Acceptability of HPV self-sampling for cervical cancer screening in an indigenous community in Guatemala

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Abbreviations Used: HPV, human papilloma virus; LMIC, low to middle income countries; PAHO, Pan-American Health Organization; PR, prevalence ratio; STD, sexually transmitted disease; VIA, visual inspection with acetic acid; WHO, World Health Organization

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Abstract

Objective: Cervical cancer rates in Latin America are higher than those in developed countries, likely due to lower prevalence of screening. Specifically, less than 40% of women in Guatemala are regularly screened; fewer in indigenous communities. Current screening strategies, Pap smears and Visual Inspection with Acetic Acid (VIA), might not be the most effective methods for controlling cancer in these settings. We thus investigated the potential of self-collection of cervical samples with human papillomavirus (HPV) testing for prevention in an indigenous community in Guatemala.

Methods: A community representative random sample of 202 indigenous women aged 18-60 residing in Santiago Atitlan, Guatemala, were surveyed to assess knowledge of and risk factors for HPV and cervical cancer. Women were then invited to self-collect a cervical sample using HerSwab collection kits to assess HPV prevalence and acceptability of self-sampling.

Results: Of 202 women who completed the survey, 178 (89%) provided a self-sample. 79% of these women found the test comfortable, 91% easy to use, and 100% reported they were willing to perform the test periodically as a screening method. Thirty-one (17%) samples were positive for at least one of 13 high-risk HPV types, and eight (4.5%) were positive for HPV 16/18.

Conclusions: Self-collection HPV testing was well accepted, suggesting it is a plausible modality for cervical cancer screening in indigenous communities. Further studies are needed to assess rates of follow-up after a positive test, and determine if these findings extend to other indigenous and non-indigenous communities in Guatemala and Latin America.

Introduction

Cervical cancer (CC) is preventable with appropriate screening and treatment. Pap smears, the most common form of screening, allow physicians to detect and manage pre-cancerous lesions before they develop into CC[1].

Due to the success of Pap screening programs, CC rates are low in most high-income countries[2,3]. Nonetheless, CC is the third most common cancer worldwide and a leading cause of death among women in low- and middle-income countries (LMICs)[4]. Unfortunately, Pap smears are infrequently used in LMICs because they are expensive and require physicians, pathologists, and cyto-technicians to perform the procedure and interpret results[3,5]. Even in LMICs with screening programs, rates of participation tend to be low[6] since Paps must be collected and analyzed at hospitals or other high-resource health facilities that women may not have access to. Additionally, if women have abnormal results, they must return for follow-up assessment/treatment, which creates greater time and financial burdens[7]. The logistics of sample collection by healthcare providers, which then must be sent to labs, tested, and returned, can also be challenging in these settings. There are also cultural barriers that preclude the use of screening methods associated with sexually transmitted diseases (STDs).

Hence, many LMICs have adopted CC screening programs using visual inspection with acetic acid (VIA). VIA involves placing acetic acid on the cervix and looking for a change in color to detect lesions. This procedure is less costly and invasive than Paps, and can be performed by trained laypersons in low-resource health facilities[7–9]. Additionally, VIAs give the option to treat women with cervical lesions immediately. Thus VIA is often called a "see/screen-and-treat" or "one-visit" approach[7]. Previous studies have shown that VIA screening helps reduce CC incidence and mortality in low-resource settings[8]. However, VIA shares some of the

same barriers associated with Paps, so despite these efforts, CC incidence and mortality remains high in many LMICs, presumably because of persistent low rates of screening with either approach.

Human papilloma virus (HPV) infections are responsible for over 90% of CC cases[10,11]. There are 13 types of high-risk HPV associated with CC development[12]. Of these, types 16 and 18 account for approximately 70% of all cases[13]. Cervical HPV tests have high sensitivity (~90%) and specificity (>80%)[14,15]. Women who test positive for high-risk HPV should follow-up with a Pap/VIA or treatment, depending on each country's setting and resources[16], but a negative test means the risk of developing CC in the next few years is minimal; lower than the risk after a negative Pap[17]. Furthermore, when Paps are performed only on women who have tested positive for HPV, the relatively low sensitivity of Pap screening is significantly improved[15,18]. Thus, primary screening for high-risk HPV before referral for Pap/VIA has been proposed as an alternative CC screening method. Unfortunately, HPV testing is expensive and requires infrastructure not readily available in many LMICs. Nonetheless, research is underway to develop low cost HPV tests that can be used with minor infrastructure requirements[19–23].

Self-collection HPV kits have been developed to allow women to collect their own cervicovaginal samples at home and send these to a testing facility through mail or other means. Studies in multiple countries have compared accuracy of HPV self-collection with physician samples, and have assessed the acceptability of self-collection in different populations[5,24–30]. Some studies have provided women with self-collection kits, but at medical facilities prior to physician-collection rather than at the woman's home. In these studies, self-collection has been shown to have similar sensitivity as physician collected samples[5,24–28], and self-collection has been found to be highly acceptable in many settings[24,26–28,31]. This suggests that self-collection

could be helpful to increase CC screening rates in LMICs, once cost- and infrastructure-efficient HPV tests have been developed. However, few studies have provided participants with the opportunity to try these in community settings outside of medical facilities; thus it is not clear if they would be an accepted form of primary CC screening.

Guatemala presents one of the highest levels of CC morbidity and mortality in the region. Age-standardized annual incidence and mortality rates are 22.3 and 12.5 per 100,000 women, respectively[11], largely because less than 40% of Guatemalan women (who have a relatively high prevalence of HPV[36–38]) have ever been screened for CC[6,39]. There have been self-collection studies conducted in Latin America, a region where CC morbidity and mortality are particularly high[5,32–35], although few have tested the acceptability of HPV self-collection in community rather than clinical settings. Moreover, HPV self-collection has not been studied in indigenous populations in Latin America, who tend to have less access to health facilities and higher levels of stigma associated with physician administered vaginal and STD tests[40]. Thus, it is important to assess the acceptability of HPV self-collection kits/tests, and determine the potential of HPV testing as a screening modality in these settings[33]. We thus conducted a cross-sectional study in an indigenous population in Lake Atitlan, Guatemala to assess knowledge of HPV and cervical cancer, provide women with the opportunity to collect a self-sample in their home and report their feelings and experiences, and assess HPV prevalence in indigenous populations.

Methods

We conducted a cross-sectional study in Santiago Atitlan, an indigenous community of 45,000 residents in Guatemala. Data was collected using electronic surveys and self-collection kits.

Study Population

This community is almost exclusively Tz'utujil, a Mayan indigenous group. We sampled 212 women, ages 18-60, from nine neighborhoods that encompass 85% of the population of Santiago Atitlan. Population data were obtained from the local municipality. We followed a stratified sampling approach: first allocating samples of size N_c to each neighborhood according to their relative population size ($c=1,...,9$), then randomly selecting a sample of N_c blocks. One house was randomly selected per block, where one woman was interviewed.

If more than one woman in a house was eligible, the woman who had the next upcoming birthday was selected. Only women ages 25 to 54 were eligible to provide a self-collected sample for HPV testing, since women outside of these ages are not eligible to receive Pap/VIA screening according to Guatemalan CC screening guidelines. Menstruating and pregnant women were also excluded from self-collection. We chose to interview women outside of the screening range because, while the focus of the study was on acceptability, we were interested in learning about the health practices and risk factors for all adult women.

Survey

The survey component was designed using the Qualtrics application. It included 143 questions about demographics, preventative health care practices, and HPV and CC knowledge and risk factors. The survey also assessed the acceptability of and feelings towards HPV self-collection. Questions were developed using the STEPS survey, UNC's Family Health Study Survey, and University of Michigan's MHOC study[39,41]. Four trained community health workers (CHWs) fluent in Tz'utujil and Spanish conducted the surveys.

The survey was written in English and then translated to Spanish by native speakers from the study team. The survey was piloted in Guatemala City and in households in Santiago Atitlan. After each pilot, surveyor notes were reviewed and appropriate revisions were made.

At the end of each day, surveys were uploaded to the server, ensuring that the participant's data could no longer be accessed, except by members of the study team.

HPV self-collected samples

We used EveMedical HerSwab self-collection HPV kits. Each kit came with an "Instructions" card written in Spanish with step-by-step infographs explaining the collection process. The CHWs were trained on the procedure and how to explain the instructions to the participants in their native language.

Upon interview completion, each eligible participant was asked about her interest in collecting a sample for HPV testing. If the participant agreed, the CHWs explained the instructions and the participant collected a sample in a private room in the household. The collection kit was comprised of a plastic handle and brush. The woman inserted the brush into her vagina and then turned a crank on the handle to extend the brush. The woman then removed the brush and cranked it back using handle. She then returned the kit to the CHWs. Afterwards, each participant was asked a 5-question survey assessing the level of ease and comfort associated with the collection, and her willingness to self-collect periodically as a form of CC screening. Finally, CHWs encouraged participants to attend free VIA screening clinics at their local public hospital.

Samples were sent for testing to an independent, non-profit laboratory in Guatemala City (Asociación de Salud Integral) and tested using the Anyplex II[42] HPV-28 kit, which tests for 13

high-risk HPV types according to the IARC classification[12], as well as 15 low-risk types (appendix).

To ensure the privacy and confidentiality of the participant's information, given the sensitivity of the survey questions and the HPV test, no contact information was collected in this pilot study, thus participants could not be contacted by the study team with their results. Instead, participants were told to call for their results 10 days after collection using an identification number. Announcements were made daily on the local radio for one month after the end of recruitment reminding women to call for their results. Participants were only informed if they tested positive for one of the 13 high-risk types.

Statistical Analyses

Post-self-collection survey questions were analyzed to determine the acceptability of HPV self-collection as a form of CC screening.

Two additional outcomes were analyzed: positive HPV result and previous Pap/VIA. Crude comparisons between these and relevant covariates were run using log-binomial regression, and then models were run adjusting for other covariates. Statistical analyses were conducted using SAS® software Version 9.4[43].

Human Subjects Approval

The University of Michigan IRB (HUM00096559) approved study protocols. All participants gave oral, informed consent prior to participation. The consent was documented by signature from one of the CHWs.

Results

Of 481 women who were asked to participate, through door-to-door recruitment, 212 women enrolled (44% acceptance rate), with 202 (95%) completing the survey. 10 women chose to withdraw and their data was destroyed. Participants' mean age was 34.5 years, and over 80% had at most primary education (Table 1). 135 women (67%) reported previous CC screening with Pap/VIA (Table 1). Women with previous Pap/VIA tended to be older, married and with a higher number of children and pregnancies, suggesting that access to screening is strongly tied to reproductive care. While only 31 (15%) participants reported previous knowledge of HPV, 188 (93%) were interested and willing to collect a self-sample for HPV testing (Table 2). Of these, 178 (88%) were eligible and provided a sample.

Self-Collection Acceptability

Of these 178 women, 79% found the kit comfortable and 91% found it easy to use. Upon collection 100% reported they were willing to use the test periodically as a form of CC screening, and over 80% said they preferred to screen themselves at home rather than with a physician in a doctor's office (Tables 2 and 3). Since identifying information was not collected, the study team was unable to actively return results, however over 90% of participants called to receive these.

HPV Prevalence

37 of 178 women (21%) tested positive for one of 28 types of HPV, and 31 (17%) tested positive a high-risk type (table 3).

HPV 16 had the highest prevalence, with 7 women testing positive, followed by HPV 53 and 56 (6 positive for each), and HPV 59 (5 positive). Of the 4 strains with the highest prevalence, all except HPV 53 are high-risk. Figure 1 shows the HPV type distribution in the study population.

HPV Infection

The number of lifetime sexual partners was significantly higher in women testing positive for HPV. Characteristics comparing women by HPV test results can be found in table 4, while characteristics comparing women by the number of sexual partners can be found in the appendix. Exposure covariates in the final model include current age, level of education, age at first pregnancy, and at first sexual encounter. Other covariates explored include age at marriage and other demographic factors.

After adjustment, the association became not statistically significant, but did show a prevalence ratio greater than one (crude PR = 2.18, CI: 1.07, 4.43, p = 0.03, adjusted PR = 1.42, CI: 0.68, 2.97, p = 0.34) (regression tables are shown in the appendix).

Previous Screening

The use of health services was statistically significantly higher in women with previous Pap/VIAs. Characteristics comparing women with and without a history of screening can be found in table 5, while characteristics comparing women by use of health services can be found in the appendix. The final adjusted model included age and education level, as well as the HPV test results. The participants' use of alcohol, as well as other demographic factors, were considered but not included in the final model.

After adjustment, the association between use of health services and previous Pap/VIA remained greater than 1, but was no longer significant (crude PR = 2.49, CI: 1.26, 4.93, p = 0.009, adjusted PR = 1.24, CI: 0.93, 1.66, p = 0.15) (regression tables are shown in the appendix).

Discussion

We assessed the acceptability of HPV self-collection as an alternative to Pap/VIA screening in an indigenous community in Latin America. We found that self-collection kits had high acceptability, were largely preferred to physician screenings, and a majority of women found it comfortable and easy to use. We found a 17.4% prevalence of high-risk HPV, which is consistent with previous studies reporting a 16.1% prevalence for Latin America[44]. We also investigated risk factors for HPV infection and previous Pap/VIAs; associations that became non-statistically significant after adjustment for other covariates. This could be due to inconsistencies with self-reporting, or perhaps because partner's sexual history, which was not assessed, might be a stronger determinant of HPV risk in this community.

This study was intended to serve as a first-step to determine the potential of HPV screening in indigenous populations, and also to provide baseline data for future longitudinal studies assessing the efficacy of HPV testing versus other screening modalities. Perhaps the most relevant finding is the high acceptability of self-collection, and the willingness of the participants to engage in the study. In fact, 95% of participants completed the survey, 93% were interested in collecting self-samples and over 90% called to receive their results, numbers higher than expected. The study was very well received in the community, with strong support from

local and health authorities, suggesting the potential to eventually implement HPV screening programs in this and other similar settings.

Strengths of the study include the multi-clustered community design, allowing us to obtain a representative sample of the population, as well as the opportunity for participants to try self-collection in their homes, rather than at a clinic, and the participation of local CHWs that performed recruitment and interviews. Because of the later, interviews were conducted in the participants' native language, potentially making them more comfortable answering sensitive questions. Additionally, data was collected electronically eliminating the risk of manual data entry errors. However, there are also important limitations. Given the cross-sectional design, participants might have misreported their history of screening and other risk factors, especially if there have been community educational programs or interventions that have suggested that women should be screened for CC. Women may not have accurately remembered if they had Pap/VIAs (recall bias), or may not even be aware if these procedures have been performed on them. Another limitation is that we were unable to assess if HPV positive women followed-up on their results. This is the topic of current work that we are conducting in multiple communities in Guatemala with a new study population that will be followed up after 6-months and 1 year. Additionally, this community has been exposed to prior health interventions and studies from multiple institutions[45–47]. While these studies did not specifically discuss HPV and CC, the exposure to health interventions could be reflected in the women's knowledge of health issues and their willingness to try self-collection. In the future it will be important to assess the acceptability of these tests in other indigenous communities with less exposure to studies and interventions.

The study results are consistent with previous studies conducted in Asia and Africa on acceptability of self-screening for HPV[25,27,29]. However, this is the first to assess self-collection in indigenous populations in Latin America. This is also one of the first studies to provide participants with the opportunity to collect a sample in a community setting, rather than simply sharing their feelings towards self-collection, or collecting at a clinic.

This work assessed the acceptability of HPV self-screening in one community in Guatemala. Guatemala is a country with 23 languages and even more distinct communities, so our findings cannot be generalized to the whole population. It will be important to attempt to replicate the study in other parts of Guatemala and Latin America. While it does appear that HPV self-collection screening could be a useful alterative to Pap/VIA in these settings, this information alone does not allow us to make any determinations about whether this method of screening will reduce CC rates in developing countries. Women testing positive for HPV should follow-up with a doctor to receive VIA/Pap or treatment. Hence, a logical next step is to conduct longitudinal studies comparing rates of follow-up care among women who have tested positive, versus those who have not been screened for HPV, as well as head-to-head comparisons between HPV-based versus Pap/VIA screening programs[48]. It is also important to continue developing new affordable and easy to use tests that could be readily implemented in low-income settings[20–22].

The ministry of health in Guatemala is in the process of refining the National Cervical Cancer Prevention and Control program [49]. Following PAHO and WHO guidelines, the ministry has compiled a list of screening programs, some including HPV testing, which could be adopted. It will be the responsibility of each province (department) to determine which program best fits

their needs and resources. We hope that our study, along with future evidence[50], will aid local and regional authorities to identify the best CC screening alternative for their own settings.

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Declaration of Interests
The authors declared that they have no competing interests.

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Table 1: General population characteristics

	N (%) or Mean (SD)
N	202
Age (y)	34.5 (8.8)
Education	
No formal	80 (39.6%)
Primary	85 (42.1%)
More than primary	37 (18.32%)
Daily Income (Q)	32.8 (19.8)
Literacy	
Yes	123 (60.9%)
No	79 (39.1%)
Married/United	173 (85.6%)
Age at marriage	19.2 (3.7)
Use health services	181 (89.6%)
Breast exam	10 (5.0%)
Mammogram	7 (3.5%)
Pap	134 (66.3%)
Last pap (N = 134)	
Less than 6 months	16 (11.9%)
6 months to a year	8 (6.0%)
1 to 5 years	81 (60.4%)
More than 5 years	29 (21.6%)
VIA	18 (8.9%)
Smoke	1 (0.5%)
Drink	28 (13.9%)
Use depoprovera	109 (54.0%)
Use pill	40 (19.8%)
Use IUD	6 (3.0%)
Use condoms	
Always	3 (1.5%)
Almost always	5 (2.5%)
Sometimes	10 (5.0%)
Rarely	8 (4.0%)
Never	164 (81.2%)
Unknown	12 (5.9%)
Number of pregnancies	3.2 (2.5)
Number of children	2.9 (1.9)
Age at first pregnancy	20.3 (4.0)
Family member with cervical cancer	13 (6.4%)
Age at first sexual relation	19.1 (3.9)
Number of lifetime partners	1.2 (0.5)
Knowledge of HPV	30 (14.9%)
Diagnosed with cervical cancer	0
Urban	165 (81.7%)
Severity of CC	
Not	2 (1.0%)
A little	3 (1.5%)
Moderate	69 (34.2%)
Very	35 (17.3%)
Extremely	93 (46.0%)

Table 2: Acceptability of Self-Collection Tests

	N (%)
N	202 *(All participants)*
HPV knowledge	30 (14.9)
Previous Pap/VIA	135 (66.8)
Intent to self collect	188 (93.1)
Urban (N = 165)	153 (92.7)
Rural (N = 37)	35 (94.6)
Self collected sample	178 (88.1)
Prefer home screening	163 (80.7)
Prefer self-screening	162 (80.2)
	N (%)
N	178 *(Test-taking participants)*
Comfort of test	
Comfortable	140 (78.7)
Neutral	13 (7.3)
Uncomfortable	25 (14.0)
Ease of test	
Easy	162 (91.0)
Neutral	3 (1.7)
Difficult	13 (7.3)
Willingness to retake test	178 (100)
Called for test results	163 (91.6)

Table 3: HPV Distribution

	N(%)
N	178
HPV positive	37 (20.8)
High risk HPV positive	31 (17.4)
Positive for types 16/18	8 (4.5)

Table 4: Characteristics of High-Risk HPV Positive and Negative Participants in Guatemala

	HR HPV + Mean (SD)/ Count (%)	**HR HPV –** Mean (SD)/ Count (%)	**P-value**
N (178)	31	147	
Age[A]	35.4 (9.6)	34.3 (8.7)	0.57
Education[B]			0.2425
No formal	12 (38.7%)	60 (40.8%)	
Primary	17 (54.8%)	62 (42.2%)	
More than primary	2 (6.5%)	25 (17.0%)	
Pap/VIA[B]	26 (83.9%)	101 (68.7%)	0.0897
Daily Income (Q)[A]	33.1 (19.0)	33.2 (20.8)	0.97
Lifetime sexual partners[A]	1.3 (0.5)	1.1 (0.4)	0.04
Age at marriage[A]	17.4 (2.9)	19.4 (3.6)	0.0041
Literate[B]	18 (58.1%)	87 (59.2%)	0.9083
Married/United[B]	26 (83.9%)	134 (91.2%)	0.2215
Use health services[B]	31 (100%)	130 (88.4%)	0.0461
Drink[B]	2 (6.5%)	19 (12.9%)	0.3099
Use depoprovera	21 (67.7%)	83 (56.5%)	0.2469
Use pill[B]	7 (22.6%)	32 (21.8%)	0.92
Use IUD[B]	2 (3.2%)	4 (2.7%)	0.28
Use condoms[B]	3 (9.6%)	17 (11.6)	0.76
Number of pregnancies[A]	4.0 (2.7)	3.1 (2.4)	0.0662
Number of children[A]	3.1 (1.9)	2.8 (1.9)	0.3769
Age at first pregnancy[A]	18.8 (3.1)	20.6 (4.2)	0.0231
Age at first sexual relation[A]	17.2 (3.0)	19.1 (3.5)	0.0027
Knowledge of HPV[B]	5 (16.1%)	22 (15.0%)	0.7897

p-values (at $p<0.05$ significance level) we obtained by: A: independent t-test B: chi-square

Table 5: Characteristics of Participants Who Had or Had Not Received Previous Screening

	Previous Pap/VIA Mean (SD)/ Count (%)	**No previous Pap/VIA** Mean (SD)/ Count (%)	**P-value**
N (202)	135	67	
Age[A]	36.3 (8.3)	30.9 (8.8)	< 0.0001
Education[B]			0.0486
No formal	53 (39.3%)	27 (40.3%)	
Primary	63 (46.7%)	22 (32.7%)	
More than primary	19 (14.1%)	18 (26.9%)	
HR HPV +[B]	26 (20.47%)	5 (9.8%)	0.0897
Daily Income (Q)[A]	33.6 (19.9)	31.2 (19.5)	0.43
Lifetime sexual partners[A]	1.2 (0.5)	1.2 (0.4)	0.61
Age at marriage[A]	18.8 (3.4)	20.1 (4.3)	0.05
Literate[B]	80 (59.3%)	43 (64.2%)	0.4999
Married/United[B]	132 (91.9%)	51 (76.1%)	0.0065
Use health services[B]	129 (95.6%)	52 (77.6%)	< 0.0001
Frequency of health visits[B]			0.142
Once a month or more	29 (21.5%)	12 (17.9%)	
Every 3-6 months	51 (37.8%)	18 (26.9%)	
Once a year or less	55 (40.8%)	37 (55.2%)	
Last visit to health services[B]			0.208
Less than 1 year	98 (72.5%)	42 (62.7%)	
1 to 5 years	23 (17.1%)	12 (17.9%)	
More than 5 years	7 (5.2%)	4 (6.0%)	
Never	7 (5.2%)	9 (13.4%)	
Breast exam[B]	9 (6.7%)	1 (1.5%)	0.17
Mammogram[B]	7 (5.2%)	0 (0%)	0.10
Drink[B]	11 (8.2%)	17 (25.4%)	0.0009
Use Depo-Provera[B]	92 (68.2%)	17 (25.4%)	< 0.0001
Use pill[B]	32 (23.7%)	8 (11.9%)	0.0482
Use condoms[B]	18 (13.3%)	8 (12%)	0.78
Number of pregnancies[A]	3.7 (2.5)	2.1 (4.3)	< 0.0001
Number of children[A]	3.1 (2.0)	2.4 (1.5)	0.0138
Age at first pregnancy[A]	20.1 (4.1)	21.0 (3.8)	0.1878
Family member with cervical cancer[B]	8 (5.9%)	5 (7.5%)	0.6951
Age at first sexual relation[A]	18.6 (3.3)	20.2 (4.8)	0.0201
Knowledge of HPV[B]	23 (17.0%)	7 (10.5%)	0.2150

p-values (at $p<0.05$ significance level) we obtained by: A: independent t-test B: chi-square

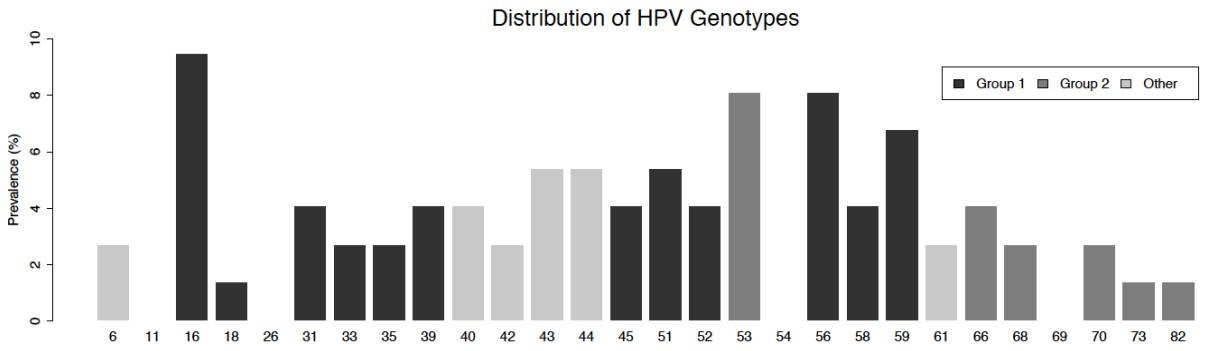

Figure 1. Distribution of HPV Genotypes among the 37 HPV positive samples. Several women had prevalent infections with more than one type, thus these percentages represent the number of infections from a specific type of HPV divided by the total number of HPV infections. Group 1: most potent HPV type, known to cause cancer at several sites or sufficient evidence for cervical cancer; group 2: limited evidence in humans with varying levels of evidence for cervical cancer, group 3: no evidence in humans for cancer.