)	1197 (2.8)
Direct referrals	7822 (40.9)	18,898 (72.2)	17,953 (71.9)	945 (78.9)
Indirect referrals	11,287 (59.1)	7273 (27.8)	7021 (28.1)	252 (21.1)
Age				
Age (y), median (range)	40 (29–64)	40 (29–64)	40 (29–64)	35 (30–60)
29–34	6570 (34.4)	8184 (31.3)	7716 (30.9)	468 (39.1)
35–39	2753 (14.4)	4856 (18.5)	4647 (18.6)	209 (17.5)
40–44	3350 (17.5)	3678 (14.0)	3511 (14.1)	167 (13.9)
45–49	3488 (18.3)	3552 (13.6)	3416 (13.7)	136 (11.4)
50–54	1423 (7.5)	2982 (11.4)	2875 (11.5)	107 (8.9)
55–59	1069 (5.6)	1874 (7.2)	1815 (7.3)	59 (4.9)
60–64	456 (2.4)	1045 (4.0)	994 (3.9)	51 (4.3)
Mean number of follow-up results (SD)	4 (1.5)	3 (1.4)	3 (1.4)	3 (1.4)
Loss to follow-up[a]	842 (4.4)	2539 (9.7)	2400 (9.6)	132 (11.0)
Referral cytology				
ASC-US	6673 (34.9)	10,866 (41.5)	10,440 (41.8)	426 (35.6)
LSIL	3831 (20.1)	7147 (27.3)	6830 (27.3)	317 (26.5)
HSIL	8605 (45.0)	8158 (31.2)	7704 (30.8)	454 (37.9)
Management				
Conservative with cytology only	6474 (33.9)	7487 (28.6)	7153 (28.6)	334 (27.9)
Conservative after biopsy	5361 (28.0)	10,808 (41.3)	10,370 (41.6)	438 (36.6)
2-step method[b]	4567 (23.9)	4820 (18.4)	4557 (18.2)	263 (22.0)
See-and-treat[c]	2707 (14.2)	3056 (11.7)	2894 (11.6)	162 (13.5)

ASC-US, atypical squamous cells of undetermined significance; *hrHPV*, high-risk human papillomavirus; *HSIL*, high-grade squamous intraepithelial lesion; *LSIL*, low-grade squamous intraepithelial lesion; *SD*, standard deviation.

[a] Identified as patients without cytologic or histologic follow-up of ≥18 months after referral; [b] Biopsy followed by treatment; [c] Immediate treatment.

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were screened through self-sampling were younger (median age, 35 vs 40 years, respectively) and had a higher percentage of high-grade referral cytology (37.9% vs 30.8%, respectively). Corresponding with the latter, a higher percentage of treatments was seen (35.5% vs 29.8%, respectively).

The distribution of CIN lesions among the grades of referral cytology is indicated in Table 2. In the hrHPV-based screening compared with the cytology-based screening, the detection rates increased for ≥CIN2 (1461 vs 999 per 100,000 screened women, respectively; +46.2%; 95% CI, 45.7–46.7), ≥CIN3 (836 vs 632 per 100,000 screened women, respectively; +32.3%; 95% CI, 31.9–32.7), and cervical cancer (38 vs 29 per 100,000 screened women, respectively; +31.0%; 95% CI, 30.6–31.4). However, overdiagnosis, defined as ≤CIN1, also increased (1487 vs 611 per 100,000 screened women, respectively; +143.4%). This resulted in a decreased positive predictive value (PPV) for the detection of ≥CIN2 from 40.2% (7686 of 19,109) in women referred for colposcopy in cytology-based screening to 34.6% (9050 of 26,171) in hrHPV-based screening.

The incidence of ≥CIN3 in women with ASC-US in cytology-based

TABLE 2
Initial CIN outcomes per grade of referral cytology[a]

Variable	No histology or no diagnosis n (%)	Histology ≤CIN1 n (%)	≥CIN2 n (%)	≥CIN3 n (%)	Cervical cancer n (%)	Total N
Primary cytology-based screening						
Referral cytology						
ASC-US	4365 (65.4)	1708 (25.6)	600 (9.0)	195 (2.9)	8 (0.1)	6673
LSIL	1337 (34.9)	1551 (40.5)	943 (24.6)	323 (8.4)	5 (0.1)	3831
HSIL	1018[b] (11.8)	1444 (16.8)	6143 (71.4)	4342 (50.5)	210 (2.4)	8605
Total	6720 (35.2)	4703 (24.6)	7686 (40.2)	4860 (25.4)	223 (1.2)	19,109
Primary hrHPV-based screening						
Total						
Referral cytology						
ASC-US	5223 (48.1)	4300 (39.5)	1343 (12.4)	459 (4.2)	14 (0.1)	10,866
LSIL	2041 (28.6)	3400 (47.5)	1706 (23.9)	593 (8.3)	13 (0.2)	7147
HSIL	645[b] (7.9)	1512 (18.5)	6011 (73.7)	4124 (50.6)	207 (2.5)	8158
Total	7909 (30.2)	9212 (35.2)	9050 (34.6)	5176 (19.8)	234 (0.9)	26,171
Physician-sampled						
Referral cytology						
ASC-US	5016 (48.0)	4143 (39.7)	1281 (12.3)	434 (4.2)	14 (0.1)	10,440
LSIL	1937 (28.4)	3265 (47.8)	1628 (23.8)	561 (8.2)	13 (0.2)	6830
HSIL	611[b] (7.9)	1446 (18.8)	5647 (73.3)	3852 (50.0)	194 (2.5)	7704
Total	7564 (30.3)	8854 (35.5)	8556 (34.2)	4847 (19.4)	221 (0.9)	24,974
Self-sampled						
Referral cytology						
ASC-US	207 (48.6)	157 (36.9)	62 (14.5)	25 (5.9)	0 (0.0)	426
LSIL	105 (33.1)	135 (42.6)	77 (24.3)	31 (9.8)	0 (0.0)	317
HSIL	37[b] (8.2)	66 (14.5)	351 (77.3)	269 (59.3)	13 (2.9)	454
Total	349 (29.2)	358 (29.9)	490 (40.9)	325 (27.2)	13 (1.1)	1197

ASC-US, atypical squamous cells of undetermined significance; *CIN*, cervical intraepithelial neoplasia; *hrHPV*, high-risk human papillomavirus; *HSIL*, high-grade squamous intraepithelial lesion; *LSIL*, low-grade squamous intraepithelial lesion.

[a] When both biopsy and treatment were performed, the highest diagnosis was used for this analysis; [b] Patients could have been lost to follow-up or have received other forms of treatment without histologic results, such as radiotherapy, cryotherapy, electrocoagulation, laser ablation, or a topical immune response modulator.

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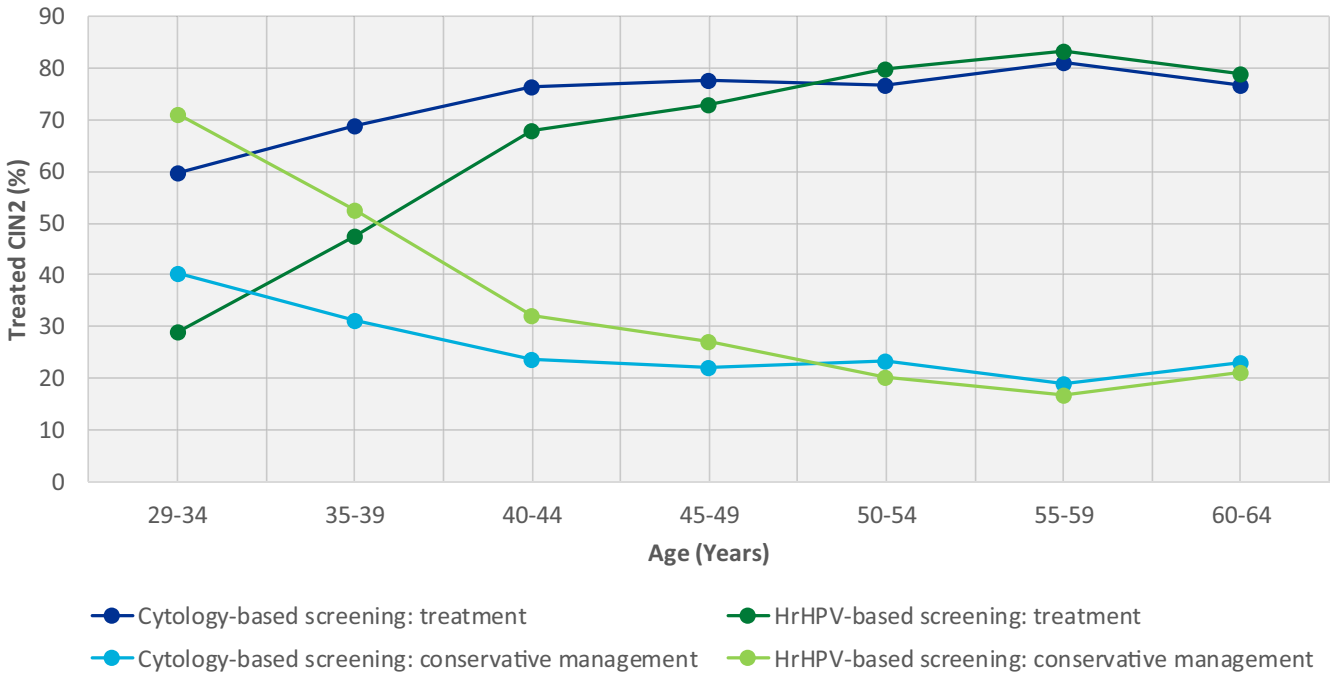
screening was 2.9% (25 per 100,000 screened women) compared with 4.2% (74 per 100,000 screened women) in hrHPV-based screening. For referrals based on LSIL, the incidence of ≥CIN3 was 8.4% and 8.3% (42 and 96 per 100,000 screened women, respectively).

When comparing the histologic results of women who are hrHPV positive and who used self-sampling vs physician sampling in hrHPV-based screening, a higher percentage of ≥CIN2 (40.9% vs 34.2%, respectively), ≥CIN3 (27.2% vs 19.4%, respectively), and cervical cancer (1.1% vs 0.9%, respectively) was seen.

The distribution of CIN grades seen in treatment specimens did not notably differ. The incidence of ≥CIN3 was similar in both groups (61.2% vs 60.9%; P=.72). When defining overtreatment as ≤CIN1, the overtreatment rate was 11.1% in cytology-based screening compared with 12.0% in hrHPV-based screening. When defined as ≤CIN2, 37.9% in the cytology-based screening vs 38.2% in the hrHPV-based screening were overtreated. Among women with ≤CIN2 in their first biopsy result, the risk of undertreatment and diagnosed with ≥CIN3 during follow-up was equal in both groups (0.4% [19/4697 vs 33/9113]; data not reported).

FIGURE 2
Management of CIN2 in the cytology-based vs hrHPV-based screening program



CIN, cervical intraepithelial neoplasia; *hrHPV*, high-risk human papillomavirus.

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Figure 2 indicates the distribution between treatment and conservative management for women with CIN2 diagnosis. In all age groups, more women received treatment than managed conservatively in cytology-based screening. Overall, 69.0% of the women were treated in cytology-based screening compared with 53.2% in hrHPV-based screening. In hrHPV-based screening, women aged <40 years were managed more often conservatively with follow-up instead of treatment.

Because there was a different age distribution between the cytology-based and hrHPV-based screening programs and between the physician-sampled and self-sampled women, we calculated the ORs for the main outcomes with adjustment for age (Table 3). However, this adjustment did not affect the outcomes. In hrHPV-based screening, there was a higher risk of receiving invasive management, defined as biopsy or treatment (OR, 1.28; 95% CI, 1.23−1.33), but there was a lower risk of receiving treatment (OR, 0.70; 95% CI, 0.67−0.73). The detection rate of ≥CIN2, ≥CIN3, and carcinoma in all referred women with a histologic outcome was lower in hrHPV-based screening. When comparing self-sampled material with physician-sampled material in hrHPV-based screening, there was a higher risk of receiving treatment (OR, 1.31; 95% CI, 1.16−1.48) and detecting ≥CIN2 (OR, 1.38; 95% CI, 1.20−1.59), regardless of age.

Comment

This study revealed increased detection of ≥CIN2, ≥CIN3, and cervical cancer with the introduction of hrHPV-based population screening. Colposcopy rates increased, mainly on the basis of the increase of low-grade cytology referrals. The increase in overdiagnosis decreases the overall PPV for ≥CIN2 detection in hrHPV-based screening compared with cytology-based screening. Overtreatment rates were similar in both screening periods. Women who participated in hrHPV-based screening through self-sampling were referred more often with high-grade cytology, had a higher rate of ≥CIN2 detection, and received treatment more often.

Strengths and limitations

This study evaluated hrHPV-based screening in the Netherlands since its implementation in 2017 with the focus on overdiagnosis and overtreatment. A major strength of this study is the large number of included patients in both screening methods. We analyzed 2.5 years of data on hrHPV-based screening, which was not on trial basis or only in certain demographic areas. We included all women who participated in the national population screening. In addition, the Netherlands is among the first countries in which the self-sampling screening is fully implemented. The results of this subgroup are reported in our study.

A limitation of this study was its retrospective nature. We did not have access to all the variables we wished for, such as medical history of the women, information about parity and future wish for children, colposcopic impression, and preferences of management of

TABLE 3
ORs of referral rate, management, and CIN detection within cytology-based and hrHPV-based screening in the Netherlands

Variable	hrHPV-based screening vs cytology-based screening		Self-sampled material vs physician-sampled material in hrHPV-based screening	
	Unadjusted ORs (95% CI)	Adjusted ORs (95% CI)[a]	Unadjusted ORs (95% CI)	Adjusted ORs (95% CI)[a]
Referrals				
Direct vs indirect referrals	3.75 (3.60–3.90)	3.79 (3.64–3.94)	1.47 (1.27–1.69)	1.44 (1.25–1.66)
Low-grade[b] vs high-grade[c] referral cytology	1.81 (1.74–1.88)	1.82 (1.75–1.89)	0.73 (0.65–0.82)	0.75 (0.67–0.85)
Management				
Invasive vs noninvasive management[d]	1.28 (1.23–1.33)	1.28 (1.23–1.33)	1.04 (0.91–1.18)	1.03 (0.90–1.17)
Treatment vs conservative management[e]	0.70 (0.67–0.73)	0.70 (0.67–0.73)	1.30 (1.15–1.46)	1.31 (1.16–1.48)
See-and-treat vs other management[f]	0.80 (0.76–0.85)	0.80 (0.75–0.84)	1.20 (1.01–1.42)	1.26 (1.06–1.49)
Detection				
≥CIN2 vs ≤CIN1[g]	0.60 (0.57–0.63)	0.61 (0.58–0.64)	1.42 (1.23–1.63)	1.38 (1.20–1.59)
≥CIN3 vs ≤CIN2[g]	0.61 (0.58–0.64)	0.62 (0.59–0.65)	1.61 (1.40–1.86)	1.57 (1.36–1.82)
Carcinoma vs ≤CIN3[g]	0.71 (0.59-0.85)	0.71 (0.59–0.85)	1.21 (0.69–2.13)	1.20 (0.68–2.11)

ASC-H, atypical squamous cells, cannot rule out HSIL; *ASC-US*, atypical squamous cells of undetermined significance; *CI*, confidence interval; *CIN*, cervical intraepithelial neoplasia; *hrHPV*, high-risk human papillomavirus; *HSIL*, high-grade squamous intraepithelial lesion; *LSIL*, low-grade squamous intraepithelial lesion; *OR*, odds ratio.

[a] Adjusted for age (years); [b] Low-grade cytology: ASC-US or LSIL; [c] High-grade cytology: ASC-H or HSIL; [d] Invasive management: biopsy or treatment. Noninvasive management: colposcopy with cytology only; [e] Conservative management: colposcopy with cytology or biopsy only; [f] See-and-treat: immediate treatment. Other management: colposcopy with cytology or biopsy only or biopsy followed by treatment; [g] Histologic outcome only.

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the patients, which could all be reasons to manage patients differently. If women were referred for colposcopy, but no additional smear, diagnostics, or treatments were performed, no information is recorded in PALGA. We therefore cannot distinguish between women lost to follow-up, women who received treatment without histologic results, and women managed conservatively without cytologic or histologic follow-up. Finally, we do not yet have the data about the second screening round onward (incidence round). This should be subject to future studies.

Interpretation

The RIVM estimated an increase of 65% in referral rates with the implementation of hrHPV-based screening,[7] which corresponds to the 70.2% increase found in our study. Although this is a serious rise in referrals, it leads to a higher detection of high-grade CIN lesions. Because former research states that the relative increase in ≥CIN2 detection in the first screening round (prevalence round) will vanish in the incidence rounds,[13,14] the detection rates of the following screening rounds should determine whether current referral criteria are still optimal. Observational studies from England and Finland report an increase in referral of 53% (7072 vs 4614 per 100,000 women) and 98% (4474 vs 2256 per 100,000 women), respectively.[14,15] However, in England, the referral criteria did not change that much, because they were referring women who were hrHPV positive with ASC-US cytology already and only women with normal cytology and persisting hrHPV are referred extra within the new screening method. Finland used to only refer ≥LSIL directly and persistent ASC-US and is now referring all women with persistent hrHPV, regardless of cytology outcome. Therefore, comparing our results with those of other countries is difficult.

The observed changes in detection rates of ≥CIN2, ≥CIN3, and cervical cancer in hrHPV-based screening vs cytology-based screening in our study are comparable with the increased rates of 23% to 50% in ≥CIN2, 36% to 48% in ≥CIN3, and ±30% in cervical cancer

in the literature.[14–20] Our study represents the first screening round of hrHPV-based screening, whereas the RIVM expects and multiple randomized controlled trials already revealed a reduction in the number of ≥CIN3 and cervical cancer during subsequent screening rounds. This is attributable to the early diagnosis of CIN lesions and cervical cancer during the first screening round.[7,13,17,18] The early diagnosis in hrHPV-based screening, owing to the higher sensitivity of hrHPV testing,[21,22] simultaneously explains the higher detection rates in our study.

Despite the increase in overdiagnosis, the rates of overtreatment did not notably differ between the 2 screening methods, which is a positive sign toward the implementation of hrHPV-based screening. These results indicate that colposcopists perform more biopsies, mainly on women who are hrHPV positive with low-grade cytology but therefore rule out high-grade CIN and prevent overtreatment. When distributing treatment vs conservative management of CIN2 per age category, a favorable shift is seen in women aged <40 years managed more conservatively (Figure 2). This is in line with the Dutch guidelines, advising conservative management in women with CIN2 and who have not yet completed childbearing, which had been implemented in 2015.[9,23]

The rate of histologic results indicating ≤CIN1 increased to 143.4%, and women were managed conservatively after biopsy nearly 2.5 times more often in hrHPV-based screening than in cytology-based screening (1745 vs 696 per 100,000 screened women, respectively). The Dutch study from Aitken et al[20] revealed 2.2 times more ≤CIN1 in hrHPV-based screening; however, they did not further differentiate between overdiagnosis or overtreatment. By determining the management strategies after referral, our study indicated that this increase is caused by overdiagnosis and not overtreatment. The PPV for detection of ≥CIN2 decreased from 40.2% to 34.6%, which is similar to the reported decrease of 37% to 33% in the observational study of Rebolj et al.[14] This decrease could be because of the immediate referral of women with low-grade cytology, leaving them no opportunity to regress.

With biopsies being an invasive form of diagnostics, the increase in the histologic results indicating ≤CIN1 is undesirable. This development most clearly manifests in women with ASC-US cytology. In hrHPV-based screening, the risk of ≥CIN3 was only 4.2% in women with ASC-US cytology. Other studies report similar rates of ≥CIN3 not only in women who are hrHPV positive with ASC-US cytology of 7%[24,25] but also in women who are hrHPV positive with normal cytology of 3%.[26] In addition, when the absolute risk of ≥CIN3 is between 2% and 10%, a clinical follow-up of 12 months is proposed, according to the risk model of Castle et al.[27] Therefore, it could be proposed to retest women with ASC-US cytology at 6 or 12 months, such as women who are hrHPV positive with normal cytology, instead of direct referral to colposcopy. Another option is an extra triage test for women who are hrHPV positive with ASC-US or another triage method than cytology for all women who are hrHPV positive, such as p16 and Ki-67 dual staining, HPV-16 and HPV-18 genotyping, viral load testing, RNA-based biomarkers, or methylation markers.[28,29] For example, the United States uses HPV-16 and HPV-18 genotyping to differentiate between direct referral to colposcopy or cytology testing as further triage.[30] Many countries, such as England, Finland, the Unites States, and the Netherlands, are using different triage strategies for women who are hrHPV positive. Therefore, further research is warranted in finding the best triage method for women who are hrHPV positive.

High-grade referrals and ≥CIN2 detection were higher in women who were hrHPV positive through self-sampling than women who were hrHPV positive through physician sampling in hrHPV-based screening. These differences remained significant after adjustment for age ($P<.05$). Unfortunately, we could not adjust for other potential confounders, because the background of these women remained unknown. The self-sampling kit is originally designed for nonresponders, who would otherwise not participate in population screening. Studies have revealed that nonresponders of previous screening rounds are more likely to participate if self-sampling is offered, and when they participate again, there is an increased risk of detecting a high-grade lesion.[31–33] However, the introduction of self-sampling did not increase total participation, implying that most self-sampling women in this study were not nonresponders but switchers. Research is warranted to further investigate these differences.

Conclusion

hrHPV-based screening has a greater sensitivity for the detection of ≥CIN2, ≥CIN3, and cervical cancer, at the expense of increased referral rates and increased overdiagnosis, resulting in a lower PPV for ≥CIN2 detection per referral. Overtreatment rates did not increase with hrHPV-based screening. Women who participated in hrHPV-based screening through self-sampling were referred more often with high-grade cytology, had a higher rate of ≥CIN2 detection, and received treatment more often. ■

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Data used in this study and those that support the findings of this study are available from the corresponding author on reasonable request.

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