Research Article

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Predictive Value of HPV Testing in Self-collected and Clinician-Collected Samples Compared with Cytology in Detecting High-grade Cervical Lesions

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Abstract

Background: Self-sampling has become an attractive proposition now that human papillomavirus (HPV) primary testing is being incorporated into cervical cancer screening programs worldwide. We compared predictive values of HPV testing based on self- and physician-collected samples, and cytology, in detecting high-grade cervical intraepithelial neoplasia (CIN).

Methods: The Cervical And Self-Sample In Screening (CASSIS) study enrolled 1,217 women ages 16–70 years prior to scheduled colposcopies. Vaginal specimens were self-collected using the validated HerSwab device. Cervical specimens were collected by gynecologists. Specimens were tested for presence of high-risk HPV (hrHPV) by the Cobas 4800 HPV test. We estimated positive predictive values (PPV) and negative predictive values (NPV) and 95% confidence intervals (CI) for a subset of women ($n = 700$) who underwent cervical biopsy and cytology at the actual CASSIS visit.

Results: hrHPV was detected in 329 women (47%) with HerSwab and in 327 (46.7%) with physician sampling. Respective values for HPV16/18 were 119 (17%) and 121 (17.3%). On histology, 134 women had CIN1, 49 had CIN2, 48 had CIN3, 5 had CIN2/CIN3, and 3 had cancers. PPVs for CIN2$^+$ of any hrHPV were 28% (95% CI, 23.2–33.1) and 29.7% (95% CI, 24.8–34.9) for HerSwab and physician samples, respectively. Corresponding values for HPV16/18 were 43.7% (95% CI, 34.6–53.1) and 43.8% (95% CI, 34.8–53.1). PPV of cytology (ASC-US+) was 26.6% (95% CI, 21.6–32.0). Corresponding NPVs (same order as PPVs) were 96.4% (95% CI, 93.9–98.1), 97.8% (95% CI, 95.6–99), 90.9% (95% CI, 88.2–93.1), 91% (95% CI, 88.4–93.2), and 94.7% (95% CI, 91.8–96.8).

Conclusions: Our results confirm that HPV self-sampling has comparable performance with a physician-collected sample in detecting cervical lesions.

Impact: HPV self-sampling has the potential to increase coverage in cervical cancer screening.

Introduction

Human papillomavirus (HPV) testing in self-collected cervicovaginal samples (HPV self-sampling for short) has been increasingly investigated as a potential screening alternative to standard physician-based sampling to complement primary cervical cancer screening programs by enhancing coverage among nonattendees. It has been implemented in the Netherlands (1) and Australia (2), and other countries, including the United States (3), United Kingdom (4), Norway (5), Denmark (6), and Switzerland (7), are evaluating its incorporation into national cervical screening programs (8). The utility of HPV self-sampling in cervical cancer screening is predicated on the availability of validated HPV assays (9). The impetus regarding HPV self-sampling in cervical cancer screening comes from the (i) proven superior clinical performance of HPV testing relative to cytology for detecting high-grade precancerous lesions, (ii) gradual implementation of

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primary HPV testing worldwide with ongoing success, and (iii) growing evidence of the efficacy and validity of HPV self-sampling (10).

Given that one of the fundamental advantages of HPV testing is that it can be done with self-collected vaginal specimens, two central questions of HPV self-sampling relate to its diagnostic accuracy and the performance and acceptability of the sampling device. Several studies that compared vaginal self-sampling with cervical physician-sampling found high concordance for HPV detection (1, 11–18) and comparable clinical accuracy to detect high-grade cervical intraepithelial neoplasia (CIN) and cancers, provided that validated assays are used (17, 19–22). In a recent meta-analysis of 56 accuracy studies, the pooled relative sensitivity of high-risk HPV (hrHPV) assays (based on PCR) on self-collected versus physician-collected samples was 99% for $CIN2^+$ or $CIN3^+$, and the positive predictive values (PPV) for either histologic endpoint were not significantly lower for self-collected samples (22). The sample sizes in the included studies ranged from 50 (23) to 16,951 (24) women, with few studies conducted in Canada (25, 26). Importantly, qualitative studies showed women both accept and prefer HPV self-sampling over physician-sampling across varying populations and age groups (27, 28).

The imminent incorporation of primary HPV testing in Canada's provincial cervical cancer screening programs (9) presents an opportunity for the future uptake of HPV self-sampling, including home- and clinic-based practice. Such an approach may also overcome challenges in relation to disparities in cervical cancer screening access in Canada (29). In anticipation, we used data from the Cervical And Self-Sampling In Screening (CASSIS) study to compare overall and age-specific predictive values of molecular testing for DNA of hrHPV genotypes on patient self-collected and physician-collected samples, as well as conventional cytology on physician-collected samples, in detecting high-grade cervical lesions among women referred to colposcopy due to abnormal cytology results.

Materials and Methods

Study design and population

Detailed methods of the CASSIS study including recruitment, eligibility screening, and data collection have been described previously (21). Briefly, a total of 1,217 women ages between 16 and 70 years took part in this cross-sectional study between June 2015 and April 2016. They were recruited among patients referred for colposcopy because of an abnormal cytology screening result or for initial treatment of a cervical lesion at three McGill University affiliated hospitals in Montreal, Canada. The study received ethics approval from McGill University and respective study hospitals' institutional review boards, and it was registered at clinicaltrials.gov (NCT02397252). Written informed consent was obtained from all participants.

Study procedures and HPV genotyping

Prior to colposcopy, women self-collected a vaginal sample using the HerSwab device (Eve Medical), referred to hereafter as HerSwab, according to explicit verbal and written illustrated instructions. After self-sampling, women underwent their scheduled colposcopic examination following the standard of care at each clinic, and a cervical sample was collected by the attending gynecologist. Collected samples, fixed in ThinPrep vials containing PreservCyt Solution (Hologic, Inc.), were tested at the Microbiology Laboratory of the McGill University Health Centre for the presence of hrHPV genotypes using the clinically validated and FDA-approved Cobas 4800 HPV Test (Roche Diagnostics), according to the manufacturer's recommendations. The test provides separate results for HPVs 16 and 18 (genotypes that account for up to 70% of cervical cancers and provide risk stratification useful for guiding clinical management), and a pooled result for 12 other hrHPV types (i.e., 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68).

In addition to the scheduled CASSIS study visit's conventional cytology, if performed, we retrieved the report from the referral cytology that triggered the colposcopy appointment. Both were graded according to the Bethesda classification as negative for intraepithelial lesion or malignancy (NILM), atypical squamous cells of undetermined significance (ASC-US), atypical squamous cells cannot exclude high-grade squamous intraepithelial lesions (ASC-H), low-grade squamous intraepithelial lesions (LSIL), high-grade squamous intraepithelial lesion (HSIL), atypical glandular cells (AGC), or cancer (30).

Biopsies were taken from all areas of the cervix with visible lesional tissue on colposcopic examination. Endocervical curettage was performed when the transformation zone could not be visualized. Histopathology was classified as normal (no dysplasia), CIN1, CIN2, CIN3, and cancer on the basis of the most severe histologic diagnosis when multiple results were noted on the pathology report. Colposcopical and histopathologic biopsy examinations were conducted by experienced McGill gynecologists and pathologists, respectively, blinded to HPV status and to the cytology report at the study visit.

Statistical analysis

We summarized participant characteristics using descriptive statistics for the overall sample, by recruitment site, and by age ($\leq$35, >35 years) for a subset of the study population restricted to women who underwent cervical biopsy and cytology at the actual CASSIS visit. For this subset, we estimated the PPV and negative predictive value (NPV) with their corresponding exact binomial 95% confidence intervals (CI) for HPV results (HPV16, HPV18, HPV16, and/or 18, any hrHPV), self- and physician-sampling, and conventional cytology (ASC-US and LSIL thresholds) in relation to biopsy-defined disease endpoints (CIN2 or worse, $CIN2^+$; and CIN3 or worse, $CIN3^+$). Analyses were also stratified by age. We inferred statistical significance on the basis of non-overlapping CIs. We used SAS v9.4 (SAS Institute Inc.) to analyze the data.

Results

Table 1 presents the characteristics of participants and hrHPV genotype distribution in the overall study population by recruitment site. The mean age was 37.7 $\pm$ 11.1 (SD) years. Median ages were 34.0 years (range, 19–63 years) for participants in clinic A, 38.0 years (range, 16–70 years) in clinic B, and 36.5 years (range, 21–66 years) in clinic C. Valid cytology results were available for 1,137 women; the majority (550 women) had normal cytology, 190 had ASC-US, 70 had ASC-H, 214 had LSIL, 96 had HSIL, 8 had AGC, and 9 had cancer. A histologic diagnosis was available for 872 of the 1,217 women; 545 women had no lesions, 161 had CIN1, 73 CIN2, 81 CIN3, 7 CIN2/CIN3, and 5 cancers. In total, there were 1,182 women in the study who completed self-sampling via HerSwab and 1,170 with physician-collected

Table 1. Characteristics of the overall study population ($N = 1,217$) by recruitment site

	Clinic A, $n = 392$ n (%)	Clinic B, $n = 643$ n (%)	Clinic C, $n = 182$ n (%)
Age			
≤35 years	221 (56.4)	281 (43.7)	85 (46.7)
>35 years	171 (43.6)	362 (56.3)	97 (53.3)
Cytology[a]			
NILM	201 (51.3)	249 (38.7)	100 (55.0)
ASC-US	82 (20.9)	87 (13.5)	21 (11.5)
ASC-H	23 (5.9)	37 (5.8)	10 (5.5)
LSIL	51 (13.0)	131 (20.4)	32 (17.6)
HSIL	24 (6.1)	63 (9.8)	9 (5.0)
AGC	1 (0.3)	4 (0.6	3 (1.7)
Cancer	1 (0.3)	8 (1.2)	0 (0.0)
Missing	9 (2.3)	64 (10.0)	7 (3.9)
Biopsy			
Not performed[b]	153 (39.0)	157 (24.4)	35 (19.2)
Performed			
Normal	100 (25.5)	330 (51.3)	115 (63.2)
CIN1	80 (20.4)	61 (9.5)	20 (11.0)
CIN2	27 (6.9)	41 (6.4)	5 (2.8)
CIN3	30 (7.7)	48 (7.5)	3 (1.6)
HSIL[c]	0	3 (0.5)	4 (2.2)
Cancer	2 (0.5)	3 (0.5)	0
HPV Positivity			
HPV16$^+$, HerSwab[d]	63 (16.9)	79 (12.6)	20 (11.2)
HPV16$^+$, Physician[e]	64 (17.2)	84 (13.5)	18 (10.3)
HPV18$^+$, HerSwab[f]	12 (3.2)	18 (2.9)	4 (2.2)
HPV18$^+$, Physician[g]	8 (2.1)	20 (3.2)	3 (1.7)
HPV16 and/or 18$^+$, HerSwab	72 (18.4)	92 (14.3)	24 (13.2)
HPV16 and/or 18$^+$, Physician	71 (18.1)	98 (15.2)	21 (11.5)
Other hrHPV$^+$, HerSwab[f]	162 (43.2)	248 (39.5)	56 (31.3)
Other hrHPV$^+$, Physician[h]	158 (42.4)	238 (38.2)	48 (27.6)
Any hrHPV$^+$, HerSwab[f]	194 (51.7)	298 (47.5)	68 (38.0)
Any hrHPV$^+$, Physician[h]	196 (52.6)	299 (48.0)	59 (33.9)

[a]On the basis of the actual colposcopy visit sample if collected, otherwise on the referral cytology report.
[b]Biopsies were not performed in the absence of visible lesional tissue on colposcopic examination.
[c]No distinction was made between CIN2 and CIN3.
[d]Data were missing for 19, 16, and 3 subjects in clinics A, B, and C, respectively.
[e]Data were missing for 19, 22, and 8 subjects in clinics A, B, and C, respectively.
[f]Data were missing for 17, 15, and 3 subjects in clinics A, B, and C, respectively.
[g]Data were missing for 19, 21, and 8 subjects in clinics A, B, and C, respectively.
[h]Data were missing for 19, 20, and 8 subjects in clinics A, B, and C, respectively.

Table 2. Characteristics of a subpopulation of women ($N = 700$) who underwent cervical biopsy and cytology at the actual CASSIS visit, by age group

	≤35 Years ($n = 328$) n (%)	>35 years ($n = 372$) n (%)
Cytology[a]		
NILM	157 (47.9)	201 (54.0)
ASC-US	46 (14.0)	46 (12.4)
ASC-H	15 (4.6)	20 (5.4)
LSIL	58 (17.7)	43 (11.6)
HSIL	30 (9.2)	23 (6.2)
AGC	2 (0.6)	3 (0.8)
Cancer	1 (0.3)	3 (0.8)
Missing	19 (5.8)	33 (8.9)
Biopsy		
Normal	204 (62.2)	257 (69.1)
CIN1	63 (19.2)	71 (19.1)
CIN2	28 (8.5)	21 (5.7)
CIN3	29 (8.8)	19 (5.1)
HSIL[b]	3 (0.9)	2 (0.5)
Cancer	1 (0.3)	2 (0.5)
HPV Positivity		
HPV16$^+$, HerSwab[c]	62 (19.1)	40 (11.0)
HPV16$^+$, Physician[d]	63 (19.5)	42 (11.7)
HPV18$^+$, HerSwab[e]	14 (4.3)	9 (2.5)
HPV18$^+$, Physician[f]	12 (3.7)	9 (2.5)
HPV16 and/or 18$^+$, HerSwab	72 (22.0)	47 (12.6)
HPV16 and/or 18$^+$, Physician	72 (22.0)	49 (13.2)
Other hrHPV$^+$, HerSwab[e]	158 (48.8)	109 (30.0)
Other hrHPV$^+$, Physician[g]	150 (46.3)	106 (29.4)
Any hrHPV$^+$, HerSwab[e]	190 (58.6)	139 (38.2)
Any hrHPV$^+$, Physician[g]	186 (57.4)	141 (39.2)

[a]Excluding referral cytology results.
[b]No distinction was made between CIN2 and CIN3.
[c]Data were missing for 4 and 9 women ages ≤35 and >35 years, respectively.
[d]Data were missing for 5 and 13 women ages ≤35 and >35 years, respectively.
[e]Data were missing for 4 and 8 women ages ≤35 and >35 years, respectively.
[f]Data were missing for 5 and 12 women ages ≤35 and >35 years, respectively.
[g]Data were missing for 4 and 12 women ages ≤35 and >35 years, respectively.

samples for HPV testing. The overall hrHPV prevalence (47.4%) was identical for self-collected samples (560/1,182) and physician-collected samples (554/1,170), and differed by recruitment site (χ^2 P<0.05). This might be explained by the lower prevalence in clinic C, which mainly offers primary health care. hrHPV genotype infections did not differ by collection method.

Table 2 presents, by age, the same characteristics for a subset of women ($n = 700$) who underwent cytology and cervical biopsy at the actual CASSIS visit. Cytology was abnormal in 46.3% of women ages 35 years and younger and 37.1% in women over 35 years of age. Respective values for histologic dysplasia were 37.8% and 30.9%. Of the 700 women, 688 completed self-sampling and 684 had physician-collected samples for HPV testing. The hrHPV detection rate was comparable between self- and physician-samples, being 47.0% (329/700) and 46.7% (327/700), respectively. Corresponding values were 58.6% (190/324) and 57.4% (186/324) in women ages 35 years or less, and 38.2% (139/364) and 39.2% (141/360) in women older than 35 years. Similar to analyses in the total study population, the prevalence of hrHPV genotypes did not differ by collection method.

Table 3 shows the PPV and NPV of HPV genotyping and cytology based on CIN2$^+$ and CIN3$^+$ disease thresholds among women with cytology and biopsy done at the actual CASSIS visit. In all HPV testing comparisons, self-sampling performed similarly to physician-sampling. The PPVs for HPV16 positivity were significantly higher than all other testing combinations for both disease thresholds. However, overall hrHPV positivity was not significantly different than cytology for both CIN2$^+$ and CIN3$^+$. For both disease endpoints, addition of HPV18 positivity to HPV16 led to a slight decrease in PPV, but HPV16/18 positivity was superior to cytology regardless of threshold. As expected, a reverse trend was observed with respect to NPVs, with the strongest rule-in combinations performing less well in ruling out disease. Except for HPV18 positivity, all testing combinations yielded NPVs above 90%. For the lowest risk tolerance level (i.e., CIN2$^+$), however, only overall hrHPV positivity and cytology at an ASC-US threshold yielded NPVs whose lower 95% confidence bounds were higher than 90%.

Likewise, the age-stratified analyses show (Table 4) somewhat lower PPVs in all test combinations and disease thresholds for young women than in older adult women, because of the lower disease prevalence among the latter. Conversely, and consistent with the lower disease prevalence among older women, NPVs

Table 3. Predictive values of HPV genotyping (self- and physician-collected samples) and cytology (physician-collected samples) to detect disease in a subpopulation of women ($N = 700$) who underwent cervical biopsy and cytology at the actual CASSIS visit

		PPV, % (95% CI)		NPV, % (95% CI)	
Disease threshold	**Definition of test positivity and threshold**	**HerSwab**	**Physician**	**HerSwab**	**Physician**
CIN2^{+a}, $n = 105$	HPV16	47.1 (37.1–57.2)	46.7 (36.9–56.7)	90.3 (87.6–92.5)	90.3 (87.6–92.6)
	HPV18	21.7 (7.5–43.7)	19.0 (5.4–41.9)	85.0 (82.0–87.6)	84.7 (81.8–87.4)
	HPV16 and/or 18	43.7 (34.6–53.1)	43.8 (34.8–53.1)	90.9 (88.2–93.1)	91.0 (88.4–93.2)
	Any hrHPV	28.0 (23.2–33.1)	29.7 (24.8–34.9)	96.4 (93.9–98.1)	97.8 (95.6–99.0)
	Cytology, ASCUS	NA	26.6 (21.6–32.0)	NA	94.7 (91.8–96.8)
	Cytology, LSIL	NA	31.3 (24.9–38.3)	NA	92.4 (89.6–94.7)
CIN3^{+b}, $n = 51$	HPV16	26.3 (17.9–36.1)	26.5 (18.2–36.1)	95.7 (93.7–97.2)	95.8 (93.9–97.3)
	HPV18	13.0 (2.8–33.6)	14.3 (3.0–36.3)	92.7 (90.5–94.6)	92.7 (90.4–94.6)
	HPV16 and/or 18	25.0 (17.4–33.9)	25.4 (17.9–34.3)	96.2 (94.3–97.6)	96.4 (94.5–97.7)
	Any hrHPV	15.0 (11.3–19.4)	14.9 (11.2–19.2)	99.4 (98.0–99.9)	99.2 (97.6–99.8)
	Cytology, ASCUS	NA	13.2 (9.5–17.7)	NA	98.3 (96.4–99.4)
	Cytology, LSIL	NA	15.9 (11.1–21.8)	NA	97.1 (95.1–98.4)

Abbreviation: NA, not available.
[a]Disease-free group includes CIN1 with the normal.
[b]Disease-free group includes CIN1 and CIN2 with the normal. Five HSIL biopsies were excluded because they could not be distinguished between CIN2 and CIN3.

were generally higher for the latter than for young women. Apart from these observations, there were generally no age-specific differences in patterns of predictive value differentials, whether positive or negative, by test combination, specimen type, and disease threshold.

Discussion

In recent years, much research has focused on the clinical utility and effectiveness of HPV self-sampling, thereby allowing women to take onus of their healthcare by playing a more active role in the screening process. We showed in this analysis of women, referred to colposcopy for abnormal cytology, similar predictive values of HPV genotyping based on self- and physician-collected samples, with comparable or better performance than conventional cytology, further confirming the value of using HPV genotyping in clinical risk evaluation. Other than the effect of disease prevalence by age, we did not observe any notable differences in test performance by age.

The comparable performance between self- and physician-collected samples for HPV testing reflects previous research, despite nonstatistically significant variations between studies published between 1993 and 2018, which are most likely due to the use of different sampling devices and HPV tests (22). An

Table 4. Predictive values of HPV genotyping (self- and physician-collected samples) and cytology (physician-collected samples) to detect disease in a subpopulation of women ($N = 700$) who underwent cervical biopsy and cytology at the actual CASSIS visit, by age group

		PPV, % (95% CI)		NPV, % (95% CI)	
Disease threshold	**Definition of test positivity and threshold**	**HerSwab**	**Physician**	**HerSwab**	**Physician**
Women ≤ 35 years ($n = 328$)					
CIN2^{+a}, $n = 61$	HPV16	48.4 (35.5–61.4)	49.2 (36.4–62.1)	88.2 (83.6–91.8)	88.5 (83.9–92.1)
	HPV18	28.6 (8.4–58.1)	25.0 (5.5–57.2)	81.6 (76.8–85.8)	81.3 (76.6–85.5)
	HPV16 and/or 18	45.8 (34.0–58.0)	47.2 (35.3–59.3)	89.1 (84.6–92.6)	89.4 (85.0–92.9)
	Any hrHPV	28.4 (22.1–35.4)	31.2 (24.6–38.4)	94.8 (89.5–97.9)	97.8 (93.8–99.6)
	Cytology, ASCUS	NA	29.0 (21.9–36.9)	NA	91.7 (86.3–95.5)
	Cytology, LSIL	NA	32.1 (23.3–41.8)	NA	88.7 (83.5–92.7)
CIN3^{+b}, $n = 30$	HPV16	28.8 (17.8–42.1)	30.0 (18.9–43.2)	95.0 (91.7–97.3)	95.4 (92.1–97.6)
	HPV18	14.3 (1.8–42.8)	16.7 (2.1–48.4)	90.9 (87.1–93.9)	90.9 (87.1–93.9)
	HPV16 and/or 18	27.5 (17.5–39.6)	29.0 (18.7–41.2)	95.7 (92.4–97.8)	96.1 (92.9–98.1)
	Any hrHPV	16.0 (11.1–22.1)	15.9 (10.9–22.0)	100.0 (97.3–100)	99.3 (96.0–100.0)
	Cytology, ASCUS	NA	14.7 (9.4–21.4)	NA	97.4 (93.6–99.3)
	Cytology, LSIL	NA	15.4 (9.1–23.8)	NA	95.0 (91.1–97.6)
Women > 35 years ($n = 372$)					
CIN2^{+a}, $n = 44$	HPV16	45.0 (29.3–61.5)	42.9 (27.7–59.0)	92.0 (88.4–94.7)	91.8 (88.2–94.6)
	HPV18	11.1 (0.3–48.2)	11.1 (0.3–48.2)	87.9 (84.0–91.1)	87.8 (83.9–91.0)
	HPV16 and/or 18	40.4 (26.4–55.7)	38.8 (25.2–53.8)	92.3 (88.9–95.0)	92.3 (88.8–94.9)
	Any hrHPV	27.3 (20.1–35.5)	27.7 (20.5–35.8)	97.3 (94.3–99.0)	97.7 (94.8–99.2)
	Cytology, ASCUS	NA	23.9 (17.1–31.9)	NA	97.0 (93.6–98.9)
	Cytology, LSIL	NA	30.4 (21.3–40.9)	NA	95.6 (92.2–97.8)
CIN3^{+b}, $n = 21$	HPV16	22.5 (10.8–38.4)	21.4 (10.3–36.8)	96.3 (93.6–98.0)	96.2 (93.4–98.0)
	HPV18	11.1 (0.3–48.2)	11.1 (0.3–48.2)	94.3 (91.4–96.5)	94.3 (91.3–96.5)
	HPV16 and/or 18	21.3 (10.7–35.7)	20.4 (10.2–34.3)	96.6 (94.0–98.3)	96.6 (94.0–98.3)
	Any hrHPV	13.7 (8.4–20.5)	13.6 (8.4–20.4)	99.1 (96.8–99.9)	99.1 (96.7–99.9)
	Cytology, ASCUS	NA	11.7 (6.8–18.3)	NA	99.0 (96.4–99.9)
	Cytology, LSIL	NA	16.5 (9.5–25.7)	NA	98.8 (96.5–99.8)

Abbreviation: NA, not available.
[a]Disease-free group includes CIN1 with the normal.
[b]Disease-free group includes CIN1 and CIN2 with the normal. Two HSIL biopsies excluded because they could not be distinguished between CIN2 and CIN3.

important caveat in comparing predictive values lies in the type of setting. We chose to conduct our investigation in colposcopy clinics to attain an artificially elevated prevalence of disease relative to screening in a primary care setting. This permitted us to attain higher precision in our PPV estimates with consequent, improved discrimination among tests and sampling methods. In the high disease prevalence setting of colposcopy clinics the PPVs will be higher for any given cervical cancer screening test than those measured in a primary care population with low disease prevalence. Conversely, and because of the same dependence on prevalence, NPVs will be lower in colposcopy clinics than in the primary care setting of true population screening.

The higher cross-sectional accuracy of HPV testing over cytology screening has been demonstrated previously (31). Our results are also in agreement with more recent studies, including one based on this study population (21). A randomized study (2013–2015) in Sweden, which compared the detection rate of histologically defined CIN2$^+$ in women performing repeated self-sampling of vaginal fluid for HPV testing ($n = 17{,}997$) to those performing screening by conventional cytology ($n = 18{,}393$ women), found that HPV self-sampling detected more than twice as many women with CIN2$^+$ than cytology (32). Another study also found that women participating in self-sampling ($n = 4{,}865$) had a higher CIN2$^+$ detection than women undergoing cytology-based screening ($n = 3{,}347$), and the PPV for CIN2$^+$ was higher in the self-sampling group than in cytology-screened women (36.5% vs. 25.6%; ref. 33).

The higher predictive values of HPV genotyping for cervical high-grade lesions compared with cytologic screening strongly supports HPV-based primary screening for identifying prevalent disease relative to cytologic screening (32, 34, 35). The PPV for detection of CIN2$^+$ was 34.5% for HPV self-sampling and 38.6% for physician-sampling compared with 37.5% for ASC-US+ and 53.1% for LSIL+ cytology. The corresponding NPVs were 84.0%, 100%, 96.4%, and 93.1% (36). The authors attributed the lower self-sampling HPV test PPV to the sampling order; self-sampling was performed at home after physician-sampling, which might have affected the former's performance. A more plausible explanation may be the slightly lower specificity associated with HPV self-sampling (22).

A comparison among several screening strategies to identify CIN2$^+$ showed that primary hrHPV testing with triage by cytology gave better performance than cotesting (PPV of 29.2% vs. 22.7%), with HPV16/18 genotyping having the highest NPV (99.7%; ref. 37), thus providing greater reassurance for women with negative results. Among 520 hrHPV-positive women from a randomized controlled self-sampling trial on screening nonattendees, HPV16 and/or 18 positivity yielded higher PPV than ASC-US+ cytology (44.4% vs. 37.0%) and lower NPV (92.0% vs. 97.2%) to identify or rule out women with CIN3$^+$ (38).

Because knowledge of the referral cytology might have guided the physician's decision to perform a biopsy, performance parameters were estimated only for a subset of the study population. In our study, the biopsy rate in colposcopies was 71.7% overall; 61.0% in clinic A, 75.6% in clinic B, and 80.8% in clinic C. This, however, reflects situations in a real-world clinical practice. Data provided from four Canadian provinces (Nova Scotia, Alberta, British Columbia, and Manitoba) for the histologic investigation rate showed that, during 2009 and 2010, a total of 11,898 of 13,210 women (90.1%) ages between 20 and 69 years had a biopsy within the subsequent 12 months following an ASC-H, HSIL, or more severe cytology result, with the biopsy rate across provinces ranging from 82.1% to 96.5% (39).

A limitation of our study is that its generalizability is restricted to the high disease prevalence conditions of a secondary or tertiary care setting of colposcopy clinics. PPVs and NPVs are directly influenced by disease prevalence and thus our findings are not readily comparable with those obtained in general screening settings. This generalizability concern is somewhat mitigated by the major strength of the CASSIS study which relates to efficiency; a similar study in a screening population would have required the recruitment of around 30,000 women. Another key strength is the use of a recently validated self-sampling device (21). Notwithstanding, further studies are warranted in healthy screening populations that will additionally allow for evaluations of operational and system-related barriers to HPV self-sampling.

Although cytology continues to be the dominant cervical cancer screening modality in Canada, primary hrHPV testing will eventually replace cytology, paving the way for the implementation of HPV self-sampling nationwide, and for population-based screening programs to reduce cervical cancer screening disparities in Canada (40). It remains to be seen how effective, operational, and sustainable population-based screening for cervical cancer and its precursors will be outside of the clinical setting, especially among disadvantaged women and underserved communities.

Disclosure of Potential Conflicts of Interest

E.L. Franco reports receiving commercial research grant from Eve Medical and Roche and is a consultant/advisory board member for Merck and GSK. No potential conflicts of interest were disclosed.

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M. El-Zein, S. Bouten, E.L. Franco
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