

# Self-Collected Samples for Testing of Oncogenic Human Papillomavirus: A Systematic Review

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## Abstract

**Background:** To investigate the role of self-sampling for human papillomavirus (HPV) testing as an alternative to cervical cancer screening by clinicians (i.e., Papanicolaou [Pap] test).

**Methods:** A systematic search of MEDLINE, EMBASE, Cochrane Library, and other sources for evidence related to the efficacy and feasibility of HPV DNA self-collection.

**Results:** A total of 25 studies were identified. In 22 comparisons across 19 studies, the concordance between samples collected by patients and those obtained by clinicians was reasonably high in the majority of cases. Women in many countries across wide age ranges were successful in collecting samples for HPV DNA testing. In four studies, the quality of the cytology from patient samples was as good as clinician samples, with more than 95% of samples yielding HPV DNA results. The studies that examined acceptability found that women were generally very positive about collecting their own samples, although some concerns were noted. No study evaluated the effect of HPV DNA self-sampling on screening participation rates, early detection, survival, or quality of life.

**Conclusions:** Self-sampling for HPV DNA testing is a viable screening option, but there is insufficient evidence to conclude that self-sampling for HPV DNA testing is an alternative to the Pap test. Although HPV DNA testing using self-collected samples holds promise for use in under-resourced areas or for women who are reluctant to participate in Pap testing programs, the evidence supporting it is limited. Further definitive research is needed to provide a solid evidence base to inform the use of self-sampling for HPV DNA testing for the purpose of increasing screening rates, especially in women who are never or seldom screened.

**Key Words:** HPV, self-collection, self-sampling, cervical cancer screening, cancer prevention, detection, cervical dysplasia

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## Résumé

**Contexte :** Explorer le rôle de l'autoprélèvement aux fins du dépistage du virus du papillome humain (VPH), à titre de solution de rechange au dépistage du cancer du col utérin effectué par des cliniciens (c.-à-d. le test de Papanicolaou [Pap]).

**Méthodes :** Une recherche systématique a été menée dans MEDLINE, EMBASE, Cochrane Library et d'autres sources afin d'y relever les données traitant de l'efficacité et de la faisabilité de l'autoprélèvement d'ADN du VPH.

**Résultats :** Au total, 25 études ont été identifiées. Dans le cadre de 22 comparaisons faisant partie de 19 études, la concordance entre les échantillons prélevés par les patientes et ceux qui ont été prélevés par des cliniciens était raisonnablement élevée dans la plupart des cas. Dans de nombreux pays et selon de vastes plages d'âges, les femmes ont réussi à prélever des échantillons aux fins du dépistage de l'ADN du VPH. Dans le cadre de quatre études, la cytologie menée à partir d'autoprélèvements était d'aussi bonne qualité que celle qui a été menée à partir d'échantillons prélevés par des cliniciens, plus de 95 % des prélèvements ayant permis d'obtenir des résultats quant à l'ADN du VPH. Les études qui se sont penchées sur l'acceptabilité ont constaté que les femmes réagissaient généralement de façon très positive face à l'autoprélèvement, et ce, bien que certaines préoccupations aient été notées. Aucune étude n'a évalué l'effet de l'autoprélèvement d'ADN du VPH sur les taux de participation au dépistage, la détection précoce, la survie ou la qualité de vie.

**Conclusions :** Bien que l'autoprélèvement aux fins du dépistage de l'ADN du VPH constitue une option de dépistage viable, nous ne disposons pas de données suffisantes pour en venir à la conclusion qu'il constitue une solution de rechange au test de Pap. Bien que le dépistage de l'ADN du VPH au moyen d'échantillons autoprélévés s'avère prometteur en ce qui concerne les régions sous-desservies ou les femmes qui hésitent à se soumettre à des tests de Pap, les données qui le soutiennent sont limitées. Des recherches définitives approfondies s'avèrent requises pour mettre au jour des données solides permettant d'étayer le recours à l'autoprélèvement aux fins du dépistage de l'ADN du VPH, et ce, dans le but d'accroître les taux de dépistage, particulièrement chez les femmes qui ne se soumettent jamais ou que très peu souvent au dépistage.

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## INTRODUCTION

Cervical cancer is a common cancer-related cause of death among women worldwide, and it is preventable through regular screening programs.<sup>1</sup> In developed countries, it is estimated that more than one half of women found to have cervical cancer have a history of no screening or infrequent screening.<sup>2,3</sup> In Canada, such women tend to have a low level of education, to live in poverty, to be newcomers to the country, to be over 50 years of age, or to be of Aboriginal descent.<sup>4</sup>

The objective of screening is to reduce mortality and morbidity from cervical cancer by detecting disease at an early stage, when treatment is most effective. In much of the developed world, women are screened for abnormalities in cervical tissue that may be precursors to cancer by undergoing the Papanicolaou (Pap) test. Pap testing performed by clinicians is accepted as an effective screening test for reducing mortality from cervical cancer.<sup>5</sup> The Pap test is conducted in the primary care setting, and the cytology sample obtained is examined in a laboratory for specific cell types that are considered abnormal. Depending on the degree of cellular changes, an abnormal Pap result requires either a follow-up test six months later or immediate colposcopy, which enables both visualization of the cervix and a biopsy.

While screening with the Pap test has been the standard for decades, there is ongoing research investigating the use of human papillomavirus (HPV) DNA testing (physician-collected samples) as a primary screening test for cervical cancer. Although this remains somewhat controversial, the detection of HPV in cervical specimens may offer an alternative to population-based cytological screening because HPV DNA testing appears to be as sensitive as the Pap test in detecting women at increased risk of cancer.<sup>6</sup> If this alternative becomes widely adopted, then self-sampling for HPV DNA testing may become an important screening tool to increase screening participation, especially in women who are seldom or never screened.

Preliminary studies suggest that HPV DNA testing may reduce loss to follow-up by producing definitive results with clear clinical management advice, which in turn might improve the likelihood of patient adherence. One study showed that 17% of patients were lost to follow-up in a group referred for immediate colposcopy (on the basis of a positive adjunctive HPV DNA test), compared with 33% in an equivalent group of patients asked to repeat cytology testing after six months.<sup>7</sup>

There are many reasons why women in both developing and developed countries do not participate in cervical screening, such as lack of access to a health care provider,

discomfort with physical examination, and cultural, religious, or personal values that prohibit examination by a male physician. HPV DNA testing has the potential to reach under-screened populations with self-sampling methods. Self-sampling has proved to be reliable in screening for sexually transmitted diseases in hard-to-reach populations; for example, self-administered tampons were shown to be both an acceptable and a sensitive method for detecting sexually transmitted diseases in women living in remote regions of Australia.<sup>8</sup> Self-collected vaginal swabs produced reliable results and were acceptable to women in Southern Asia for the detection of reproductive tract infections.<sup>9</sup>

It is clear that more information on self-sampling for HPV DNA testing is needed. To that end, this review examines the feasibility, acceptability, and effectiveness of self-sampling for HPV DNA testing. In theory, self-sampling has the potential to improve screening and follow-up rates in women who are never or seldom (> 3 years between tests) screened by clinicians, thereby contributing to reduced mortality and morbidity from cervical cancer.

## METHODS

This systematic review was developed by the HPV Self-collection Guidelines Panel as a collaborative effort between the Cancer Care Ontario Screening Guidelines Steering Committee and the Program in Evidence-based Care, using methods adapted from the Practice Guidelines Development Cycle.<sup>10</sup>

The Program in Evidence-based Care and the multidisciplinary members of the HPV Self-collection Guidelines Panel are editorially independent of Cancer Care Ontario, the Ontario Ministry of Health and Long-Term Care, and the Ontario Women's Health Council.

### Literature Search Strategy

The following databases were searched for relevant reports on HPV DNA self-testing published between January 1985 and December 2004: MEDLINE, EMBASE, HealthSTAR, CINAHL, the Cochrane Library, Women's Studies International, Web of Science, Social Sciences Index, PsycINFO, the Campbell Library, Studies on Women and Gender Abstracts Online, Contemporary Women's Issues, the Canadian Medical Association Infobase, and the National Guideline Clearinghouse.

In addition, unpublished sources were sought using Google and through an Internet search of Health Canada, the National Health Service Department of Health, the Australian Government Department of Health, the RAND Corporation, the Institute of Medicine, the World Health Organization, the Agency for Health Research and Quality, and the National Institutes of Health for relevant reports.

Article bibliographies to December 2004 were also searched for relevant evidence.

Where sophisticated search engines were available, the literature was searched by combining disease-specific terms (cervix dysplasia or cervical intraepithelial neoplasia or cervix neoplasms or papillomavirus or papillomavirus, human or papillomavirus, infections) with test-specific terms (self-collected.tw. or self-test.tw. or self-obtained.tw.) for any study design. Where limited search facilities were available, the terms papillomavirus and self-collected or self-test or self-obtained or self-administered, or simply papillomavirus or HPV were used.

### Study Selection Criteria

Articles were included in the systematic review of the literature if they reported data relating to the self-collection of HPV DNA samples as they related to any of the following:

- The potential harms and benefits of self-sampling
- The feasibility of women successfully performing self-sampling
- The adequacy of self-collected samples for analysis
- The accuracy of self-sampling
- The acceptability of self-sampling to women
- The appeal of self-sampling to women
- Whether specific characteristics of women influence preferences regarding self-sampling
- Whether self-sampling is appropriate for women who are never or seldom (at intervals > 3 years) screened by clinicians.

Randomized controlled trials, case-control studies, prospective cohort studies, retrospective cohort studies, and technical reports were considered eligible for inclusion in the systematic review of the evidence. When reports examined the subjective outcomes of appeal, perspectives, characteristics, or acceptability of self-sampling to women, the results of surveys (interviews, focus groups, questionnaires) were also deemed eligible.

Studies were excluded if they were reported in a language other than English, were reported prior to 1985, or were published as abstracts, letters, or editorials. Studies were also excluded if there were no data on the research methodology used to develop the report.

## RESULTS

### Literature Search Results

As shown in Table 1, 25 studies reported in 31 papers were identified and considered eligible for inclusion in the systematic review of the evidence.<sup>11-41</sup>

No randomized trials or comparative cohort studies followed patients after HPV DNA testing to assess intermediate- or long-term outcomes from screening with self-sampling versus clinician sampling. Other than using an “experimental” procedure in the form of self-sampling, the studies were essentially observational in nature. All studies were prospective, and informed consent was obtained from participants. A common study design involved women collecting samples for HPV DNA testing using one or more methods of self-sampling (swab, brush, tampon, lavage, or pad), followed or preceded by a gynaecological examination by a clinician (physician or nurse). The clinician collected a sample for HPV DNA testing, obtained a cervical smear for cytology, and, in most cases, performed a colposcopic examination with cervical biopsy.

### Outcomes

#### What are the potential benefits and harms of self-sampling?

Evidence for the benefits and harms of HPV DNA testing is limited and largely restricted to the assessment of true-positive, false-negative, and false-positive rates (discussed under accuracy below). No studies evaluated the impact of self-sampling for HPV on screening participation rates, early detection, survival, or quality of life.

#### Is it feasible for women to perform self-sampling for HPV DNA testing successfully?

A large number of women aged 14 to 88 across 25 studies in 14 countries were able to obtain samples using a variety of self-testing techniques, including vaginal swab, cytobrush, pad, tampon, vaginal lavage, vulvar swab, and urine collection. Four studies reported clearly on the proportion of participants who returned samples from self-collection.<sup>19,26,35,40</sup> In a study that required women to perform eight swabs and use four tampons for varying lengths of time, 15% did not complete all the sampling.<sup>19</sup> In a study by Nobbenhuis et al., the most common reasons reported for not doing the self-test (among 15 women, or 21% of recruits) were forgetting and nervousness about the colposcopy examination.<sup>26</sup> Serwadda et al. reported that 93% of participants in rural Uganda provided samples using vaginal swabs; the samples were collected at home and handed to a field worker.<sup>35</sup> In a study of urban American women by Morrison et al., 68% returned samples collected by cervicovaginal lavage 10 to 36 days after colposcopy.<sup>40</sup>

Five studies reported on the difficulty of performing self-sampling or understanding the instructions.<sup>12,19,23,25,26</sup> Dannecker et al. reported that five of 333 women (1.5%) found it difficult to use a vaginal brush for self-collection.<sup>12</sup> Harper et al. asked women if they experienced any difficulty putting tampon samples collected at home into tubes of

**Table 1. Evidence available from studies eligible for the systematic review**

Author (year)	Number of patients enrolled (number analyzed)	Study origin	Setting	Patient Self-test method	Accuracy	Success	Acceptability
Kim (2004) <sup>11</sup>	347 (340)	Korea	Gynaecologic clinic	Pad	✓	-	-
Dannecker (2004) <sup>12</sup>	435 (435)	Germany	Internal medicine clinic	Vaginal brush	✓	✓	✓
Kahn (2004) <sup>13</sup>	101 (99)	USA	Teen health centre	Vaginal swab	✓	✓	-
Forrest (2004) <sup>14</sup>	200 (200)	UK	community	Vaginal swab	-	-	✓
Garcia (2003) <sup>15</sup>	334 (334)	USA/Mexico/Peru	Colposcopy clinic	Vaginal brush	✓	✓	-
Palmisano (2003) <sup>16</sup>	334 (334)	USA	Colposcopy clinic	Vaginal swab	✓	✓	-
Harper (2003) <sup>17*</sup>	103 (103)	USA	Colposcopy clinic	Vaginal swabs, tampon	-	-	-
Harper (2002) <sup>18*</sup>					✓	-	✓
Harper (2002) <sup>19*</sup>					✓	✓	✓
Flores (2003) <sup>20†</sup>	7876 (7732)	Mexico	Screening program	Vaginal swab	-	-	✓
Salmeron (2003) <sup>21†</sup>					✓	-	-
Flores (2002) <sup>22†</sup>					-	-	-
Dzuba (2002) <sup>23†</sup>					-	✓	✓
Belinson (2003) <sup>24‡</sup>	9183 (8497)	China	Community	Vaginal brush	✓	-	-
Tisci (2003) <sup>25‡</sup>					-	✓	✓
Nobbenhuis (2002) <sup>26</sup>	71 (71)	Netherlands	Colposcopy clinic	Cervicovaginal lavage	✓	✓	✓
Lorenzato (2002) <sup>27</sup>	253 (253)	Brazil	Screening program	Vaginal swab	✓	-	-
Chang (2002) <sup>28</sup>	1194 (1194)	Taiwan	Community	Vaginal swab	✓	-	-
Belinson (2001) <sup>29</sup>	2047 (1997)	China	Community	Vaginal swab	✓	-	-
Rompalo (2001) <sup>30</sup>	793 (706)	USA	STI clinic	Vaginal swab	✓	-	-
Gravitt (2001) <sup>31</sup>	268 (268)	USA	Study participant	Vaginal swab	-	-	✓
Sellers (2000) <sup>32</sup>	245 (200)	Canada	Colposcopy clinic	Vaginal swab Vulvar swab Urine specimen	✓	-	✓
Wright (2000) <sup>33</sup>	1415 (1365)	Africa	Community	Vaginal swab	✓	-	-
Hillemans (1999) <sup>34</sup>	247 (247)	Germany	Colposcopy clinic	Vaginal brush	✓	-	✓
Serwadda (1999) <sup>35</sup>	960 (898)	Africa	Study participant	Vaginal swab	-	✓	-
Harper (1999) <sup>36</sup>	97 (93)	USA	Gynaecologic clinic	Tampon	✓	-	-
Coutlee (1997) <sup>37</sup>	230 (224)	Canada	Study participant	Tampon	✓	✓	-
Moscicki (1993) <sup>38</sup>	114 (114)	USA	Study participant	Vaginal swab	✓	-	-
Forslund (1993) <sup>39</sup>	343 (NR)	Sweden	Colposcopy clinic	Urine specimen	✓	✓	-
Morrison (1992) <sup>40</sup>	25 (17)	USA	Colposcopy clinic	Cervicovaginal lavage	✓	✓	-
Fairley (1992) <sup>41</sup>	48 (48)	Australia	Dysplasia clinic	Tampon	✓	-	-

NR: not reported; STI: sexually transmitted infection.

\*Three reports of the study by Harper, et al.

†Four reports of the Morelos HPV Study.

‡Two reports of the SPOCCS II Study.

**Table 2. Proportion of self-collected samples adequate for HPV analysis**

Author (year)	Number of patients	Method of collection	Setting	Sample collector	Satisfactory samples %
Kahn (2004) <sup>13</sup>	99	Vaginal swab	Clinic	Patient	98
		Cervical swab	Clinic	Clinician	99
Garcia (2003) <sup>15</sup>	334	Vaginal brush	Clinic	Patient	99
		Cervical brush	Clinic	Clinician	98
Palmisano (2003) <sup>16</sup>	334	Vaginal swab	Clinic	Patient	~70
		Cervical swab	Clinic	Clinician	100
Harper (2002) <sup>19</sup>	103	Tampon	Clinic	Patient	NR
		Cervical swab	Clinic	Clinician	NR
Coutlee (1997) <sup>37</sup>	224	Tampon	Clinic	Patient	99
		Cervicovaginal lavage	Clinic	Clinician	99
Forslund (1993) <sup>39</sup>	343	Urine specimen	Clinic	Patient	96
		Cervical brush	Clinic	Clinician	100
Morrison (1992) <sup>40</sup>	17	Cervicovaginal lavage	Home	Patient	94
		Cervicovaginal lavage	Clinic	Clinician	100

preservative and putting the tubes into mailing kits; of those who completed the survey (65%), none reported difficulties.<sup>19</sup> In a trial involving Mexican women, their comprehension of the self-sampling procedure rated an average score of 4.5 on a 5-point scale, where 1 = poor and 5 = good.<sup>23</sup> Tisci et al. reported that rural Chinese women with low education encountered difficulties because they did not understand the directions; problems included contamination of the sampling brush, difficulty locating the vagina, spillage of the transport medium, and difficulty distinguishing between the top and bottom of the container.<sup>25</sup> In the trial reported by Nobbenuis et al., 12% of Dutch women experienced difficulties using cervicovaginal lavage.<sup>26</sup>

#### **With self-sampling, are samples obtained by women adequate for analysis?**

Seven reports described the quality of samples obtained by self-testing.<sup>13,15,16,19,37,39,40</sup> In four studies,<sup>13,15,37,39</sup> more than 95% of samples yielded cells for HPV DNA testing (Table 2). In one study, it was noted that although 4% of samples were inadequately labelled and 6% of samples leaked during shipment, the samples still yielded cells sufficient for HPV DNA testing.<sup>19</sup> It was also reported that neither cycle stage nor recent sexual intercourse affected HPV DNA results from self-collected samples.<sup>19</sup> In the remaining studies, Palmisano et al. reported that self-collected samples showed a lack of amplification (samples were considered to be amplified if the beta-high band appeared on genotyping strips), which they postulated might have been a result of insufficient collection of cells using vaginal swabs.<sup>16</sup> In the small study reported by Morrison et al.,<sup>40</sup> 94% of the

patient-collected samples and 100% of the clinician-collected samples were adequate for analysis.

#### **What is the accuracy of self-sampling for HPV DNA as a screening tool for cellular abnormalities of the cervix?**

Most studies reported on the sensitivity, specificity, positive predictive value, or negative predictive value of self-sampling, or provided enough data for those measures to be calculated.

#### **Biopsy as Reference Standard**

Fourteen studies that reported HPV DNA and biopsy results are summarised in Table 3. These studies are categorized according to whether patients had colposcopy performed in all cases or had colposcopy only with a positive HPV DNA test or abnormal cytology. In one study,<sup>12</sup> colposcopy was performed on a random sample of HPV-negative women.

In the first eight studies (seven of which recruited consecutive women referred to colposcopy clinics), all study participants underwent colposcopy.<sup>11,15,19,26,27,32,34,40</sup> Three studies took place among previously unscreened populations,<sup>24,29,33</sup> three at a cervical cancer screening service,<sup>21,27,28</sup> and one at an internal medicine clinic.<sup>12</sup> In five studies, only patients positive for HPV or with an abnormal cytology were recalled for a gynaecological examination and colposcopy.<sup>21,24,28,29,33</sup>

Observed positive predictive values (i.e., the proportion of patients with a positive HPV DNA test who were found to

**Table 3. Accuracy of HPV test to predict cervical intraepithelial neoplasia (CIN 2/3) or cervical cancer on biopsy**

Author (year)	Number of patients	Positive biopsy %	Method	Sample collector	Sensitivity %	Specificity %	PPV %	NPV %
All patients underwent colposcopy								
Kim (2004) <sup>11</sup>	340	72	Pad	Patient	75	100	100*	61*
			Cervical brush	Clinician	NR	NR	NR	NR
Garcia (2003) <sup>15</sup>	334	30	Vaginal brush	Patient	49	73	44	77
			Cervical brush	Clinician	82	67	52	90
Harper (2002) <sup>19</sup>	103	6	Tampon	Patient	83	89	50	98
			Cervical swab	Clinician	NR	NR	NR	NR
Nobbenhuis (2002) <sup>26</sup>	71	46	Lavage	Patient	81	68	70	79
			Lavage	Clinician	91	43	58	84
Lorenzato (2002) <sup>27</sup>	253	26	Vaginal swab	Patient	50*	86*	53*	82*
			Cervical brush and spatula	Clinician	75*	88*	69*	91*
Sellors (2000) <sup>32</sup>	200	24	Vaginal swab	Patient	86	54	43	91
			Vulvar swab	Patient	62	63	40	80
			Urine specimen	Patient	45	70	38	76
Hillemans (1999) <sup>34</sup>	247	15	Cervical brush	Clinician	98	52	46	99
			Vaginal brush	Patient	92	NR	NR	NR
Morrison (1992) <sup>40</sup>	17	53	Lavage	Patient	100*	14*	54*	100*
			Lavage	Clinician	100*	29*	58*	100*
Colposcopy for HPV positive or abnormal cytology or random sample of HPV negative (data corrected for verification bias)								
Dannecker (2004) <sup>12</sup>	435	6	Vaginal brush	Patient	100	71	10	100
			Cervical brush	Clinician	NR	NR	NR	NR
Salmeron (2003) <sup>21</sup>	7732	1.3	Vaginal swab	Patient	71	89	9	100
			Cervical brush	Clinician	93	92	15	100
Belinson (2003) <sup>24</sup>	8497	4	Vaginal brush	Patient	88	77	15*	99*
			Cervical brush	Clinician	97	80	18*	100*
Chang (2002) <sup>28</sup>	1194	5	Vaginal swab	Patient	96	92	35	99*
			Cervical brush or spatula	Clinician	NR	NR	NR	NR
Belinson (2001) <sup>29</sup>	1997	4	Vaginal swab	Patient	83	86	21	99
			Cervical brush and spatula	Clinician	95	85	23	100
Wright (2000) <sup>33</sup>	1365	4	Vaginal swab	Patient	66*	81*	13*	98*
			Cervical brush	Clinician	84*	83*	17*	99*

NR: data not reported; PPV: positive predictive value; NPV: negative predictive value.

\* Reviewer's calculation.

**Table 4. Accuracy of HPV test to predict abnormal cytology on cervical smear**

Author (year)	Number of patients	Abnormal cytology	Method	Sample collector	Sensitivity %	Specificity %	PPV %	NPV %
Kahn (2004) <sup>13</sup>	99	23% ASCUS, LSIL, HSIL	Vaginal swab	Patient	70	62	36*	87*
			Cervical swab	Clinician	70	66	38*	88*
Palmisano (2003) <sup>16</sup>	334	phase I: 67% ASCUS, LSIL, HSIL phase II: 43% ASCUS, LSIL, HSIL	Vaginal swab	Patient	32*	79*	76*	37*
			Vaginal swab	Patient	50*	79*	64*	68*
Rompalo (2001) <sup>30</sup>	706	19% ASCUS, LSIL, HSIL	Vaginal swab	Patient	54*	68*	28*	86*
			Cervical swab	Clinician	58*	68*	30*	88*
Moscicki (1993) <sup>38</sup>	114	13% Atypia or LGSIL	Vaginal swab	Patient	80*	76*	33*	96*
			Cervical swab	Clinician	73*	75*	31*	95*

NR: data not reported; ASCUS: atypical squamous cells of undetermined origin; LSIL: low-grade squamous intra-epithelial lesions; HSIL: high-grade squamous intra-epithelial lesions; LGSIL, low-grade squamous epithelial lesion

\*Reviewers calculation.

have a cytological abnormality of the cervix) of HPV DNA testing from self-collected samples were low in patients recruited for screening (9–35%),<sup>12,21,24,29,33</sup> compared with those in patients referred for colposcopy (38–100%).<sup>14,15,19,26,27,32,34,40</sup> While observed negative predictive values (i.e., the proportion of patients with negative HPV DNA results who do not have a cytological abnormality of the cervix) were excellent in the screening studies, it must be kept in mind that only patients with abnormal HPV or Pap test results were referred for further evaluation.<sup>21,24,28,29,34</sup> Those data should be interpreted with caution because the true outcome in most women with negative HPV tests is unknown.

In a direct comparison, Sellors et al. observed higher sensitivity with samples collected using vaginal swabs than with those collected using vulvar swabs or urine samples, but they observed higher specificity with urine sampling.<sup>32</sup> HPV DNA testing of samples collected by clinicians tended to have higher sensitivity than those collected by patients, but there is considerable variation among studies in sensitivity rates for both.

### Cytology as Reference Standard

Four studies used cytology as a reference standard or reported HPV DNA and cytology data that could be used to calculate accuracy<sup>13,16,30,38</sup> (Table 4). None of those studies recruited women from the general population. Sensitivity and specificity values varied among those studies, with no obvious differences between self-collected and clinician-collected samples.

### How does self-sampling for HPV compare with sampling by a clinician?

Nineteen studies reported data on agreement between self- and clinician-collected samples in the form of a kappa statistic or provided data that the reviewers could use to calculate kappa. Kappa provides a fairly crude measure of agreement beyond that expected by chance; values can range between 0 and 1, with 1 indicating perfect agreement. Although criteria vary, kappa values above 0.8 are generally considered to indicate very good agreement and values between 0.6 and 0.8 indicate reasonable/substantial agreement.<sup>42</sup>

In 22 comparisons reported from 19 studies, agreement between results from samples collected by patients and those obtained by clinicians ranged from 0.24 to 0.96 (Table 5).

There was reasonable or very good agreement between patient- and clinician-collected samples (kappa > 0.6) in six studies of vaginal swabs for self-collection,<sup>13,18,27,31,32,38</sup> three studies of tampons,<sup>18,23,41</sup> one of a cytobrush,<sup>34</sup> one of cervicovaginal lavage,<sup>40</sup> and one of a collection pad.<sup>11</sup> Poor agreement (kappa < 0.6) was observed for collection with a vaginal swab in two studies,<sup>30,33</sup> a tampon in one study,<sup>22</sup> a cytobrush in three studies,<sup>12,15,24</sup> lavage in one study,<sup>26</sup> a vulvar swab in one study,<sup>33</sup> and urine in two studies.<sup>32,39</sup>

### Is self-sampling for HPV DNA testing acceptable to women?

Ten studies (11 papers) evaluated and reported on the acceptability of self-collection for HPV DNA testing or on women's willingness to submit a self-collected HPV DNA sample.<sup>12,14,18–20,23,25,26,31,32,34</sup> Only two of the studies<sup>23,25</sup> reported on the development of the instruments that they used to measure acceptability or on validity and reliability.

**Table 5. Agreement between HPV results from self-test and clinician-test**

Author (year)	Number of patients	Method of collection		Cohen's kappa (patient vs. clinician)
		Patient	Clinician	
Harper (2003) <sup>17</sup>	103	Vaginal swab	Cervical swab	0.74
		Tampon	Cervical swab	0.63
Sellors (2000) <sup>32</sup>	200	Vaginal swab	Cervical brush + swab	0.76
		Vulvar swab	Cervical brush + swab	0.55
		Urine specimen	Cervical brush + swab	0.41
Kahn (2004) <sup>13</sup>	99	Vaginal swab	Cervical swab	0.72
Rompalo (2001) <sup>30</sup>	706	Vaginal swab	Cervical swab	0.48
Gravitt (2001) <sup>31</sup>	268	Vaginal swab	Cervical swab	0.73
Moscicki (1993) <sup>38</sup>	114	Vaginal swab	Cervical swab	0.84*
Wright (2000) <sup>33</sup>	1365	Vaginal swab	Cervical brush	0.45
Lorenzato (2002) <sup>27</sup>	253	Vaginal swab	Cervical spatula and brush	0.62
Dannecker (2004) <sup>12</sup>	435	Vaginal brush	Cervical brush	0.24
Garcia (2003) <sup>15</sup>	334	Vaginal brush	Cervical brush	0.50
Belinson (2003) <sup>24</sup>	8497	Vaginal brush	Cervical brush	0.49
Hillemans (1999) <sup>34</sup>	247	Vaginal brush	Cervical brush	0.66*
Nobbenhuis (2002) <sup>26</sup>	71	Cervicovaginal lavage	Cervical brush	0.53
		Cervicovaginal lavage	Cervicovaginal lavage	0.47
Morrison (1992) <sup>40</sup>	17	Cervicovaginal lavage	Cervicovaginal lavage	0.64*
Harper (1999) <sup>36</sup>	93	Tampon	Cervical swab	0.49
Coutlee (1997) <sup>37</sup>	224	Tampon	Cervicovaginal lavage	0.76
Fairley (1992) <sup>41</sup>	48	Tampon	Cervical spatula	0.70
Kim (2004) <sup>11</sup>	340	Pad	Cervical brush	0.96
Forslund (1993) <sup>39</sup>	343	Urine specimen	Cervical brush	0.54

\* Reviewer's calculation

There was considerable variation in how variables were measured and reported. Most often, participants were asked to select, rate, or rank either a method of collection (self vs. clinician) or factors associated with the method of collection. Collectively, the most commonly assessed factors were willingness to perform self-sampling, preference, and acceptability. These outcome measures are summarized in Table 6.

Six studies asked participants for their collection preference. Most found that self-collection was preferable to physician collection,<sup>20,23,26,32,34</sup> but in one study 63% of women did not have a strong preference.<sup>12</sup> Two studies compared the acceptability of self-collection and physician-collected methods, and found that both were acceptable to the women, although self-collection was rated higher on acceptability.<sup>23,32</sup> One study examined the willingness to

provide a self-sample compared with a clinician-collected sample, and found that participants were more willing to submit a self-sample (83% vs. 51%).<sup>31</sup> Others reported a high willingness to perform self-sampling in general,<sup>14,18,26</sup> at home<sup>12,23</sup> or in the clinic.<sup>25</sup>

Comfort and/or discomfort were examined in five studies.<sup>18,19,23,25,30</sup> One study<sup>18,19</sup> reported a mean discomfort score of 1.28 (1 = not bothersome; 5 = extremely bothersome) for self-collection using a tampon. The discomfort increased with the duration of exposure to the tampon. Dzuba et al. reported that 71% of 1069 women in the Morelos HPV Study reported some pain from self-sampling using a Dacron swab, but more women (95%) reported pain with a Pap test.<sup>23</sup> Thirteen percent of women interviewed in the study by Tisci et al. experienced pain with

**Table 6. Acceptability of self-collection for HPV testing**

Author (year)	Setting	Willingness to perform	Acceptability	Preference
Dannecker (2004) <sup>12</sup>	Internal medicine clinics (Germany)	97% willing to do at home	NR	23% self (brush) 14% clinician 63% no preference
Forrest (2004) <sup>14</sup>	Community sample (Britain)	93.5% willing to self-sample 95.5% willing as part of national screening program	NR	NR
Flores (2003) <sup>20</sup>	Screening program (Mexico)	NR	NR	68% preferred self-sampling 32% preferred Pap test
Tisci (2003) <sup>25</sup>	General public (China)	91% prefer to do test at clinic	49% believed other women would accept self-sampling	NR
Harper (2002) <sup>18</sup> (2002) <sup>19</sup>	Colposcopy clinic (USA)	97% willing to use tampon for annual screening 94% willing to use swab for annual screening (18)	63% expressed no concerns with tampon use for self-sampling 79% expressed no concerns with swab use for self-sampling (19)	NR
Dzuba (2002) <sup>23</sup>	Screening program (Mexico)	79% willing to do at home if health care worker delivered kit	Significant difference between acceptability score for self (21.7) vs. Pap (19.5)	68% self (swab) 32% clinician 4% no preference
Nobbenhuis (2002) <sup>26</sup>	Colposcopy clinic (Holland)	21% did not perform self-sampling	88% found self-sampling acceptable (i.e., easy)	23% Pap; 77% self (lavage)
Gravitt (2001) <sup>31</sup>	Study participant (USA)	83% agreed to submit a self-collected sample for HPV testing 51% agreed to have a clinician-collected sample taken for HPV test	NR	NR
Sellors (2000) <sup>32</sup>	Colposcopy clinic (Canada)	NR	98% urine sampling 93% vulvar sampling 88% vaginal sampling 79% physician sampling	Patient sampling ranking: 90% urine sampling #1 77% vulvar sampling #2 77% vaginal sampling #3 77% physician sampling #4
Hillemans (1999) <sup>34</sup>	Colposcopy clinic (Germany)	NR	NR	94% favoured self-sampling (brush) over physician

NR: data not reported.

self-sampling using a vaginal brush, and 12% reported bleeding.<sup>25</sup>

### What appeals to women with respect to self-sampling?

Four studies commented on what might appeal to women and on what they might not like about self-sampling.<sup>14,18,19,23,26</sup> Those who preferred having a Pap test performed by a physician overwhelmingly cited confidence in the procedure (93%) as the reason for their preference.<sup>23</sup> The most common explanation for women to prefer the

Pap test in one study was that they did not have a problem with gynaecological examinations or that the self-test was impractical.<sup>26</sup> Harper et al. found that vaginal dryness was the most common concern associated with self-sampling using a tampon<sup>19</sup> and that a minority (13%) were concerned about toxic shock syndrome. Of the 21% of women who were concerned about the use of a swab for self-sampling, most were afraid that the test would not be done properly or that the swab would break.<sup>19</sup> Participants in one study found that self-sampling was difficult with the lavage method.<sup>26</sup> The women indicated that they were unsure if a

sufficient quantity of fluid had been aspirated and questioned the efficacy of lavage as a method for self-sampling.<sup>26</sup> Forrest et al. found that a large percentage of women were concerned about doing the self-test properly (55%) and that this was particularly concerning for Indian (66%) and African-Caribbean (70%) women compared with white (33%) or Pakistani (49%) women.<sup>14</sup> However, most women (96.5%) did not believe that self-sampling was contrary to religious or cultural beliefs.<sup>14</sup> Dzuba et al. found that women reported more comfort (71%) and/or less embarrassment (55%) as reasons for preferring self-sampling.<sup>23</sup>

### **What are the characteristics of women who are interested in performing self-sampling?**

Two studies examined the impact of participant demographics on acceptability outcome measures.<sup>23,25</sup> Dzuba et al. reported that women in a higher income bracket were more likely to prefer the self-sampling method.<sup>23</sup> Tisci et al. found that better-educated women felt more comfortable performing self-sampling.<sup>25</sup>

In a third study of British women from four groups (Indian, Pakistani, African-Caribbean, and white), no significant difference was found between groups with regard to their willingness to perform the self-test.<sup>14</sup>

### **Will women who are never or seldom screened by clinicians perform self-sampling?**

Only one study targeted women who were never or seldom screened. In the study reported by Tisci et al., women were recruited from two counties in rural China and were eligible to participate only if they had not been screened for cervical cancer in the past 10 years.<sup>25</sup> The authors of that study examined a number of possible barriers to self-sampling. The most common barrier reported was that women did not know why HPV DNA testing was important (84.7%); however, other factors related to comfort, safety, cleanliness, fear, and understanding created potential barriers for a very small minority of women (0.4%–2.4%).

## **DISCUSSION**

Across the 25 studies identified, women were generally successful in collecting samples for HPV DNA testing, using a wide variety of self-collection techniques, including swabs, brushes, tampons, lavage, and pads. Where reported, the quality of the cytology in patient-collected samples was comparable with that of clinician-collected samples, but the agreement between HPV DNA test results from self-collected and clinician-collected samples was variable. Most of the studies reported on the sensitivity, specificity, positive predictive value, or negative predictive value of self-sampling; however, since the study designs varied, a wide range of sensitivity and specificity values were

observed among both patient- and clinician-collected samples.

There was considerable variability across studies regarding acceptability of self-sampling. Regardless of the outcome variable, women were quite positive about self-sampling. The majority of women were willing to perform self-sampling, did not find it difficult or painful, and preferred self-sampling to physician sampling. These positive results are tempered somewhat by the lack of rigour applied to developing measures to assess acceptability (e.g., questionnaires) and by the limited generalization of findings from the studies.

The characteristics of women who are interested in performing self-sampling have not been well studied. Two studies suggested that higher incomes and better education were associated with positive views about self-sampling.<sup>23,25</sup> Thus, one might speculate that these women would be more interested in performing self-sampling. However, neither of those studies directly assessed who was actually more interested in performing or more willing to perform self-sampling, because only consenting women participated. A third study examined the willingness to perform self-sampling across four ethnic groups and found high acceptability in all groups.<sup>14</sup>

Overall, the totality of the evidence suggests that self-sampling for HPV DNA testing is a viable screening option in under-resourced areas or for women who are reluctant to participate in clinician-led primary screening programs. The concordance between samples collected by patients and those obtained by clinicians is reasonably high, women in many countries across wide age ranges have successfully collecting samples for HPV DNA testing, the quality of the cytology from patient samples and clinician samples is similar, and women generally are positive about collecting their own samples.

HPV DNA self-sampling represents an important tool for reaching women who are never or seldom screened and who are at risk for cervical cancer. If HPV DNA self-sampling technologies were commercially available, a number of policy implications would arise. Logistical issues, such as dispensing tests, funding test analysis, informing women of confidential test results, and ensuring the provision of follow-up care, would need to be addressed. A sustained public education campaign would also be required to explain the significance of HPV and the implications of a positive test result to women and their health care professionals. Mechanisms would have to be in place to ensure that laboratories could receive samples from women directly.

Current Ontario screening guidelines recommend recall and follow-up to remind women and clinicians when a

woman is overdue for screening or when no treatment has been received after abnormal test results. The availability of self-sampling without a supportive infrastructure to include these essential components would not likely improve screening participation. Thus, if and when the self-test is commercially available, access to other related services must be ensured.

## CONCLUSION

Self-sampling of cervical cytology may play a key role in identifying women at risk of cervical cancer. Further definitive research, not just additional research, is needed to provide evidence that will address the use of self-sampling to increase screening participation, especially among the most vulnerable groups of women who are never or seldom screened.

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