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ORIGINAL RESEARCH ARTICLE

High-risk HPV testing vs liquid-based cytology for cervical cancer screening among 25- to 30-year-old women: A historical cohort study

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Abstract

Introduction: High-risk human papilloma virus (hrHPV) DNA testing is more sensitive than cytology screening, achieving greater protection against cervical cancer. Controversy exists regarding the preferred screening method for women 25–30 years of age. At this age, infection with HPV is common and usually transient. Consequently, hrHPV screening in this age group is fraught with high false-positive screening results, leading to more colposcopies and unnecessary treatments with the potential for harm. In the present study, we aimed to compare the results of two screening methods in relation to high-grade cervical intraepithelial lesion detection rate in the young age group of 25–30 years.

Material and methods: Retrospective information on cervical cytology, hrHPV testing, colposcopy referrals and histologic results, from one screening round, were retrieved from the Maccabi HealthCare Health Maintenance Organization centralized database during the study period from March 1, 2017 to April 1, 2019 for 25- to 30-year-old women. Screening with hrHPV testing for types 16, 18 and 12 other hrHPV types was compared with the conventional PAP liquid-based cytology (LBC) test. Odds ratio (OR) of detection with 95% confidence interval (CI) was calculated for cervical intraepithelial neoplasia (CIN) grade 3 or higher (CIN 3+).

Results: During the study period, 42 244 women 25–30 years old underwent cervical cancer screening; of them, 20 997 were screened with LBC between March 1, 2017 and March 1, 2018 and compared with 21 247 who were screened with hrHPV between April 1, 2018 and April 1, 2019. Testing for hrHPV resulted in a higher colposcopy referral rate compared with primary LBC screening: 9.8% vs 7.8%, respectively; (OR 1.28; 95% CI 1.2–1.37; $p < 0.001$). Screening with hrHPV led to significantly higher detection of CIN 3+ lesions (OR 1.4; 95% CI 1.2–1.6; $p < 0.001$) compared with

Abbreviations: ASCUS, atypical squamous cells of undetermined significance; CI, confidence interval; CIN, cervical intraepithelial neoplasia; FDA, Food and Drug Administration; hrHPV, high-risk human papilloma virus; HSIL, high-grade squamous intraepithelial lesions; LBC, liquid-based cytology; LSIL, low-grade squamous intraepithelial lesions; MHS, Maccabi HealthCare Services; OR, odds ratio.

LBC. HPV infections with non-16/18 hrHPV (other hrHPV) were the most prevalent (84.8%).

Conclusions: In women 25–30 years old, primary hrHPV screening was associated with a higher detection rate of CIN 3+ compared with cytology screening and should be considered for primary screening in this age group.

KEYWORDS
25–30 age group, cervical cancer screening, cervical intraepithelial neoplasia, colposcopy, hrHPV, liquid-based cytology

1 | INTRODUCTION

Cervical cancer screening by cytology has successfully decreased cervical cancer incidence and mortality.[1] This decline results from increased detection and treatment of preinvasive and early-stage invasive cervical cancer lesions.[2] The development of cervical intraepithelial neoplasia (CIN) and cervical cancer is a known consequence of an infection with oncogenic (high-risk) human papillomavirus (hrHPV) genotypes.[3,4] Therefore, DNA testing for hrHPV genotypes has been proposed as an alternative primary screening method with or without cytology. In addition, hrHPV DNA testing is more sensitive than cytological screening[5–7] and provides greater protection against cervical cancer.[8]

Guidelines for cervical cancer screening have adopted hrHPV screening over cytology in the past decade. The American Cancer Society recommends hrHPV cervical cancer screening every 5 years starting at the age of 25 years.[9] However, the American College of Obstetricians and Gynecologists[10] and the United States Preventive Services Task Force[11] still recommend cervical cancer screening by cervical cytology and not by hrHPV testing in women 21–29 years old, using high-risk hrHPV testing alone, or in combination with cytology (co-testing) in women 30–65 years old.[10,11]

The controversy regarding the preferred screening method in women 25–30 years old arises as infection with HPV is common and usually transient in these young women, and even if CIN develops, they frequently regress spontaneously.[12] Consequently, hrHPV screening in the young age group is fraught with high false-positive screening results, leading to more colposcopies and unnecessary treatments with potential harm.[13] Furthermore, young vaccinated women exhibit a lower prevalence of high-grade squamous intraepithelial lesions (HSIL) and might have abnormal cytology resulting from a transient infection with HPV types associated with a lower cancer risk.[14,15] This may lead to a high rate of false-positive findings and subsequent excessive procedures.[9]

In Israel, there is no national screening program for cervical cancer prevention. Maccabi HealthCare Services (MHS), which has 2 200 000 insured members, consisting of 25% of the Israeli population, started using HPV-DNA as primary screening in March 2018, with partial genotyping and reflex cytology for positive hrHPV. The hrHPV screening was applied to all ages (ie from 25 to 65), every 3 years. Previously, screening at MHS was based only on liquid-based cytology (LBC) every 3 years. In the present study, we aimed to compare the results of the two screening methods in relation to high-grade cervical intraepithelial lesion detection rate in the of 25–30-year-old age group.

Key message

This study confirmed that in the age group of 25–30 years, screening with hrHPV testing is associated with significantly higher detection rates of high-grade cervical intraepithelial neoplasia compared with liquid-based cytology.

2 | MATERIAL AND METHODS

On March 1, 2018, MHS converted to hrHPV testing as primary cervical screening in women ≥25 years old. Until that date, PAP LBC was the main cervical cancer screening method. We compared data for all 25- to 30-year-old women who were screened for cervical cancer from the following two screening periods according to the method used in the laboratory:

(i) March 1, 2017 to March 1, 2018 – primary PAP LBC screening.
(ii) April 1, 2018 to April 1, 2019 – primary hrHPV-DNA screening.

We allowed a 1-month pause between the two periods to avoid transition period bias. Retrospective information on cervical cytology, hrHPV testing, colposcopy referrals and histologic results were retrieved from the MHS centralized database. The pathological data included samples that were routinely collected and processed at the National Central Pathology Institute of MHS. Data were identified using specific MHS codes for every pathology/cytology result examined. Women with samples categorized as a medical test by the physician who obtained the sample, due to symptoms or other medical suspicions, and hence not a screening test, were excluded from the study.

The screening algorithm was modified from the Food and Drug Administration (FDA) and European guidelines (Figure 1).[16,17] The hrHPV-negative women were referred for routine screening every 3 years. Women who were hrHPV-positive for types 16/18 were

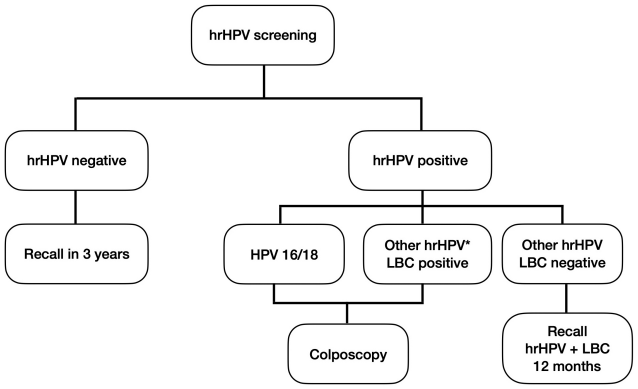

FIGURE 1 Screening algorithm using hrHPV testing

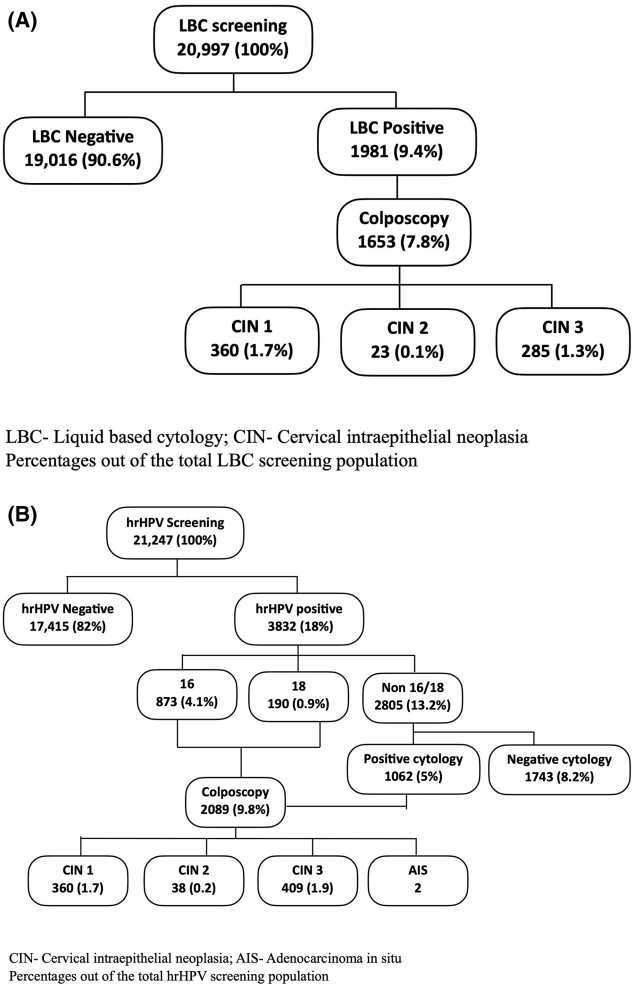

FIGURE 2 Screening results: (A) LBC screening period and (B) hrHPV screening period

referred for colposcopy, regardless of the reflex cytology result. In addition, women who were hrHPV-positive for other high-risk non-16/18 types were referred for colposcopy if the cytology was ≥ atypical squamous cells of undetermined significance (ASCUS). If the cytology was normal, recall hrHPV and cytology testing in 12 months was advised. If, the hrHPV result remained positive after 12 months, the women were referred for colposcopy, regardless of the reflex cytology result.

Abnormal cytology results were classified in the database as low- or high-level cervical cytology. Low-level cervical cytology included low-grade squamous intraepithelial lesion (LSIL) and ASCUS. High-level cervical cytology included HSIL, atypical squamous cells that cannot rule out HSIL (ASC-H) and atypical glandular cells (AGC). In the primary LBC screening period, women with abnormal cytology (≥LSIL) or occasionally with ASCUS were referred for colposcopy. During the primary hrHPV screening period, women found positive for hrHPV 16/18 (irrespective of the cytologic results) or positive for other hrHPV with abnormal cytology were referred for colposcopy. Colposcopy-guided biopsies were performed at the physician's discretion if colposcopic abnormal changes were observed. Histology reports from colposcopy-guided biopsies following the pathologic screening test results were collected. Women included in the LBC group were followed until September 1, 2019 and in the hrHPV screening group until October 1, 2020.

Cytology results, colposcopy referrals, premalignant and malignant lesion detection rates were compared between hrHPV-based vs cytology-based screening tests. Because regression rates of CIN 2 are very high in women below age 30, we used CIN3+ detection rates as our primary outcome.

2.1 | Primary screening testing

Screening methods were based on the usual MHS practice. The cervical specimens were collected in PreservCyt ThinPrep® preservative fluid containers (Hologic). The same samples were used for cytology evaluation and hrHPV DNA testing. Samples were stored at room temperature for up to 6 weeks before testing. The LBC test was conducted according to the manufacturer's (Hologic) protocol, using FDA-approved Imagers.[18]

The FDA-approved hrHPV test was carried out using Cobas 4800x platform, according to the manufacturer's protocol.[19] DNA was first extracted using an automated Cobas 480x tool, followed by Real-Time PCR detection using a Cobas 480z instrument.

The test detects 14 types of hrHPV in three individual assays on the same sample, obtaining separate results for types 16, 18 and for the other 12 hrHPV types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) grouped with no specific genotype distinction.

2.2 | Statistical analyses

Data were analyzed using SPSS software, version 23.0 (SPSS Inc).

We defined a screening test as positive if further clinical management according to the recommended protocol was needed. The Chi-square test was used for categorical variables. Odds ratios and their 95% confidence intervals (95% CI) for differences between hrHPV and cytology screening were calculated. $p < 0.05$ was considered statistically significant.

2.3 | Ethics statement

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki and was approved by the Helsinki Committee Bait Balev – Maccabi on October 22, 2018 (reference no. 0085-18-BBL). Informed consent is not needed according to the Israeli Ministry of Health in this kind of retrospective study using unidentified data.

3 | RESULTS

A total of 42 244 women aged 25–30 were included in the study. The cervical screening protocols in the two periods are shown in Figure 2A,B.

The comparison between the two screening periods is shown in Table 1. Significantly more women had positive screening test results in the primary hrHPV screening than in the LBC screening; 3832 (18%) women were hrHPV-positive vs 1981 (9.4%) women with abnormal cytology, respectively (OR 2.1; 95% CI 1.9–2.3; $p < 0.001$). HPV infections with non-16/18 (other hrHPV) were the most prevalent (3249/3832; 84.8%). HPV 16 was found in 22.8% (873/3832) and HPV 18 in 4.9% (190/3832) of the HPV-positive women. Abnormal cytology results of ≥ASCUS were observed in 42.6% (1634/3832) of women who tested positive for hrHPV.

The distribution of the different abnormal cytology results according to the different hrHPV types for women who underwent primary HPV screening, is presented in Table 2. HPV 16 infection was significantly more prevalent in women with HSIL cytology than with other hrHPV only (25.2% vs 6.8%, $p < 0.001$). Moreover, women with HPV 16/18 infection were significantly more likely to have any concurrent abnormal cytology than women with other hrHPV infection (289/583; 49.5% vs 1062/2805; 37.9% OR 1.6; 95% CI 1.3–1.9; $p < 0.001$) and 3.5 times more likely to have high-grade cytology (139/583; 23.9% vs 189/2805; 6.8%; OR 4.3; 95% CI 3.4–5.5, $p < 0.001$).

3.1 | Referral for colposcopy

During the primary hrHPV screening, 2089 (9.8%) women were referred for colposcopy (Figure 2B, Table 1) due to the presence of either HPV types 16 and/or 18 (1027/2089, 49.2%) or other hrHPV with abnormal cytology (1062/2089, 50.8%) (Table 2). Although colposcopy referrals were significantly higher in the primary hrHPV screening period (9.8% vs 7.8%; OR 1.26; 95% CI 1.18–1.35; $p < 0.001$) (Table 1), the number of colposcopy referrals to detect one CIN3+ lesion were similar between the primary LBC and primary hrHPV screening groups (5.8 and 5.08, respectively; $p = 0.06$).

3.2 | Detection of CIN lesions

Table 1 indicates that CIN 3+ was detected in 411 of the 21 247 women screened with hrHPV (1.93%) and 285 out of 20 997 women

TABLE 1 Screening outcomes for primary high-risk human papillomavirus (hrHPV) testing period and primary liquid-based cytology (LBC) period

	Primary hrHPV, $n = 21\,247$ (%)	Primary LBC, $n = 20\,997$ (%)	Odds ratio for hrHPV testing vs LBC (95% CI)	*P*-value
Positive screening test	3832 (18)[a]	1981 (9.4)	2.1 (1.9–2.3)	<0.001
HPV 16	873 (4.1)	NR		
HPV 18	190 (0.9)	NR		
Other HPV[b]	3249 (15.3)	NR		
Abnormal cytology[c]	1634 (7.7)	1981 (9.4)	0.8 (0.7–0.8)	<0.001
Low-level cervical cytology	1204 (5.7)	1708 (8.1)	0.7 (0.6–0.7)	<0.001
High-level cervical cytology	430 (2.0)	273 (1.3)	1.6 (1.3–1.8)	<0.001
Primary referral for colposcopy	2089 (9.8)	1653 (7.8)	1.3 (1.2–1.4)	<0.001
Abnormal histology				
CIN1	360 (1.7)	360 (1.7)	0.9 (0.8–1.1)	0.43
CIN2+	449 (2.1)	308 (1.5)	1.4 (1.3–1.6)	<0.001
CIN3+	411 (1.9)	285 (1.3)	1.4 (1.2–1.7)	<0.001

Abbreviations: CI, confidence interval; CIN, cervical intraepithelial neoplasia; CIN+, with higher grade dysplasia including adenocarcinoma in situ; LBC, liquid-based cytology; NR, not relevant.

[a]Including mixed HPV infections.

[b]Non-16/18 hrHPV types.

[c]Abnormal cytology = ≥ASCUS (atypical squamous cells of undetermined significance).

TABLE 2 The hrHPV and cytology results by infecting human papillomavirus (HPV) genotype in the primary hrHPV screening group. Values given as number (%)

	HPV 16+ ($n = 873$)	HPV 16 only ($n = 491$)	HPV 18+ ($n = 190$)	HPV 18 only ($n = 82$)	HPV 16 and/or 18[a] ($n = 583$)	Other hrHPV only[b] ($n = 2805$)
Normal cytology	381 (43.6)	245 (49.9)	80 (42.1)	49 (59.7)	294 (50.4)	1743 (62.1)
Low-level cervical cytology	272 (31.2)	117 (23.8)	77 (40.5)	24 (29.3)	150 (25.7)	873 (31.1)
High-level cervical cytology	220 (25.2)	129 (26.3)	33 (17.4)	9 (11.0)	139 (23.9)	189 (6.8)

Note: "+" sign indicates the presence of more than one hrHPV type.

[a]Non-16/18 hrHPV types.

[b]Infections with HPV 16, 18 or co-infection of 16 + 18.

TABLE 3 Histology results from colposcopy-guided biopsies by infecting human papillomavirus (HPV) genotype and cytology in the primary hrHPV screening group. Values given as number (%)

HPV type	16 only		18 only		16 and/or 18[a]		16 and/or 18+		Other hrHPV only[b]
Cytology	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
No. of women	246	245	34	48	289	294	318	162	2805
CIN1	20 (8.1)	32 (13.1)	7 (20.6)	9 (18.8)	27 (9.3)	42 (14.3)	48 (15.1	28 (17.3)	383 (13.7)
CIN2	8 (3.2)	2 (0.8)	1 (2.9)	0	10 (3.5)	2 (0.7)	7 (2.2)	6 (3.7)	22 (0.8)
CIN3	98 (39.8)	24 (9.8)	5 (14.7)	1 (2.1)	105 (36.3)	25 (8.5)	106 (33.3)	25 (15.4)	213 (7.6)
AIS	0	1 (0.4)	0	1 (2.1)	0	2 (0.7)	0	0	0
CIN2+	106 (43.1)	27 (11.0)	6 (17.6)	2 (4.2)	115 (39.7)	29 (9.9)	113 (35.5)	31 (19.1)	235 (8.4)
CIN3+	98 (39.8)	25 (10.2)	5 (14.7)	2 (4.2)	105 (36.3)	27 (9.2)	106 (33.3)	25 (15.4)	213 (7.6)

Note: Abnormal cytology = ≥ASCUS (atypical squamous cells of undetermined significance).

"+" sign indicates the presence of co-infection with other hrHPV types.

Abbreviations: AIS, adenocarcinoma in situ; CIN, cervical intraepithelial neoplasia; CIN+, with higher grade dysplasia including adenocarcinoma in situ.

[a]Non-16/18 hrHPV types; only abnormal cytology applicable, as women with normal cytology were not referred for colposcopy.

[b]Infections with HPV 16 or 18 or co-infection of 16 + 18.

screened with LBC (1.35%). Primary hrHPV screening led to significantly higher detection of CIN 3+ (OR 1.4; 95% CI 1.2–1.7, $p < 0.001$).

Table 3 reveals that 36.3% of women with HPV 16 and or 18 infections with abnormal cytology (≥ASCUS) were diagnosed with CIN 3+ lesions compared with 7.6% in women infected by non-16/18 hrHPV types (OR 2.7; 95% CI 2.1–3.4; $p < 0.0001$). Having HPV 16 and/or 18 infections with abnormal cytology was associated with a significantly increased risk of CIN 3+ compared with having HPV 16 and/or 18 with negative cytology (36.3% vs 9.2%; OR 3.9; 95% CI 2.5–6.2; $p < 0.001$). Similarly, co-infections of HPV 16/18 with other HR HPV and abnormal cytology were associated with a significantly higher rate of CIN 3+ than were co-infections of HPV 16/18 with other HR HPV and normal cytology (33.3% vs 15.4%; OR 2.7; 95% CI 1.7–4.4; $p < 0.001$).

Table 4 presents the colposcopy results of 16/18-positive women with negative cytology who were referred for colposcopy according to the screening algorithm. CIN3+ was found in 52/456 (11.4%) women, most of them due to HPV 16 infection either alone (25/245; 10.2%) or with co-infection with other hrHPV types (21/136; 15.4%). Two women with negative cytology were found to have adenocarcinoma in situ (Table 4; Figure 2B).

3.3 | Recall screening

About 1743 women that had other non-16/18 hrHPV results with normal cytology in the primary screening were asked to return for recall hrHPV and cytology testing within 12 months. Of these, 1194 (68.5%) underwent recall hrHPV screening in the study period. Figure 3 shows the detection rate of hrHPV and CIN according to the study protocol. The infection cleared in 464 women (38.9%), who were referred for routine screening with hrHPV after 3 years. The other 730 women (61.1%) had persistent hrHPV infection and were referred for colposcopy. The median time to recall testing was comparable between the groups, 331 days in the positive recall screen group and 317 in the negative recall screen group. Overall, recall testing further diagnosed 51 more women with CIN 3+ who did not have any abnormal primary cytology results.

4 | DISCUSSION

This study confirmed that cervical cancer screening with hrHPV in the controversial age group of 25–30 exhibits an increased odds

TABLE 4 Histology results from colposcopy-guided biopsies of HPV 16/18 -positive, cytology-negative women in the primary hrHPV screening group. Values given as number (%)

	HPV 16 only ($n = 245$)	HPV 16+ ($n = 136$)	HPV 18 only ($n = 48$)	HPV18+ ($n = 32$)	HPV 16 and/or 18[a] ($n = 294$)	HPV 16 and/or 18+ ($n = 162$)
CIN1	32 (13.1)	25 (18.4)	9 (18.8)	5 (15.6)	42 (14.3)	28 (17.3)
CIN2	2 (0.8)	5 (3.7)	0	1 (3.1)	2 (0.7)	6 (3.7)
CIN3	24 (9.8)	21 (15.4)	1 (2.1)	4 (12.5)	25 (8.5)	25 (15.4)
AIS	1 (0.4)	0	1 (2.1)	0	2 (0.7)	0
CIN2+	27 (11.0)	26 (19.1)	2 (4.2)	5 (15.6)	29 (9.9)	31 (19.1)
CIN3+	25 (10.2)	21 (15.4)	2 (4.2)	4 (12.5)	27 (9.2)	25 (15.4)

Note: "+" sign indicating the presence of co-infection with other hrHPV types.

Abbreviations: AIS, adenocarcinoma in situ; CIN, cervical intraepithelial neoplasia; CIN+, with higher grade dysplasia including adenocarcinoma in situ.

[a]Infections with HPV 16 or 18 or co-infection of 16 + 18.

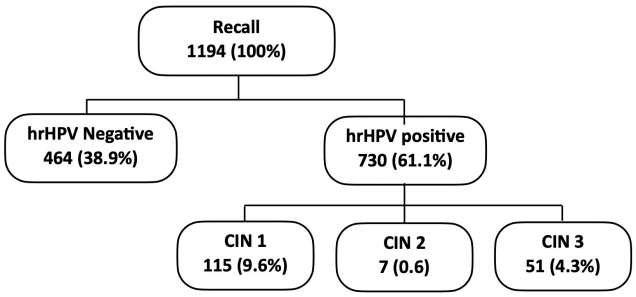

FIGURE 3 Detection rate of hrHPV and CIN at recall testing

ratio for detecting cervical intraepithelial lesions compared with LBC screening. In addition, hrHPV screening revealed about 43% more CIN 3+ than LBC screening. These results are in line with recent studies. Ronco et al.[8] showed that HPV-based screening was more specific than cervical cytology alone, providing up to 60%–70% greater protection against invasive cervical carcinomas compared with cytology. The ATHENA study comparing cervical screening in women aged ≥25 years reported that HPV testing was significantly more sensitive in detecting CIN3+ than cytology alone.[20]

Furthermore, a recently published large observational study reported that in the age group of 25–30 years, routine primary hrHPV screening increased the detection of CIN 3 and cervical cancer by approximately 40% and 30%, respectively, compared with LBC.[21] These studies were the rationale for the American Cancer Society guidelines recommendation to initiate screening at age 25 with HPV testing.[9] However, the 2018 United States Preventive Services Task Force guidelines still recommend initiating cervical cancer screening with HPV after the age of 30 years and using primary LBC screening in younger women.[11] This was based on a meta-analysis by Melnikow et al.[13] of randomized and observational studies, demonstrating higher false-positive rates with HPV testing due to higher rates of transient infection in the younger age group. Moreover, hrHPV screening at an early age causes subsequent overdiagnosis of regressive CIN with HPV screening.[6] This discordance is further illustrated in the recently published American Society for Colposcopy and Cervical Pathology Guidelines,[22] which accepts the American Cancer Society recommendations to initiate screening at age 25 with hrHPV testing,[9] while still endorsing the 2018 United States Preventive Services Task Force recommendations.[11] Our results, as well as those of others,[21,23] demonstrate that hrHPV screening results in higher referral rates to colposcopy. However, the number of colposcopies performed to detect one CIN3+ lesion were similar between the primary LBC and primary hrHPV groups. Moreover, by following the hrHPV screening algorithm, out of 294 women positive for HPV 16/18 with negative cytology, 29 women (9.1%) were diagnosed with CIN 3+ lesions. Two of them were found to have adenocarcinoma in situ (AIS), reflecting the limitation in diagnosing glandular lesions when using cytology-based screening. A recall examination further revealed 51 of 1194 (4.2%) women with CIN3+ who were non-16/18 hrHPV-positive with prior negative cytology. Thus, regular screening based on LBC alone would have missed these precancerous lesions in this young age group. Among women who were positive for non-16/18 other hrHPV with negative cytology, only 68.5% underwent the recommended recall test at 12 months. This percentage is lower than in the data presented by Rebolj et al.,[21] which shows 83% attendance at 12 months. The fact that the recall test further diagnosed more CIN3+ cases indicates the importance of the recall test and suggests that there is a need for an active approach in this young age group.

These results emphasize the added value of primary hrHPV screening over LBC screening. It is expected that the colposcopy rate will decline as HPV vaccination coverage expands and a growing fraction of HPV-vaccinated women reach the age to begin screening.[24] Higher vaccination uptake could mitigate the overdiagnosis and overtreatment harms that might coincide with the proven benefits of hrHPV screening. In Israel, an HPV vaccination program was initiated in 2015 and currently has a coverage of approximately 60%.[25] In the present study, HPV 16 and 18 were present in 56% of the HSIL cytology and in 25.4% of the CIN3+ lesions. In the coming years, screening of vaccinated cohorts will result in lower incidence of HPV 16 and 18 infections and of other high-risk types with an

even better performance of primary HPV than primary cytology screening in this young age group.

The positive HPV rate in our study (18%) was lower than the HPV rate for a similar age reported in England (28%). This might be due to earlier initiation of screening at 24 years in that trial, as the prevalence of hrHPV is higher in younger women.[21] The ATHENA trial showed a slightly higher prevalence of non-16/18 hrHPV compared with our study (21.1% vs 15.3%), as well as HPV 16 (5.3% vs 4.1%) and HPV 18 (1.6% vs 0.9%) in the same age groups.[25] It is known that Israeli women have significantly lower rates of cervical cancer.[26] Our lower hrHPV infection rates might serve as an explanation for this phenomenon.

Our study has a few novel traits. First, it is one of the most extensive studies reporting primary HPV testing results in the controversial age group of 25–30 years. Another novel aspect of our study is that MHS has a centralized laboratory, which used the same test (Cobas or thin prep) for every exam. This probably minimizes the risk for inter-lab/test covariates.

Our study also has several limitations.

- Due to its retrospective design, in which we included all women who underwent screening in the studied years, unintended selection bias may have occurred.
- We could not access data on the basic characteristics of the women (ie HPV vaccination, tobacco use, number of partners, etc.), which might serve as potential confounders. However, we believe that our large cohort and selection of the groups in the same manner to include all 25- to 30-year-old asymptomatic women who underwent routine screening during the study periods, diminishes these potential bias factors.
- No long-term follow-up was available; this study was not planned to reach a follow-up of 36 months to include the following screening test.
- MHS coded only pathological results; thus, we did not have information regarding the number of colposcopy guided biopsies with normal histology. This might have subjected our study to verification bias. Such information may be also used to reduce colposcopy referral and serve asr follow-up information regarding subsequent progression.
- According to our referral strategy, women with a primary result of other hrHPV with negative cytology were not referred for colposcopy. This might serve as another verification bias because the colposcopy referral was genotype-dependent.
- We assumed that the vast majority of women who were referred for colposcopy eventually underwent colposcopy in the MHS facilities. However, a small portion of these women might have done so outside the MHS, which could cause information bias.

5 | CONCLUSIONS

This study confirms that primary hrHPV screening at age 25–30 years results in a significantly higher detection rate of CIN 3+ compared with cytology screening, although with a higher rate of primary colposcopy referrals. Long-term follow-up is needed to establish clinical outcomes.

AUTHOR CONTRIBUTIONS

OF was involved in data collection, analysis and manuscript writing. HG-Z was involved in data collection and manuscript writing. TF and EY-S were involved in data collection and manuscript revision. JB was involved in manuscript revision. ES was involved in data analysis and manuscript revision. TL was involved in data analysis and manuscript writing. This work was performed in partial fulfilment of the MD thesisrequirements of the SacklerFaculty of medicine, Tel Aviv University.

CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available from the corresponding author (OF) upon reasonable request.

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REFERENCES

1. Vaccarella S, Lortet-Tieulent J, Plummer M, Franceschi S, Bray F. Worldwide trends in cervical cancer incidence: impact of screening against changes in disease risk factors. *Eur J Cancer*. 2013;49:3262-3273.
2. Metropolitan Detroit Cancer Surveillance System. Cancer statistics in metropolitan Detroit 2012. *CA: Cancer J Clin*. 2012;00:1-20.
3. Schiffman M, Kjaer SK. Chapter 2: natural history of anogenital human papillomavirus infection and neoplasia. *J Natl Cancer Inst Monogr*. 2003;2003:14-19.
4. Wright TC, Schiffman M. Adding a test for human papillomavirus DNA to cervical-cancer screening. *N Engl J Med*. 2003;348:489-490.
5. Cuzick J, Arbyn M, Sankaranarayanan R, et al. Overview of human papillomavirus-based and other novel options for cervical cancer screening in developed and developing countries. *Vaccine*. 2008;26:K29-K41.
6. Ronco G, Giorgi-Rossi P, Carozzi F, et al. Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial. *Lancet Oncol*. 2010;11:249-257.
7. Feinberg T, Yehuda-Shnaidman E, Wolf T, et al. HPV screening test for the detection of precancerous cervical lesions and cervical cancer in Israeli women. *Acta Cytol*. 2021;65:494-500.
8. Ronco G, Dillner J, Elfström KM, et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. *Lancet*. 2014;383:524-532.
9. Fontham ETH, Wolf AMD, Church TR, et al. Cervical cancer screening for individuals at average risk: 2020 guideline update from the American Cancer Society. *CA Cancer J Clin*. 2020;70:321-346.
10. ACOG. Practice bullet in cervical cancer screening and prevention practice bulletin No. 168. *Obstet Gynecol*. 2016;128:e111-e130.
11. Curry SJ, Krist AH, Owens DK, et al. Screening for cervical cancer us preventive services task force recommendation statement. *JAMA*. 2018;320:674-686.
12. Ho GYF, Bierman R, Beardsley L, Chang CJ, Burk RD. Natural history of cervicovaginal papillomavirus infection in young women. *N Engl J Med*. 1998;338:423-428.

13. Melnikow J, Henderson JT, Burda BU, Senger CA, Durbin S, Weyrich MS. Screening for cervical cancer with high-risk human papillomavirus testing. *JAMA*. 2018;320:687.
14. Bhatia R, Kavanagh K, Cubie HA, et al. Use of HPV testing for cervical screening in vaccinated women-insights from the SHEVa (Scottish HPV prevalence in vaccinated women) study. *Int J Cancer*. 2016;138:2922-2931.
15. Palmer T, Wallace L, Pollock KG, et al. Prevalence of cervical disease at age 20 after immunisation with bivalent HPV vaccine at age 12-13 in Scotland: retrospective population study. *BMJ*. 2019;365:l1161.
16. Huh WK, Ault KA, Chelmow D, et al. Use of primary high-risk human papillomavirus testing for cervical cancer screening: interim clinical guidance. *Gynecol Oncol*. 2015;136:178-182.
17. Elfström KM, Arnheim-Dahlström L, von Karsa L, Dillner J. Cervical cancer screening in Europe: quality assurance and organisation of programmes. *Eur J Cancer*. 2015;51:950-968.
18. ThinPrep® Stain User's Manual https://www.hologic.com/sites/default/files/package-insert/MAN-01390-001_006_02.pdf
19. cobas® 4800 system Operator's Manual Software Version 1.0. 2009. https://media.supplychain.nhs.uk/media/documents/HFL705/Marketing/24380_HFL705_cobas_4800_Manual_V1-0_EN.pdf. 2009
20. Wright TC, Stoler MH, Behrens CM, Sharma A, Zhang G, Wright TL. Primary cervical cancer screening with human papillomavirus: end of study results from the ATHENA study using HPV as the first-line screening test. *Gynecol Oncol*. 2015;136:189-197.
21. Rebolj M, Rimmer J, Denton K, et al. Primary cervical screening with high risk human papillomavirus testing: observational study. *BMJ*. 2019;364:1-10.
22. Marcus JZ, Cason P, Downs LS, Einstein MH, Flowers L. The ASCCP cervical cancer screening task force endorsement and opinion on the American Cancer Society updated cervical cancer screening guidelines. *J Low Genit Tract Dis*. 2021;25:187-191.
23. Ogilvie GS, Krajden M, van Niekerk D, et al. HPV for cervical cancer screening (HPV FOCAL): complete round 1 results of a randomized trial comparing HPV-based primary screening to liquid-based cytology for cervical cancer. *Int J Cancer*. 2017;140:440-448.
24. Castle PE, Xie X, Xue X, et al. Impact of human papillomavirus vaccination on the clinical meaning of cervical screening results. *Prev Med*. 2019;118:44-50.
25. Wright TC, Stoler MH, Behrens CM, et al. The ATHENA human papillomavirus study: design, methods, and baseline results. *Am J Obstet Gynecol*. 2012;206:46.e1-46.e11.
26. Menczer J, Kogan L, Schejter E, Liphshiz I, Barchana M. A population-based study of selected demographic characteristics of Israeli-Jewish women with cervical squamous cell carcinoma. *Arch Gynecol Obstet*. 2011;283:629-633.

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