Prevalence and Genotype Distribution of Human Papillomavirus in Women with Cervical Histopathology in Haiti

by

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Thesis submitted in partial fulfillment of
the requirements for the degree of Master of Science in the Department of
Global Health in the Graduate School
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ABSTRACT

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Abstract

The development of HPV vaccines has generated a great deal of hope that the burden of cervical cancer may be eliminated over the next several decades. However, this enthusiasm may be premature if the genotypes associated with high-grade cervical dysplasia and cancer in other countries does not match the select HPV genotypes that were targeted by current vaccines. The objective of this study was to document the profile of high-risk HPV genotypes that are associated with moderate and high-grade dysplasia in a subset of women living in Port-au-Prince and Leogane, Haiti. Preliminary data collected around the world and by Family Health Ministries in Haiti suggest that the high-grade disease seen in many communities may have a different spectrum than the US and Europe. The cross-sectional study was conducted in two medical clinics situated in the cities of Port-au-Prince and Leogane, Haiti. Genotype-specific distribution from cervical samples collected from 269 women was correlated with corresponding cytopathology results. Genotypes associated with HSIL or invasive cancer were HPV-16 (POR 6.8; 95% CI 2.62-17.86), HPV-18 (POR 4.3; 95% CI 1.46-12.40), HPV-35 (POR 4.3; 95% CI 1.63-11.33), and HPV-58 (POR 7.9; 95% CI 1.95-32.00). HPV-58 appeared to have a higher oncogenic potential than HPV-16 and HPV-18. There was a difference in the HPV genotypic profile found in cervical disease in this Haitian population compared to the United States and Europe. It may be less cost-effective to introduce existing HPV prophylactic vaccines to Haiti; resources may be better spent treating existing disease until more appropriate vaccines are developed.

Dedication

This thesis is especially dedicated to my mother, Mary Njeri Matubia, a champion of women's reproductive health and my Guardian Angel

I also dedicate this thesis to the women of Haiti for their continuous strength and resilience during challenging times and their spirit of hope.

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Introduction

Cervical cancer is the leading cause of cancer deaths among women in developing countries. There are about 510,000 cases of cervical cancer reported each year, of which nearly 80% are from low-income countries (WHO, 2009). In Haiti, cervical cancer mortality ranks among the world's highest according to the *The WHO/ICO Information Centre on HPV and Cervical Cancer*. Furthermore, the incidence rate continues to rise at a rapid pace each year, underscoring the need for preventative measures and access to treatment. However, as the poorest nation in the western hemisphere, Haiti lacks the resources necessary for effective cervical cancer screening and treatment programs.

Infection with high-risk or oncogenic types of the Human Papillomavirus (HPV) has been established as a necessary cause of cervical cancer (Bosch, Lorincz, Munoz, Meijer, & Shah, 2002). Therefore, it is crucial that prevention of the spread of HPV be considered a major priority where most cervical cancer deaths occur. Successful implementation of prophylactic vaccines against the virus would have a tremendous impact on reducing this burden, and would provide a cost-effective approach in the prevention of cervical cancer in Haiti. However, this may not be the best public health intervention if the HPV genotypic spectrum that is considered high risk and has a potential for progressing to cervical cancer does not mimic the genotypic spectrum covered by the vaccines.

Currently, there are two prophylactic vaccines on the market that prevent two high-risk HPV types, HPV-16 and HPV-18, which are predicted to cause about 70% of cervical cancer worldwide. However, the vaccines are costly and are not readily available in poor countries. Both HPV vaccines require a three-dose series that has an estimated cost of US$360. Furthermore, even if this price was subsidized, it may not be cost-effective to provide these vaccines if they do not effectively prevent the HPV genotypes causing disease. Particularly in countries with low access to treatment, HPV vaccination effectiveness should be measured with the reduction of cervical cancer deaths (Cutts, et al., 2007). Therefore, it is imperative to consider which HPV types are prevalent and more likely to cause cervical cancer disease within a population before implementing an expensive vaccination program

A wider spectrum of disease-causing HPV types exists in developing nations than covered by existing vaccines. In a study conducted in Tanzania to determine the prevalence of cervical cancer HPV infections and HPV types, Mayaud and colleagues concluded that vaccination strategies targeting HPV-16 and HPV-18 would only cover 21% of the cases of cervical dysplasia in the studied population (Mayaud, et al., 2003). Additional HPV types would need to be included in the vaccine in order to achieve significant protection against cervical cancer. Similarly, in an unscreened, rural Gambian community, Wall & Borysiewicz (2005) established that high-risk HPV types, 16, 33, and 58 were most prevalent. HPV-33 and HPV-58 are not covered by either of the two

existing vaccines. Wall & Borysiewicz also found that the high-risk HPV types found in this Gambian population were similar to those found in other West African countries, notably Nigeria. In Zambia, a study found that HPV types 16 and 18 were not the only prevalent high-risk HPV types; HPV types 52, 58, 35, 53, 31, 51, and 45 were observed in women who presented high grade lesions (Sahasrabuddhe, et al., 2007).

This evidence reinforces the importance of multivalent HPV vaccines, and underscores the need for type-specific HPV incidence and prevalence research. This knowledge will be vital in countries where resources available for screening and treatment programs are limited; helping ensure that the most appropriate treatments will be delivered. Not only should incidence and prevalence of HPV types within a population be established, but the relative importance of different HPV genotypes, other than HPV-16 and HPV-18, that may be associated with cervical dysplasia and cancer should also be understood.

According to the World Health Organization's *Human Papillomavirus and Related Cancers, Summary Report (2010),* there are very limited data on the prevalence and distribution of HPV genotypes in Haiti. Moreover, there is lack of substantial evidence that the existing vaccines could be effective within this population. Yet cervical cancer mortality is the highest compared to mortality from other cancers in women of all ages in Haiti (WHO/ICO, 2009). The objective of this study was to establish the prevalence of HPV types in Haiti, to investigate the high-risk HPV genotypes associated

with moderate and high grade dysplasia including cancer in those positive for HPV, and to assess the potential impact of introducing the existing HPV vaccines in this population.

Data and Methods

Study participants

We conducted a cross sectional study in two medical clinics situated in the cities of Port-au-Prince and Leogane The two clinics are run by Family Health Ministries, a non-profit organization that has worked in these communities for over 15 years. The study protocol was approved by institutional review boards in the United States and in Haiti. Recruitment of study participants was mainly done through word of mouth. Women were eligible to participate if they (a) were between 30-50 years of age, (b) had at least one sexual partner in their lifetime, (c) were not pregnant at the time of testing, (d) did not have their menstrual period at the time of testing, and (e) had not had a hysterectomy. Eligible and consenting participants were interviewed by trained personnel using a questionnaire designed to collect information on socio demographics, and reproductive health information. The participants were also educated on cervical cancer prevention, including the importance of appropriate follow-up. Of the 1330 subjects who tested positive for HPV DNA, 269 had cervical biopsies obtained for abnormal findings on colposcopy and were included in the final study group.

Study design

High-risk HPV genotypes found in the cytopathology specimens were correlated with the stage of dysplasia found on biopsy. The principle of measurement was the HPV

and histology status of the participant, and the measure of frequency was the prevalence of HPV genotypes in cervical dysplasia.

The independent variable was the high-risk genotype of the HPV infection. The dependent variable was measured as the presence of disease in biopsy tissue(s) obtained from high-risk HPV positive participants. Other cofactors associated with the risk of acquiring HPV infections were also considered. To determine the prevalence of type-specific infection, high-risk HPV genotypes were correlated to corresponding abnormal biopsy results, and subsequently, these associations were statistically analyzed. The majority of cervical samples were collected from women who live in the surrounding areas, close to the clinical sites in Port-au-Prince and Leogane.

Ethical considerations

All eligible participants provided informed consent. The consent forms were translated into Haitian Kreyol, and bilingual personnel were available to facilitate the consenting process. Each participant was required to sign the consent form to signify comprehension; illiterate participants provided consent by placing an "x" on the consent form. A subject ID number was assigned to identify each specimen. To ensure confidentiality, no other participant-identifiers such as demographic information were used outside the specimen collection site. There were minimal risks associated with the collection of cervical specimens and performing biopsies, but in the event of an adverse effect, participants were advised to contact the participating clinic for evaluation.

Specimen collection and HPV DNA typing

Samples of cervical exfoliated cells were collected from each participant by using the Digene Cervical Sampler (QIAGEN, formerly Digene Corporation, Gaithersburg, Maryland). Collection was done by inserting a Digene Cervical Sampler brush 1-1.5 cm into the cervical Os and rotating the brush three full turns in a counterclockwise direction. These samples were suspended in Specimen Transport Medium™ (STM) and sent to QIAGEN (Gaithersburg, Maryland) where HPV DNA status for high-risk types (HPVs 16,18,31,33,35,39,45,51,52,56,58,59,68), were tested using *Hybrid Capture* 2 HPV DNA Test. HPV positive samples were analyzed for genotypes by using a GP5+/Gp6+ L1 consensus PCR reaction where amplicons were then analyzed in a multiplex Luminex assay.

Histology

Participants positive for HPV DNA were asked to return for follow up. This involved a visual inspection of the cervix with diagnostic colposcopy after applying 5% acetic acid to the cervix. All abnormal appearing areas were biopsied. Cervical tissue obtained from biopsies was preserved in formaldehyde vials and shipped to the United States for histological diagnosis. Histology results were reported using the 2001 Bethesda System of cervical cytology reporting (TBS). Results were categorized as negative, atypical cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesion (LSIL) encompassing CIN I, and high-grade squamous

intraepithelial lesion (HSIL) encompassing CIN II - CIN III and carcinoma, and invasive carcinoma.

Statistical analysis

HPV positive participants who underwent cervical evaluation and had histological abnormalities were included in the final analysis. Descriptive and summary statistics (means for continuous variables and proportions for categorical variables) of socio demographic characteristics and HPV diagnosis were used during univariate analysis. Frequency distributions of HPV genotypes and the significance of the difference in this prevalence were calculated using bivariate and multivariate analyses.

Definition of outcome

The histology results were classified according to a dichotomous variable based on the degree of cervical dysplasia. Negative, ASCUS and LSIL (CIN I) results were considered to be disease free. LSIL results were grouped together with the negative results because the likelihood of these infections developing into HSIL or cancer is very low; most LSIL infections regress spontaneously. Significant cervical disease included HSIL and invasive carcinoma.

Definition of exposure

Exposure was defined as infection with at least one of the identified high-risk HPV genotypes. These genotypes are HPV-16, HPV-18, HPV-31, HPV-33, HPV-35, HPV-39, HPV-45, HPV-51, HPV-52, HPV-56, HPV-58, HPV-59, and HPV-68.

Definition of cofactors

Socio-demographic characteristics that are known cofactors associated with HPV infection were added to the statistical analysis. The cofactors considered for each woman were: (1) the number of years of sexual activity, (2) parity (Castellsague & Munoz, 2003), (3) the number of lifetime sexual partners, and (4) marital status noting if her male partner had other polygamous relationships (Bayo, et al., 2002). It is culturally acceptable and common in Haiti for a husband or male partner to have sexual relationships and children with other women.

Bivariable and Multivariable Analysis

The association of HPV genotypes and the selected cofactors with the severity of cervical dysplasia was evaluated using the Pearson's chi-square test (χ^2). HPV genotypes that were associated with HSIL or cancer ($P<0.05$) in bivariate analysis were retained for multivariate regression modeling. HPV genotypes that were retained were: HPV-16, HPV-18, HPV-35, and HPV-58. Similarly, to assess whether the cofactors were associated with the exposure (HPV infection); bivariate analysis using the chi-square test

was conducted. Cofactors that were both significantly associated with HPV infection and HSIL or cancer were considered as candidates for inclusion in regression modeling.

Before modeling, the presence of collinearity between the selected HPV types from the bivariate analysis was evaluated. This was done by constructing 2 X 2 tables comparing the relationships between pairs of the four HPV genotypes retained for modeling. It was rare for these four genotypes to be found in combination. As such only four individuals (less than 2% of the sample) were positive for two or more of the retained genotypes. It was therefore decided to exclude those with two or more of the selected HPV genotypes and create a single summary 5-category variable (None of the HPV types, HPV-16 but not the other three, HPV-18 but not the other three, HPV-35 but not the other three, and HPV-58 but not the other three) to represent exposure to HPV infection.

Logistic regression was used to estimate prevalence odds ratios (POR) and 95% confidence intervals for the association of HPV infection and the stage of cervical dysplasia. A likelihood ratio test was conducted comparing the full model to the reduced model to confirm that dropping these variables would provide a comparable fit to the data as the full model. All statistical analysis was performed using STATA statistical analysis software, version 11.0 (STATA Corp., College Station, Texas).

Results

Table 1: Characteristics of the study population

Characteristics	Cohort (n = 269)	
	No.	%
Age		
30-34	73	27.1
35-39	73	27.1
40-44	54	20.1
45-49	36	13.4
Marital status		
Single	42	15.6
Married	112	41.6
Living together	94	34.9
Previously married*	13	4.8
Number of years of sexual activity		
≤10	23	9.9
11-20	128	55.2
≥ 20	81	34.9
Lifetime number of sexual partners		
1	89	34.1
>1	172	65.9
Parity		
0	28	10.4
1-3	146	54.3
≥4	85	31.4
Contraceptive use		
None	192	71.1
Oral contraceptives	21	7.8
Other [b]	56	20.8
Histology results		
Normal-LSIL	176	66.5
HSIL-cancer	90	33.5
HPV Distribution		
Other high-risk HPVs [c]	125	46.5
HPV-16 only	32	11.9
HPV-18 only	23	8.6
HPV-35 only	25	9.3
HPV-58 only	13	4.8

[a] Previously married include divorced and widowed women
[b] Other contraceptives include Depo-Provera, Norplant, IUD, tubal ligation and condoms
[c] Does not include HPV-16, HPV-18, HPV-35, and HPV-58

The socio demographic characteristics are summarized in Table 1. A total of 269 women were included in this study. The mean age was 38.5 years (*SD*= 6.1). Most of the participating women were either married (43%) or were living with a male partner (36%). A majority of the women (55%) reported that their male partner had children with another woman. More than 66% of the women had more than one sexual partner in their lifetime and about 77% were not using any contraceptive method. The mean number of children born to a woman was 3 children (*SD*= 2).

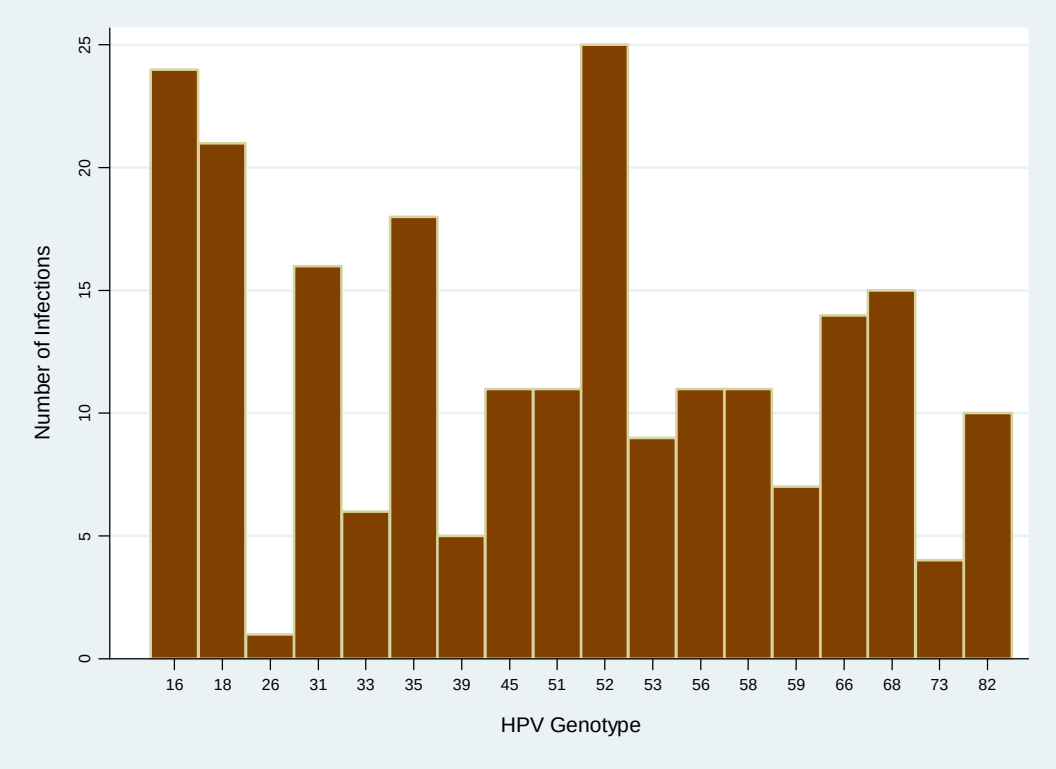

Figure 1: The distribution of HPV genotypes in 269 women. Each type includes single and multiple infections.

The distribution of prevalent HPV genotypes irrespective of the presence of multiple genotypes is shown in Figure 1. The most prevalent HPV genotypes detected in both single and multiple infections were HPV-16 (11%), HPV-52, (11%), HPV-18 (10%), HPV-35 (8%), HPV-31 (7%).

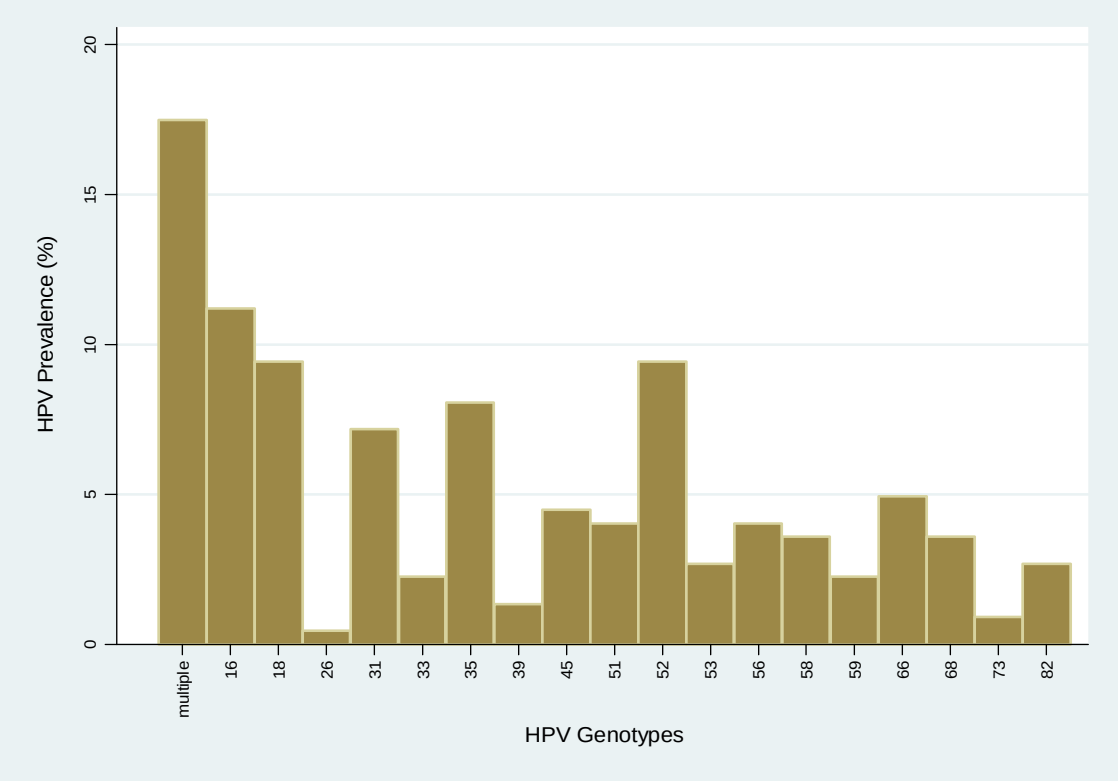

Figure 2: Distribution (percent) of HPV genotypes in multiple infections compared to single infections.

We observed single HPV type infection in 83% of the HPV positive women (Figure 2). Multiple HPV infections were present in 39 women (17%), of which 15 (39%) of these infections were found in women with HSIL or cancer. There was no significant difference in the prevalence of HSIL or cancer among women with single HPV genotypes (84%) compared to those with multiple genotypes (16%) ($p = 0.886$).

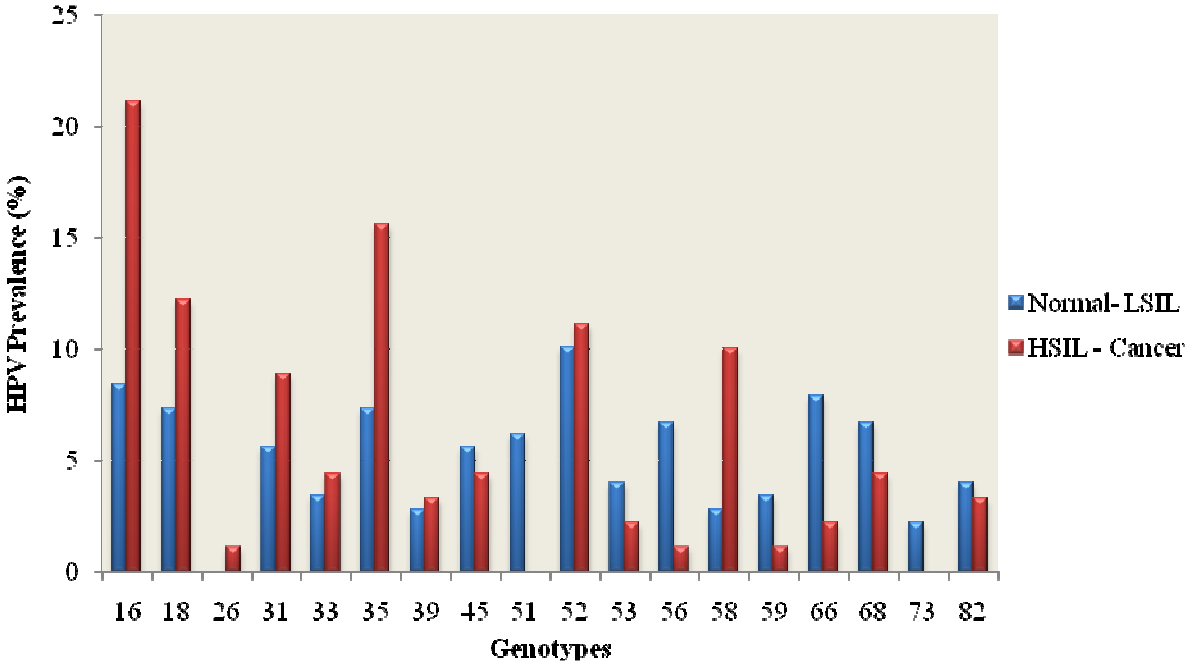

Figure 3: The proportion (percent) of women with normal-LSIL (n=179) or HSIL-invasive cancer (n=90) infected with different HPV genotypes.

The prevalence of HPV genotypes in women with $\leq$ LSIL compared to those with $\geq$ HSIL is shown in Figure 3. The most common HPV genotypes found in women who had LSIL were HPV-52 (10%), HPV-16 (8%), HPV-66 (8%), HPV-18 (7%), HPV-35

(7%), HPV-56 (7%), and HPV-68 (7%). In women who were diagnosed with HSIL or invasive cancer, HPV 16 (22%), HPV-35 (16%) HPV-18 (14%), HPV-52 (11%), HPV-58 (10%), and HPV-31 (9%) were the most common genotypes respectively.

Table 2: Bivariate associations between HPV genotypes and histology results

HPV Genotype	Normal - LSIL N (%)	HSIL - Cancer N (%)	P>|0.05|
HPV 16	15 (8.4)	20 (22.2)	0.001 *
HPV 18	13 (7.3)	13 (14.4)	0.06
HPV 26	0 (0)	1 (1.1)	0.158
HPV 31	10 (5.6)	8 (8.9)	0.306
HPV 33	6 (3.4)	4 (4.4)	0.655
HPV 35	13 (7.3)	14 (15.6)	0.033 *
HPV 39	5 (2.8)	3 (3.3)	0.806
HPV 45	10 (5.6)	4 (4.4)	0.691
HPV 51	11 (6.2)	0 (0.0)	0.016 *
HPV 52	19 (10.1)	11 (11.1)	0.693
HPV 53	7 (4.0)	2 (2.2)	0.467
HPV 56	12 (6.7)	1 (1.1)	0.044 *
HPV 58	5 (2.8)	9 (10.0)	0.012 *
HPV 59	6 (3.4)	1 (1.1)	0.276
HPV 66	14 (7.9)	2 (2.2)	0.067
HPV 68	12 (6.7)	4 (4.4)	0.46
HPV 73	4 (2.2)	0 (0)	0.153
HPV 82	7 (4.0)	3 (3.3)	0.813

* Pearson's chi-square ($\chi 2$)

Table 2 shows HPV that the genotypes that were more likely to be associated with HSIL or cancer include HPV-16 ($\chi 2$ (1, N = 269) = 10.14, p =.001), HPV-35 ($\chi 2$ (1, N = 269) = 4.56, p =.033), HPV-51 ($\chi 2$ (1, N = 269) = 5.77, p =.016), HPV-56 ($\chi 2$ (1, N = 269) = 4.07, p = .044), HPV-58 ($\chi 2$ (1, N = 269) = 3.95, p =.012). Non significant trends were seen with HPV-18 ($\chi 2$ (1, N = 269) = 3.54, p =.060) and HPV-66 ($\chi 2$ (1, N = 269) =3.36, p =.067).

Table 3: Bivariate associations between select socio demographic characteristics and histology results

Characteristic	Normal - LSIL N (%)	HSIL - Cancer N (%)	P>|0.05|
Number of years of sexual activity			0.021*
≤10	16 (9.8)	7 (10.1)	
11-20	99 (60.7)	29 (42.0)	
≥ 20	48 (29.5)	33 (47.8)	
Lifetime number of sexual partners			0.041*
1	68 (38.2)	21 (25.3)	
>1	110 (61.8)	62 (74.7)	
If partner has other woman			0.988
Yes	94 (53.7)	43 (53.8)	
No	73 (41.7)	33 (41.3)	
Do not know	8 (4.6)	4 (5.0)	
Parity			0.015*
0	25 (14.1)	3 (3.7)	
1-3	104 (58.8)	42 (51.2)	
≥4	48 (27.1)	37 (45.1)	

* Pearson's chi-square ($\chi 2$)

Table 4: Bivariate associations between socio demographic characteristics and HPV infection

Characteristic	Other high-risk HPVs N (%)	HPVs 16,18,35 & 58 N (%)	P>|0.05|*
Number of years of sexual activity			0.257
≤10	8 (7.2)	10 (13.2)	
11-20	58 (52.3)	42 (55.3)	
≥ 20	45 (40.5)	24 (31.6)	
Lifetime number of sexual partners			0.401
1	36 (29.0)	30 (34.5)	
>1	88 (71.0)	57 (65.5)	
If partner has other woman			0.988
Yes	94 (53.7)	43 (53.8)	
No	73 (41.7)	33 (41.3)	
Do not know	8 (4.6)	4 (5.0)	
Parity			0.114
0	9 (7.3)	14 (16.1)	
1-3	75 (61.0)	45 (51.7)	
≥4	39 (31.7)	28 (32.2)	

* Pearson's chi-square ($\chi 2$)

After bivariate analysis, the number of years of sexual activity, parity, and lifetime of sexual partners were significantly associated with HSIL or cancer ($p<0.05$) but were not significantly associated with HPV infection ($p<0.05$). This lack of significance may have been due to the limited sample size (Table 3-4). Despite these results, all of the above variables were included as possible risk factors in the initial regression model because of existing literature. Similarly, HPV-18 was also included in the model despite

borderline significance because of the compelling empirical data supporting the role of HPV-18 in the progression of cervical cancer. Moreover, this genotype is also included in the vaccine, therefore it was important to include it in subsequent analysis.

Table 5: Crude prevalence odd ratios with 95% confidence intervals (95% CI) for having HSIL or invasive cancer compared to normal –LSIL according to HPV genotype.

Variable	Prevalence Odds Ratio (POR)	[95% CI]
HPV Genotype		
HPV 16	5.30	2.33 - 12.09
HPV 18	3.33	1.32 - 8.37
HPV 35	3.93	1.61 - 9.60
HPV 58	5.81	1.76 - 19.20

Using normal-LSIL as the reference in the unadjusted model, the HPV genotypes that remained associated with HSIL or invasive cervical cancer were HPV-16 (POR 5.3; 95% CI 2.33-12.09), HPV-18 (POR 3.3; 95% CI 1.32-8.37), HPV-35 (POR 4.0; 95% CI 1.61-9.60), and HPV-58 (POR 5.8; 95% CI 1.76-19.20) (Table 5).

Table 6: Adjusted odd ratios with 95% confidence intervals (95% CI) for having HSIL or invasive cancer compared to normal –LSIL according to HPV genotype.

Variable	Prevalence Odds Ratio (POR)	[95% CI]
HPV Genotype		
HPV 16	6.84	2.62 - 17.86
HPV 18	4.25	1.46 - 12.40
HPV 35	4.29	1.63 - 11.33
HPV 58	7.89	1.95 - 32.00

Table 6 shows the results of the final parsimonious model obtained by backward elimination. When controlling for parity and lifetime number of sexual partners >1, the HPV genotypes that remained strongly associated with HSIL or invasive cervical cancer were HPV-16, HPV-18, HPV-35 and HPV-58.

Discussion

Despite the high prevalence of cervical cancer in Haiti, no data are available regarding HPV genotype prevalence and which of the major HPV genotypes are more likely to cause disease in this population. Given this lack of information, it was important to investigate the high-risk HPV genotype profile to determine the efficacy of a cervical cancer prevention and treatment program in Haiti.

Preliminary results from the Leogane population using liquid-based cytology to stratify the stage of disease suggested that there was a significant difference in the prevalence of high-risk HPV genotypes found in HSIL or cancer than those in the United States and Europe. However, because cytology has a lower specificity (Wright & Wright, 2007), this study was done to confirm those findings using cervical biopsy, which is the gold standard for diagnosing cervical dysplasia. Although the sample size of women who had cervical biopsies is smaller, the socio demographic characteristics examined were representative of those women screened for HPV but were excluded from the study; therefore, the prevalence and distributions found could be generalized to the larger screened population.

In this study, HPV-16 and HPV-18 were not the sole dominant HPV genotypes in this population, which differs from other similar studies. Previous research has suggested that these two genotypes increase the odds of high grade dysplasia or invasive cervical

cancer. Conversely, our results indicate that HPV-35 was the second most frequent HPV type in HSIL or invasive cervical cancer followed by HPV-18. Women who had HPV-35 were four times more likely to progress to HSIL or invasive cervical cancer than those who did not have HPV-16, HPV-18, HPV-35, and HPV-58. Among those who had HPV-58, the probability of HSIL or invasive cervical cancer increased 8-fold compared to those who did not have a single infection of HPV-58. The strikingly strong association between HPV-58 and HSIL or invasive cervical cancer in this analysis suggests that this genotype could be most the oncogenic in this population. Prior studies have shown a relatively high frequency of HPV-58 in abnormal histopathology. In China, the presence of HPV-58 was found in high prevalence among Chinese women particularly in women with cervical cancer (Chan, et al., 1999). Similarly, HPV-58 was the most common genotype found in both LSIL and HSIL in a study conducted in Mexico (González-Losa, et al., 2004). This study also found that the frequency of HPV-58 and HPV-16 in invasive cancer was the same at 31%.

Co-infection with multiple HPV genotypes has been associated with an increased risk of high grade lesions and cervical cancer (Trottier, et al., 2006). However, in our study, single infections were more common than multiple infections and there was no statistical difference found between the association of multiple-type infections and HSIL or invasive cervical cancer. These results indicate that the detection of multiple high-risk

HPV genotype infections in this population is not a significantly better predictor of HSIL or invasive cervical cancer than single high-risk HPV genotype infections.

Consistent with our hypothesis, there was a difference in the prevalence of HPV genotypes found in cervical disease in this Haitian population compared to the United States. A majority of the HPV prevalence studies in the world are based on research conducted in Europe and North America. However, a distribution of high-risk genotypes that deviates from those covered by the vaccine has been demonstrated in several African studies. There is strong evidence that HPV-35 and HPV-58 may play an important part in the progression of cervical cancer particularly in certain regions such as Sub-Saharan Africa and Latin America and the Caribbean and should be considered in future HPV vaccine development. In The Gambia, Wall and colleagues found that among participants with HSIL, HPV-16, HPV-35, and HPV-58 were the most prevalent (SR Wall & Borysiewicz, 2005). There is noticeable similarity in HPV genotype distribution between The Gambia and the Haitian study participants. A study conducted in Pretoria, South Africa, showed that the most prevalent HPV genotypes in HSIL were HPV-35, followed by HPV-58 and HPV-66, which differs from those reported worldwide (Said, et al., 2009). In Mozambique where HPV-35 and HPV-58 were found to be most common among women with cervical dysplasia, 58% of those who had HPV-35 and 75% of those who had HPV-58 also had HSIL or cancer (Castellsagué, et al., 2001).

Currently, there is a considerable global push to administer the HPV vaccines for the prevention of cervical cancer. These prophylactic vaccines protect against infections from HPV-16 and HPV-18. In our study population these vaccines would only protect against 36% of HSIL or invasive cervical cancer. Moreover, there is preliminary data indicating that both bivalent and quadrivalent vaccines may provide cross-protective immunity against other nonvaccine oncogenic HPV genotypes specifically HPV-31 and HPV-45 (Brown, et al., 2009). However, further clinical research is needed to clarify this cross-protective property. If cross protection is confirmed, the results from our study project that the present vaccines would protect against an additional 4.9% of HSIL or invasive cervical cancer, bringing the overall protection to at least 41%.

Conclusion

It is known that infections with HPV-16 and HPV-18 are predictors of cervical cancer worldwide but in this study HPV-35 and HPV-58 were also found to play an important role in cervical disease progression among Haitian women. This initial analysis questions the benefit of introducing currently available HPV vaccines into this population. Vaccination strategies should target HPV genotypes that to cause cervical cancer, particularly in developing countries, in order effectively reduce the disease burden. Walraven (2003) predicts that the use of effective vaccines would have a remarkable impact on the global cervical cancer burden, especially in developing countries where other alternatives for prevention are not feasible. However, these

strategies can only be successful once there is a detailed understanding of the role of other HPV genotypes in the etiology of cervical cancer in these populations.

Limitations

While there is a noticeable trend of a wider variety of high-risk HPV types that cause disease, studies in developing countries have been limited by their small sample sizes. This study has similar shortcomings. The wide confidence intervals indicate that the sample since was inadequate to accurately determine relative risk of disease. Moreover, the cross-sectional design of our study makes it impossible for us to ascertain that infection with specific HPV genotypes virus preceded dysplasia or disease.

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