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CYTOLOGY AND HPV TESTING IN DETECTION OF CERVICAL HIGH GRADE SQUAMOUS INTRAEPITHELIAL LESIONS

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Summary. The first organized national cytology screening program for detecting cervical lesions in Croatia was initiated at the end of 2012. This screening program is currently under review. The working proposal is to screen women aged 20–29 by cytology alone, those aged 30–34 by cytology and hrHPV cotesting, and woman 35–64 years old by high risk Human papillomavirus (hrHPV testing) without cytology cotesting. *The objective* is to contribute to the selection of cervical screening options among various possibilities in our population. *Methods:* We conducted a retrospective analysis of preceding cervicovaginal cytology and hrHPV test results in biopsy proven HSIL between January 1, 2016 and December 31, 2016. This included 143 HSIL cases from patients aged 18–85. *Results:* In detecting HSIL Pap test has been abnormal in 99% (142/143), and hrHPV test in 80% (115/143). The cytology, analyzed within one year prior to the HSIL biopsy, has reported ASC-H/HSIL in 87% (125/143) cases, whereas 12% (17/143) and 0.7% (1/143) have reported ASC-US/LSIL and negative respectively. The hrHPV negative test has been found in 13% (5/39) of the 20–29 age group, 21% (7/33) of the 30–34 age group, and 22% (15/68) of the 35–65 age group. *Conclusions:* Our data suggest that approximately 22% of analyzed woman in the 35–64 age group may be misdiagnosed for HSIL, when using HPV testing as the only cervical screening method. The widespread replacement of cytology by hrHPV testing should be subject to further investigation and given careful consideration.

Introduction

Cytology based screening for cervical cancer has significantly decreased both cervical cancer rates and mortality since its widespread implementation in high income countries in the early 1970s.[1–3] Cervical cancer screening detects preinvasive cervical lesions, allowing less harmful treatment possible before the disease becomes invasive, as well as detecting the invasive disease. Persistent human papillomavirus (HPV) infection is a crucial part of the causative pathway in cervical cancer pathogenesis and may be detected prior to development of preinvasive disease.[4]

Screening is performed using cervical cytology (Pap test) or a hrHPV (high risk Human papillomavirus) test, or by applying both of them.[5–7] The annual Pap test to screen for cervical cancer was the most successful cancer screening test ever developed.[8] The Pap test can be analyzed as a conventional Pap (CP) triple smear (vaginal/cervical/endocervical) or as a liquid based cytology (LBC) sample. In terms of cytology and hrHPV cotesting, the greatest LBC advantage is that the same sample can be used for both methods.[9] In Croatia, the vast majority of the Pap smears are CP due to lower cost. The LBC has been developed as an alternative to CP to improve specimen adequacy and increase the sensitivity for detecting relevant cervical abnormalities.[9,10] The results of the latter approach are, however disparate.[11,12]

In many countries with long term experience of organized cytology based screening an effort to prolong the screening interval and thus lower the burden on the health care system has been introduced.[13–15] Since hrHPV infection precede cervical epithelial abnormalities, the hrHPV detection can prolong the screening interval. The efficacy of prolonged human papilloma virus (HPV)-based screening has been documented in numerous studies.[5,16–22] However, some of the mentioned,[5,21,22] as well as additional studies[23,24] present data of hrHPV tested negative HSIL (high-grade squamous intraepithelial lesion) and invasive carcinoma cases. Despite these findings, in some national screening programs of high income countries primary hrHPV testing has been introduced for cervical cancer screening (Australia, New Zealand, Netherlands).[7] In most other high income countries, the national screening programs are still based on primary cytology or cytology (mostly LBC) and hrHPV cotesting with tendency to change to primary hrHPV testing in the close future.[6,7,25] In the United States of America (USA), the current American Society of Clinical Oncology (ASCO) 2016 recommendations are primary hrHPV screening for women aged 25–65 every 5 years,[26] whereas the newest 2018 American Cancer Society (ACS), the American Society for Colposcopy and Cervical Pathology (ASCCP), the American Society for Clinical Pathology (ASCP), the US Preventive Services Task Force (USPSTF), and the American College of Obstetricians and Gynecologists (ACOG) guidelines recommend primary cytology every 3 years for women aged 21–29, and for women aged 30–65 cytology and hrHPV cotesting every 5 years or cytology alone every 3 years.[27] The Japanese cervical cancer study concluded that the best strategy is cytology and hrHPV cotesting with HPV 16/18 detection.[28]

The first probationary program for cervical cancer screening in Croatia was performed more than half a century ago in one district of Zagreb.[29] Since that time, due to opportunistic screening, cervical cancer morbidity and mortality in Croatia have been significantly decreased. Although a significant number of women regularly perform a gynecologic exam and a Pap smear once per year, as has been recommended, there is still an unknown but not negligible proportion of the population that remains unscreened.[30] The first organized national cytology based screening program for detecting cervical cancer in Croatia started at the end of 2012.[31] Due to many problems, this program is under review, being placed on hold.[32]

The newest Croatian working proposal for cervical cancer screening involves women aged 20–29 by cytology alone, those aged 30–34 by cytology and hrHPV cotesting, and only by hrHPV testing for those aged 35–65.[33]

Material and Methods

Histopathologic diagnoses refer to the interpretation of surgical pathology specimens, including cervical biopsies, endocervical curettage specimens, and/or diagnostic, excisional procedures using loop electrosurgical excision procedures or cold knife cervical conisation. HSIL diagnoses included cervical intraepithelial neoplasia (CIN) grade 2 and 3 (CIN2, CIN3) as well as and descriptive CIN due to damaged tissue, but suggesting HSIL.

In our study, 143 cases of histology proven HSIL with available both preoperative Pap and hrHPV tests results have been included. In particular, we have examined the available preoperative Pap test results and the hrHPV testing results in the Hospital database for all cases.

The last Pap test has been a conventional cervical smear analyzed mostly in our laboratory and the results have been reported in a form known as "Zagreb 2002".[34] For cytologic-histologic correlation we considered Pap smears taken within 4 months and up to one year prior to a biopsy were supplemented with concomitantly collected ones, unless there was no Pap test preceding to biopsy in that interval.[35]

The analysis is complemented by the Pap smears recorded in our Hospital database for the period from one to five years prior to biopsy. In this context in terms of two-tiered terminology (LSIL/HSIL),[4,36] negative cytology is considered major undercall, ASC-US and LSIL (ASC-US/CIN1) minor undercall, whereas ASC-H and HSIL (ASC-H/HSIL) as agreement.[37]

The hrHPV tests have been performed in our and other institutions, within the period of up to three years prior to histology diagnosis. Mostly, the hrHPV detection method has not been recorded in the Hospital database, so differences between methods couldn't be separately analyzed.

Results

Age distribution

The mean age for all 143 HSIL lesions has been 36,5 (median 34; range 18–85). For the 13 cases of CIN2, the mean age has been 29.5 (median 28; range 20–47); for the 113 cases of CIN3, the mean age has been 36,0 (median 34; range 18–65); and for the 17 descriptive CIN cases, the mean age has been 43.2 (median 37; range 27–85).

Cytologic-histologic correlation

The last cytology predicted CIN2 has been confirmed histologically as CIN2 in 69% (9/13) of cases, whereas in 31% (4/13) of cases the cytology predicted CIN1 instead. Regarding histological confirmed CIN3, the cytology predicted CIN3 in 70% (79/113) of cases, whereas the other results were classified as CIN2 in 17% (20/113) of cases, CIN1 in 8% (9/113) of cases, ASC-US in 4% (4/143) of cases and one negative case Pap test (0.7%;1/143) *(Table 1.)*.

Table 1. Last prior Pap smear results compared to histology diagnosis

Cytology	Histology			
	CIN2		CIN3	
	No.	%	No.	(%)
Negative			1	0.9*
ASC-US			4	3.5
CIN1	4	30.8	9	7.9
CIN2	9	69.2	20	17.8
CIN3/ASC-H			79	69.9
Total	13	100	113	100

CIN1 – cervical intraepithelial neoplasia gradus 1; CIN2 – cervical intraepithelial neoplasia gradus 2; CIN3 – cervical intraepithelial neoplasia gradus 3; ASC-US – atypical squamous cells of undetermined significance; ASC-H – Atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion. * CIN3 on cervical polyp

Prior PAP test results according to the time prior the biopsy

The cytology, analyzed within one year prior to HSIL biopsy, has predicted ASC-H/HSIL in 87% (125/143) of cases, while 12% (17/143) and 0.7% (1/143) have been reported as ASC-US/LSIL and negative respectively.

In the period of one to three years prior to histological diagnosis of HSIL 39 Pap results have been accessible and reported as: ASC-H/HSIL 67% (26/39), ASC-US/LSIL 18% (7/39) and negative15% (6/39). For the period of three to five years of 29 available Pap test the reports have been: ASC-H/HSIL 34% (10/29), ASC-US/LSIL 24% (7/29) and negative 42% (12/29).

Prior hrHPV test results

The hrHPV test result have been negative for 20% (28/143) of HSIL biopsies. According to CIN2, CIN3 and descriptive CIN hrHPV test was negative in 15%

Table 2. Prior Pap smear results according to time

Time preceding biopsy, years	Negative		ASC-US/LSIL		ASC-H / HSIL		Total	
	No.	%	No.	%	No.	%	No.	%
< 1	1	0.7	17	11.9	125	87.4	143	100
1–3	6	15.4	7	17.9	26	66.7	39	100
3–5	12	41.4	7	24.1	10	34.5	29	100

HSIL – high grade intraepithelial lesion; ASC-US – atypical squamous cells of undetermined significance; LSIL – low grade intraepithelial lesion; ASC-H – atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion.

Table 3. Prior hrHPV test according to histopathologic diagnosis

	Descriptive CIN		CIN2		CIN3		Total	
	No.	%	No.	%	No.	%	No.	%
HPV+	13	76	11	85	91	81	115	80
HPV–	4	24	2	15	22	19	28	20
Total	17	100	13	100	113	100	143	100

Descriptive CIN – descriptive histopathologic diagnosis due to damaged tissue, but suggesting HSIL;CIN2 – cervical intraepithelial neoplasia gradus 2; CIN3 – cervical intraepithelial neoplasia gradus 3; HPV+ – hrHPV (high risk human papillomavirus) test positive; HPV– – hrHPV test negative

Table 4. hrHPV test according to the age

Age	HPV+		HPV–		Total N
	No.	%	No.	%	No.
< 20			1	100	1
20–29	34	87	5	13	39
30–34	26	79	7	21	33
35–65	53	78	15	22	68
>65	2	100			2
Total	115	80	28	20	143

HPV+ – hrHPV (high risk human papillomavirus) test positive; HPV– – hrHPV test negative

(2/13), 19% (22/113) and 24% (4/17) respectively *(Table 3.)*.

Prior hrHPV test results according to the age

The hrHPV test has been analyzed according to the age of patient as well. The hrHPV negative test has been found in 13% (5/39) of the age group 20–29, 21% (7/33) of the age group 30–34, and 22% (15/68) of the age group 35–65. Both women older than 65 were hrHPV positive, and one 18 years old was hrHPV negative *(Table 4.)*.

Discussion

Cervical cytology has reduced morbidity and mortality in the last 70 years significantly worldwide, but its limitations are well known.[5,36,38] Due to direct relationship between hrHPV infection and cervical carcinogenesis, it has been demonstrated that hrHPV infection is a necessary condition for the development of pre/invasive and invasive cervical cancer.[4] As hrHPV types are detected in more than 99% of invasive cancer cases and in the vast majority of high grade preinvasive cases, HPV detection may be a reasonable alternative as a screening test for the detection of precursor lesion that would progress to cancer if not treated.[5,16,26] The superior sensitivity of hrHPV testing is established in the literature, but there are variations in performance depending on the hrHPV method used and the study population.[39,40]

Cytologic-histologic correlation

Among the 143 patients with HSIL histological diagnosis the latest conventional Pap smear has been abnormal in all but one case, 99.3% (142/143). Abnormal cytology reports have been CIN3 or ASC-H (87%; 125/143), CIN2 (23%;33/143), CIN1 (9%;13/143), and ASC-US (4%;4/143) cases.

Regarding the cytologic-histologic correlation, the 69% (9/13) CIN2 has been correctly predicted by cytology, while 31% (4/9) were underdiagnosed as CIN1. There have been no negative Pap smears, nor overdiagnosed cases in this group. Pajtler et al.,[38] correctly predicted only 30% (8/27) of CIN2, while 22% (6/27) were underdiagnosed as CIN1, and 48% (13/27) were overdiagnosed as CIN3. Al-Nafussi et al.[41] similar to Pajtler et al.[38] correctly predicted CIN2 in 35% (103/292), and CIN1 in 22% (63/292), but 15% (45/292) were negative Pap reports, 9% (25/292) borderline and 19% (56/292) CIN3.[41]

According to our results, the histologic CIN3 has been correctly predicted in 70% (79/113) by cytology, whereas 17% (29/113) were underdiagnosed as CIN2, 8% (9/113) as CIN1, 4% (4/113) as ASC-US and 0.7% (1/143) as negative report. The single negative case involves a woman with cervical polyp, with the Pap smear that has been concomitantly collected with a polyp biopsy. The histopathology report was CIN3 on the part of the endocervical polyp, while further cone biopsy has been negative for epithelial abnormalities. The Pap slide has been reviewed and no abnormalities have been

found. However, this negative slide should be excluded according to recommendations, but this one was the only Pap smear available for analysis.[35] Pajtler et al. reported 90% (233/258) cytologic accuracy for CIN 3, while underdiagnoses were made as CIN2 and CIN1 in 6% (16/258) and 3% (7/258) of cases respectively, and 1% (2/258) were overdiagnosed as carcinoma.[38] Al-Nafussi et al. confirmed CIN3 correctly in 46% (178/383), whereas the negative Pap reports were in 2% (9/383), underdiagnosed as borderline, CIN1 and CIN2 in 7% (25/383), 14% (52/383), and 31% (119/383) respectively.[41]

The World Health Organization (WHO) introduced the two-tiered system for lower anogenital tract terminology (LAST).[4,42] Nevertheless, new studies confirm the well known fact that CIN2 can regress spontaneously, especially in young women.[4,43,44] Our results present a rather minor proportion of underdiagnosed CIN2 and CIN3 cases as well as Pajtler at al.[38] Therefore, retaining subclassification within three tiered system seems fully justified, allowing individual approach that is of particular importance for young women planning pregnancy due to possible opstetric complications.[45–47]

Prior PAP test results according to the time prior the biopsy

Reports of our last cytology within one year prior to HSIL biopsy have predicted ASC-H/HSIL in 87% cases, ASC-US/LSIL in 12% cases, with one additional negative case. Comparing to our results, four months prior to diagnostic biopsy, Zhao et al., among 2074 patients with LBC Pap test found 55% (1150/2074) ASC-H/HSIL, 44% (909/2074) ASC-US/LSIL cases, and a few cases (1%;15/2074) of atypical glandular cells/adenocarcinoma in situ (AGC/AIS).[24]

For more than a year prior to biopsy, data of Pap smears are limited in our Hospital database. Namely, most of the women have been previously followed at their primary care gynecologists, and their Pap smears have been analyzed in different laboratories. There were only 39 available Pap smears one to three years prior to biopsy reporting 67% (26/39) ASC-H/HSIL, 18% (7/39) ASC-US/LSIL whereas 15% (6/39) were negative. In similar period Zhao et al.[24] found among 1488 patients, 11% (166/1488) HSIL, 45% (673/1488) ASC-US/LSIL, few AGC whereas 34% (510/1488) were negative. In the ARTISTIC trial[19] during three year follow up, for histology proven HSIL lesions the baseline Pap has been 55% (250/454) HSIL, 38% (171/454) ASC-US/LSIL and 7% (33/454) negative. In the POBASCAM trial[18] during the same follow up, for histology proven HSIL the baseline cytology has been 47% HSIL (120/255), 25% (64/255) ASC-US/LSIL and 21% (70/255) negative.

In the period three to five years prior to biopsy, 29 Pap results were available in our Hospital database reporting 34% (10/29) ASC-H/HSIL, 24% (7/29) ASC-US/LSIL with 42% (12/29) negative reports. The largest comparable study is provided by Kaiser Permanente[5] on more than 330.000 women aged 30 and above, screened using conventional Pap smears. For 2223 patients with histology confirmed HSIL, baseline cytology (up to 5 year prior diagnosis) involved 18% (409/2223) ASC-H/HSIL, 33% (720/2223) ASC-US/LSIL and 74% (1041/2223) negative.[5] Almost 200.000 women have been double negative Pap and hrHPV at enrollment, so that the second cotesting was performed up to three years after the enrolment. The HSIL have been detected in 333 cases: the second Pap smear has been 15% (49/333) ASC-H/HSIL, 54% (179/333) ASC-US/LSIL and 28% (94/333) negative reported.[5] Our study, as well as the others, strongly confirm that more negative Pap smears are detected as the period prior to biopsy is increased.

Prior hrHPV test results

In our study the hrHPV testing prior to histologically proven HSIL was negative in 20% (28/143) cases. Zhao et al.[24] in the period of 4 months to three years before HSIL biopsy identified 24% (110/454) hrHPV negative test, similar to the Kaiser Permanente study[5] with 20% (455/2223) baseline hrHPV negative tests, as well as 19% (65/333) in the second hrHPV testing (in baseline double negative women). In the last published Kaiser Permanente results 16.1% (1602/9975) negative hrHPV tests were preceding biopsy proven CIN3.[21] In contrast, the POBASCAM[18] trial as well as ARTISTIC trial[19] presented lower hrHPV negative rates preceding HSIL biopsy, with 9% (23/255) and 7% (31/454) respectively.

Prior hrHPV test results according to age

Following European recommendations for cervical cancer screening[6] the newest proposal of the Croatian working screening group suggest that primary hrHPV screening should be for the age group 35–65 years. However, the highest rate of negative hrHPV tests (22%;15/68) were found in this group. Similarly, in the age group of 30–35 and proposed screening by Pap and hrHPV cotesting, high number of hrHPV negative cases has also been found (21%;7/33). In the age group 20–29 the lowest rate of negative hrHPV tests (13%; 5/39) confirm the recommended proposal. Similar results for the younger age are presented in in histologically confirmed HSIL in the multicentric study of Castellsauge et al.[48]

Conclusion

Cytology in Croatia is well recognized as a method of cervical cancer screening[30] and the results presented herein confirm its reliability. Indeed, this research is suggestive that the possibility of the widespread replacement of cytology by hrHPV testing, should be subject to further investigation (such as a pilot study) and given careful consideration. Furthermore, in the context of potentially implementing hrHPV testing as the primary tool in the national organized cervical cancer

screening program in Croatia, the reliability of the different methods used for the detection of hrHPV should be established, since performance may vary between tests and countries. The reasons for hrHPV negative HSIL cases are often unclear and have been attributed to low viral load, inadequate sampling of infected cervical lesions, interfering substances, rare HPV genotypes, as well to a subset of the true non-HPV driven HSIL cases.[23] Further investigation and larger sample size is necessary to distinguish between these possibilities.

Overall, the primary task for cervical cancer prevention is to integrate as many women as possible into the nationally organized screening program. In this respect, the establishment of a national computerized database of clinic (colposcopic findings) and laboratory (cytology, histology and hrHPV) records would prove especially useful.

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CITOLOGIJA I HPV TESTIRANJE U OTKRIVANJU INTRAEPITELNIH PROMJENA VRATA MATERNICE VISOKOG STUPNJA

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Ključne riječi: Papanicolaou test; humani papilomavirus; cervikalna intraepitelna neoplazija; probir na karcinom cerviksa

Sažetak. Citološki probir ranog otkrivanja raka vrata maternice značajno je smanjio morbiditet i mortalitet od ove bolesti zadnjih pedesetak godina širom svijeta, a naročito u razvijenim zemljama koje već desetljećima provode sustavni nacionalni probir i imaju dostupne nacionalne baze podataka prethodnih citoloških, kolposkopskih, mikrobioloških i patohistoloških nalaza. Najvažniji cilj probira je otkrivanje rizične populacije prije nastanka invazivne bolesti kako bi liječenje bilo što manje invazivno. To je posebno važno zbog činjenice da često obolijevaju žene reproduktivne dobi koje još planiraju trudnoću. Boljim razumijevanjem karcinogeneze i uloge infekcije humanim papilomavirusom visokog rizika (hrHPV) razvijeni su komercijalni testovi za otkrivanje ove infekcije i prije razvoja epitelnih promjena. Time je dodatno omogućeno produljenje vremenskog intervala probira. Hrvatski nacionalni program ranog citološkog otkrivanja raka vrata maternice pokrenut je nakon višedesetljetnih priprema krajem 2012., ali se zbog određenih nedostataka trenutno revidira. Trenutni prijedlog pilot programa predviđa citološki probir žena dobne skupine 20 do 29 godina, kotestiranje citologijom i hrHPV testa žena od 30 do 34 godine te primarno hrHPV testiranje žena od 35 do 65 godina.

Cilj ovog rada je doprinijeti izboru najbolje opcije za rani probir raka vrata maternice u Hrvatskoj.

Materijali i metode. U ovom retrospektivnom istraživanju analizirali smo dostupne podatke iz bolničkog informatičkog sustava (BIS) za žene kojima je tijekom 2016. godine u našem patohistološkom laboratoriju rađena analiza promjena vrata maternice. Izdvojene su 143 žene s patohistološkom dijagnozom intraepitelne promjene vrata maternice visokog stupnja (eng. HSIL) i dostupnim prethodnim nalazima citologije i hrHPV testiranja.

Rezultati. Prosječna dob žena bila je 36,5 godina s rasponom od 18 do 85 godina. Citološki nalaz predvidio je cervikalnu intraepitelnu neoplaziju CIN2 kod 69% (9/13) te CIN3 kod 70% (79/113) histoloških dijagnoza CIN2 i CIN3. U vremenskom razdoblju do godinu dana prije biopsije, citološki nalaz je bio abnormalan kod 99,3% (142/143) žena, u 12% (17/143) slučajeva atipične stanice skvamoznog epitela neodređenog značenja (eng. ASC-US) ili skvamozna intraepitelna neoplazija niskog stupnja (eng, LSIL) te u 87% (125/143) slučajeva skvamozna intraepitelna neoplazija visokog stupnja (eng. HSIL) ili atipične stanice skvamoznog epitela – ne može se isključiti HSIL (ASC-H). U vremenskom razdoblju od jedne do tri godine prije biopsije citološki nalaz je bio abnormalan kod 85% (33/39) žena, u 18% (7/39) slučajeva atipične stanice skvamoznog epitela neodređenog značenja (eng. ASC-US) ili skvamozna intraepitelna neoplazija niskog stupnja (eng, LSIL) te u 67% (26/39) slučajeva skvamozna intraepitelna neoplazija visokog stupnja (eng. HSIL) ili atipične stanice skvamoznog epitela – ne može se isključiti HSIL (ASC-H). U vremenskom razdoblju od tri do pet godina prije biopsije citološki nalaz je bio abnormalan kod 59% (17/29) žena, u 24% (7/29) slučajeva atipične stanice skvamoznog epitela neodređenog značenja (eng. ASC-US) ili skvamozna intraepitelna neoplazija niskog stupnja (eng, LSIL) te u 35% (10/29) slučajeva skvamozna intraepitelna neoplazija visokog stupnja (eng. HSIL) ili atipične stanice skvamoznog epitela – ne može se isključiti HSIL (ASC-H). hrHPV test rađen unutar tri godine od biopsije bio je abnormalan u 80% (115/143) slučajeva. Prema dobnim skupinama hrHPV test je bio negativan u grupi 20 do 29 godina u 13% (5/39) slučajeva, u grupi 30 do 34 godina u 21% (7/33) te u grupi 35 do 65 godina u 22% (15/68).

Zaključak. Citologija je prepoznata kao dobra metoda probira raka vrata maternice posebno u Hrvatskoj gdje je ta grana medicine vrlo razvijena. Prikazani rezultati potvrđuju pouzdanost i dijagnostičku točnost ove metode. Prije prijelaza na primarni hrHPV probir trebalo bi napraviti dobro definiranu pilot studiju koja uključuje kotestiranje. Pažljivo treba razmotriti koja metoda hrHPV tipizacije bi se uključila u primarni probir, jer različite metode u različitim sredinama nemaju iste rezultate. hrHPV negativni slučajevi HSIL-a kao i invazivnog karcinoma vrata maternice opisani su u brojnim radovima u literaturi, a najčešće se objašnjavaju kao: neadekvatno uzet uzorak za tipizaciju, malen broj čestica virusa u uzorku, onečišćenje uzorka tvarima koje ometaju analizu kao i malom broju zaista hrHPV negativnih slučajeva. Najvažniji cilj organiziranog nacionalnog probira je uključivanje što više žena u takav program. Da bi se to postiglo važno je uspostaviti nacionalnu bazu podataka koja uključuje citološke nalaze, rezultate hrHPV tipizacije uključujući točno korištenu metodu, kolposkopske te patohistološke nalaze.