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Original research

Investigating under-reported human papillomavirus genotypes in Grenadian women through self-sampling for cervical cancer screening

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ABSTRACT

Objective. To compare the adequacy, agreement, and acceptability of Papanicolaou testing (cytology) for cervical cancer screening using self-collected samples compared to physician-collected samples in Grenada in the Caribbean. Furthermore, the study identifies the human papillomavirus (HPV) genotypes present among asymptomatic women testing positive for HPV, the etiologic cause of cervical cancer.

Methods. Participants were divided into two groups and two cervical samples were collected from the women in each group: a self-collected sample and a physician-collected sample. Cervical specimens were tested for cytology and HPV. HPV genotyping was performed on positive specimens.

Results. Self-collected samples were adequate and in agreement with physician-collected samples, showing no difference between the two sampling methods. Oncogenic high-risk HPV genotypes were identified in cervical samples which were positive for atypical squamous cells and low-grade squamous intraepithelial lesions. The high-risk HPV genotypes found, notably HPV 45 and 53, differed from those most commonly reported. Although the commonly reported high-risk genotypes HPV 16 and 18 were found, so were 31, 33, 35, 52, 66, 68, and 82.

Conclusions. Using self-collection facilitated the discovery of unexpected HPV genotypes among asymptomatic women in Grenada. These findings add new information to the literature regarding cervical cancer and neoplasia screening and HPV genotypes in the Caribbean. This genotype information may impact surveillance of women with low-grade lesions, HPV vaccine selection, and possibly further vaccine research. Research regarding HPV in Caribbean pathology samples of cervical neoplasia and cancer is needed.

Keywords Human papillomavirus viruses; papillomavirus infections; Papanicolaou test; uterine cervical neoplasms, diagnosis; early detection of cancer; community health services; Caribbean region; Grenada.

Worldwide, cervical, anogenital, and head-and-neck cancers are linked to persistent infections of high-risk human papillomavirus (HPV) genotypes, of which the HPV 16 and 18 genotypes contribute the highest proportion of cervical cancer cases (1). Within the Caribbean, cervical cancer prevalence is higher than in high-income countries. Caribbean countries have reported high-risk HPV genotypes that deviate from the HPV 16/18 predominance. A systematic review of the literature by Scott-Williams et al. (2) on cervical cancer in the Caribbean from 1958 to 2022 states that "An exceptionally wide variation of HPV types exists within the Caribbean: HPV-16, 18, 33, 35, 42, 44, 45, 51, 52, 53, 55, 56, 58, 59, 66, 68, and 70." This review notes the need for more research on cervical cancer in the Caribbean (2). Cancer in women is dominated by breast cancer in 159 countries and cervical cancer in 23 countries, with cervical cancer being the leading cause of death in 36 countries. Global

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Cancer Statistics 2020 (GLOBOCAN) estimates 19 million new cancer cases and almost 10 million cancer deaths worldwide. Cervix cancers numbered 604 127 cases and 341 831 deaths (3). HPV is the etiological cause of cervical cancer, with high-risk oncogenic genotypes of HPV associated with 99% of cases. Over 200 HPV genotypes have been identified. Genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, and 70 are known to be oncogenic (4–7), while genotypes 26, 53, and 66 are considered probable high-risk and are combined with the high-risk group (8). HPV 53 is classified as either oncogenic or potentially oncogenic (5). Low-risk HPV genotypes include HPV 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, and 81 (8). HPV 70 has been categorized as high-risk phylogenetically (4, 5); however, it is more accurately classified as low-risk by epidemiological studies given its uncommon detection in patients with invasive cervix cancer or carcinoma in-situ (5). HPV genotypes 16 and 18 are responsible for approximately 70% of cervical cancers, with HPV 45 being the third most common (4–9).

Cervical cancer is preventable when lesions are detected early through regular screening (10). High acceptance of cervical self-sampling by women globally can potentially increase screening (11–14). Gupta et al. (15) reported increased compliance in diagnosis and management among under-screened populations when abnormalities were first identified through self-sampling. Similarly increased compliance using self-screening was reported in an at-risk population in Guatemala (16). In the Cervical and Self-Sample in Screening (CASSIS) study, El-Zein et al. (17) compared self-sampling to physician-sampling in over 1 200 women in Canada, and while there was strong agreement between the two samples, participants preferred self-screening over the standard Papanicolaou (Pap) smear (17). A study by Recio et al. (18) across three sites in the United States of America, utilizing the same self-sampling device as employed in this study, resulted in no significant difference between self-sampled and physician-sampled specimens. The incidence and mortality rates of cervical cancer in the Caribbean and Latin America are among the highest in the world. Cancer is the second leading cause of death in the Caribbean, and without intervention, the rates are projected to increase by 66% during this decade (10). Cervix cancer rates in the Caribbean are 13.7 per 100 000 women with mortality rates of 8.2 per 100 000 women. These rates are high compared to statistics for the United States: 6.2 per 100 000 women, 2.1 deaths per 100 000 women; and for Northern Europe: 10.4 per 100 000 women, 2.2 deaths per 100 000 women (3). Country or regional data for the prevalence of HPV types have been used to estimate the contribution of the various HPV types in invasive cervical cancer (6). Perkins et al. (19) recently stated that essentially all cervical cancers worldwide are caused by persistent infections with one of 13 carcinogenic HPV genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68.

Between 2007 and 2021, Caribbean countries and territories including Cuba, Guadeloupe Jamaica, Puerto Rico, and Saint Vincent and the Grenadines reported oncogenic genotypes HPV 16 and 18. However, other genotypes included HPV 31, 33, 35, 45, 51, 52, 58, and 66 (20–29). In Puerto Rico, Jamaica, and Cuba, HPV 16 was the most common high-risk HPV genotype detected (20–22). In Guadeloupe, high-risk HPV 31 was most common in women with cervical dysplasia and invasive cancer, followed by HPV 33, 16, 44, and 26, with HPV 18 in only 5% of cases (23). In Saint Kitts and Nevis, high-risk HPV genotypes were 52, 35, 51, 45, and 31, whereas in Saint Vincent and the Grenadines, high-risk HPV genotypes were 45, 35, 31, 18, and 51 (24). In Barbados, high-risk HPV 45 was the most common, followed by HPV 16, 52, and 58 (25). In Tobago, HPV 45 was detected as the most prevalent high-risk genotype (26). A 2020 Cuban study identified three genotypes not common to any of the other Caribbean islands: high-risk HPV 53, 68, and 69 in women with positive Pap tests. Among the Caribbean islands, HPV genotypes 16 and 31 were the most prevalent, followed by 33, 53, 61, and 66 (27). Other high-risk genotypes reported in the Caribbean were HPV 35, 51, and 66; high-risk HPV 18 was less common or not reported (20–27).

In Grenada, which comprises the three islands of Grenada, Carriacou, and Petite Martinique, the prevalence of cervical cancer was recently documented as 52 per 100 000 women over a 10-year period, with an associated mortality rate of 17 per 100 000 women (28), exceeding WHO's estimated cervical cancer mortality rate for the region (29). Similar to other Caribbean islands, a pilot study in Grenada showed a predominance of high-risk HPV genotypes in addition to 16 and 18. Routine cervical screening is readily accessible in Grenada, but utilization falls below WHO guidelines with only about 4 000 Pap smears evaluated annually from a population of over 29 000 women (29). These disparities place Grenadian women at significant risk when compared to women in the United States, where the incidence of cervical cancer has dropped over 50% in 30 years due to widespread screening (30). HPV DNA testing, recommended for early virus detection before cellular changes, further strengthens screening efforts.

As primary prevention, HPV vaccines have been introduced throughout Latin America and the Caribbean. Bivalent vaccines offer protection against high-risk HPV 16 and 18, with the quadrivalent vaccine adding protection against low-risk HPV 6 and 11 genotypes. The 9-valent HPV vaccine prevents infection by genotypes 6, 11, 16, 18, 31, 33, 45, 52, and 58 with an efficacy of 97% (31). Vaccine selections are based on vaccine availability and cost (32).

While cervical self-sampling has gained widespread acceptance, its evaluation in the Caribbean has been limited and has not been studied in Grenada. The objective of this research was to evaluate the adequacy, agreement, and acceptability of cervical self-sampling compared to physician-sampling for cytology. A secondary objective was to identify the HPV genotypes in positive samples from asymptomatic women in Grenada.

MATERIALS AND METHODS

The study was performed at the University Health Services clinic at St. George's University (SGU) in Grenada. The clinic adheres to health and safety standards including but not limited to availability of personal protective equipment, appropriate disposal of biohazard waste, and secure patient records. The study was approved by the SGU Institutional Review Board. All participants provided verbal and written consent for use of their private data with the understanding that their identities would remain anonymous.

A total of 144 women were recruited by radio advertising and university communication. Inclusion criteria were asymptomatic women over age 20 with an intact cervix and a history of heterosexual activity. Exclusion criteria included menstruation on the study day, total hysterectomy, and an unwillingness

to participate in both the self-sampling and the physician-obtained cervical cytology arms of the study. There was no upper age limit as many of the participants had never been screened.

Participants were assigned into two groups when registering on the day of the study. Group 1 commenced with self-sampling, followed by physician-obtained sampling. Group 2 began with physician-obtained cervical sampling, followed by self-sampling. Alternating which technique was performed first controlled for the effect of sampling order.

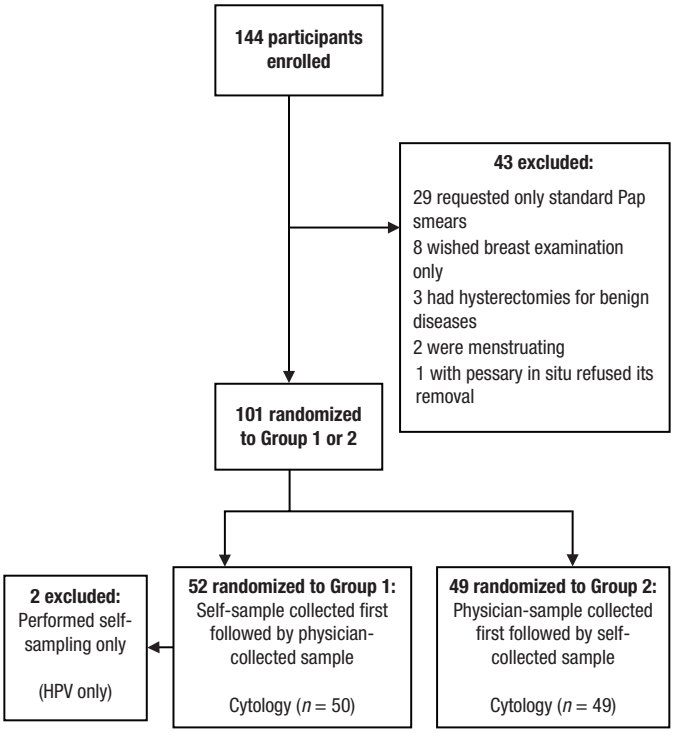
The flowchart in Figure 1 shows the cervix cancer screening study of asymptomatic Grenadian women, comparing physician-obtained sampling with self-sampling for cervical cytology.

The iSelf-Screen™, a cervical cancer screening tool, was used for the self-sampling screening. Both a traditional physician-obtained sample and a self-sample were obtained from the same women during the same clinic visit, and a survey was conducted to compare levels of comfort associated with self-sampling. HPV testing and cytology were endpoints.

Cytologic testing was conducted at Select Reference Laboratories LLC, North Carolina, United States of America. Laboratory technicians were blinded to the method of specimen collection. Adequacy was defined as an adequate transformation-zone sampling of at least 10 well-preserved endocervical or squamous metaplastic cells, single or in clusters. Diagnostic interpretation was made using the Bethesda system of classification (33):

- Negative for intraepithelial lesion or malignancy (NILM)
- Atypical squamous cells of undetermined significance (ASC-US)
- Atypical squamous cells, cannot exclude HSIL (ASC-H)
- Low-grade squamous intraepithelial lesion (LSIL)
- High-grade squamous intraepithelial lesion (HSIL)
- Cancer.

FIGURE 1. Selection of participants for comparing self-sampling to physician-obtained cervical cytology and HPV testing



Source: Prepared by the authors based on the study data.

The objective of two cytology samples was to assess agreement by level of concordance between the self-sampling and physician-sampling methods in identifying abnormal cervical cells within the collected sample pairs.

HPV testing was performed on the first cervical specimen for each participant, and if positive, HPV genotypes were identified. HPV genotyping employed polymerase chain reaction (PCR) to detect type-specific HPV E6/E7 DNA. Confirmation testing was conducted through gene hybridization which used both microsphere-based genotyping and conventional nested PCR. HPV genotypes were identified through fragmentation patterns and confirmative Sanger sequencing. High-risk and low-risk genotypes were determined based on the Select Reference Laboratories system. High-risk genotypes included 16, 18, 31, 33, 35, 45, 52, 53, 56, 58, 66, 69, and 82, while low-risk subtypes encompassed 6, 11, 54, 61, 62, 71, 72, 81, 83, 84, and 89.

Following sample collections, participants completed a questionnaire evaluating the acceptability of using the self-sampling device. The questionnaire utilized a dichotomous scale of "Yes" or "No" responses to all questions, except for one, which used a four-point Likert scale to assess respondents' discomfort during self-sampling. A comment section for open responses was also included.

RESULTS

Of the 144 registrants, 101 women met the inclusion criteria. Of these, 99 completed both the physician-obtained and self-sampling components of the study. Two women in Group 1 performed self-sampling only and were excluded from the cytology analysis. However, their HPV results were included as an intention to treat. Hence, 99 cytology pairs and 101 HPV results were reported (Figure 1).

The ages of participants ranged from 21 to 72 years, with the median being 34 and 35 years in Groups 1 and 2, respectively. The sample consisted of professional and non-professional workers, students, and unemployed women. There was no meaningful difference in the demographic profiles of the groups based on age, occupation, or location of residence.

Comparing physician-obtained cervical cytology to self-sampling, 99 sample pairs (198 liquid-based cytology samples) were evaluated. Eighty-nine sample pairs were deemed sufficient in cellularity for evaluation of both specimens. Table 1, indicating 90% adequacy overall for sampling in the study (95% CI [82, 94]), also indicates high comparability in adequacy between sampling methods. Of the 10 unsatisfactory specimens, three sample pairs were unsatisfactory in cellularity by both techniques, of which two pairs were in post-menopausal women.

Using the Bethesda classification system of NILM, ASC-US, ASC-H, LSIL, HSIL, and Cancer, 76 sample pairs were diagnosed as normal cytology (NILM). Seven pairs were identified as abnormal (ASC-US, ASC-H, or LSIL) (Table 2). Comparing the diagnostic results of the 89 sample pairs with adequate cytology in both self- and physician-collected samples, as shown in Table 2 there was evidence of substantial agreement

TABLE 1. Adequacy of cervical cytology obtained by self-collected compared to physician-collected cytology

Adequacy of pairs of samples	Samples obtained (n = 99)
Both self-collected and physician-collected samples were adequate	89
Self-collected sample was inadequate, but physician-collected sample was adequate	6
Self-collected sample was adequate, but physician-collected sample was inadequate	1
Both self-collected and physician-collected samples were inadequate	3

Source: Prepared by the authors based on the study data.

TABLE 2. Agreement of diagnostic results of self-collected and physician-collected cervical cytology samples categorized as normal or abnormal (n = 89)

		Results of physician-collected sample	
		Normal	Abnormal
Results of self-collected sample	**Normal**	76	3
	Abnormal	3	7

Source: Prepared by the authors based on the study data.

between the sampling techniques (Cohen's kappa = 0.662, 95% CI [0.411, 0.913]).

There was no evidence that the order of sampling (self-sampling first or physician-sampling first) affected the diagnosis for a sample as being either normal or abnormal (Table 3, Mantel–Haenszel test p = 0.774). There was also no evidence that the order of sampling affected whether a sample was unsatisfactory (Table 3, McNemar's test p = 0.480).

As shown in Table 3, 34 of 80 (43%) women with normal cytology on the first specimen were found to have HPV from across the entire spectrum of genotypes, including 11 high-risk genotypes. Five women had ASC-US and were found to have low-risk HPV 61, but also high-risk HPV 16, 31, 45, 53, and 58. One woman with ASC-H had high-risk HPV 35, 45, and 53. Among eight women with LSIL, HPV genotypes included 54, 61, 62, and 84, which are low-risk; however, notably high-risk genotypes 16, 18, 56, 58, and 69 were also identified. No low-risk HPV 6 or 11 were identified in these low-grade lesions. No HSIL or cancer was identified.

In Group 1 (self-sampling first) 26 of 50 (52%) women were positive for HPV, while 26 of 49 (53%) women in Group 2 (physician-sampling first) were positive. Positive HPV results were included for two additional samples in women who completed only the self-sampling technique since identification of HPV was also an endpoint. Hence, genotyping was performed on 54 positive cervical samples.

Eleven women were positive for multiple genotypes, either low-risk or high-risk genotypes. Five of these women had a mix of both high and low-risk HPV genotypes. Four HPV specimens were assessed as "unknown genotype," which was interpreted as the test detecting the presence of viral DNA, but the specific type of extracted DNA could not be identified.

In the 54 samples positive for HPV, 24 HPV genotypes were found, of which 10 (42%) were low-risk and 14 (58%) were high-risk genotypes (Table 4). Several women had more than one genotype. A total of 74 occurrences of an HPV genotype were found, of which 34 (46%) were low-risk and 40 (54%) were high-risk genotypes. Low-risk genotypes included 6, 54, 61, 62, 71, 72, 81, 83, 84, and 89, while high-risk genotypes included 16, 18, 31, 33, 35, 45, 52, 53, 56, 58, 66, 68, 69, and 82. As shown in Table 4, the most commonly occurring genotype was low-risk HPV 61 (13 occurrences) followed by high-risk HPV 53 (7 occurrences). One or more high-risk HPV genotypes were detected in 29 of 54 HPV-positive women. No low-risk HPV 11 was identified.

In completing the paper questionnaire at the conclusion of the two cervical samplings, not every woman completed each question. Among the responses, 90 of 98 (92%) women thought

TABLE 3. Cervical cytology by group categorized by the Bethesda system and HPV genotypes

	Self-sample collected first			Physician-sample collected first		
	Group 1 (n = 50)			Group 2 (n = 49)		
	Self-collected sample	Physician-collected sample	HPV genotypes[a]	Physician-collected sample	Self-collected sample	HPV genotypes[a]
NILM	40	42	--	40	38	--
NILM HPV negative	22	--	--	24	--	--
NILM HPV positive	18	--	**45**, **53**, **58**, 61, 62, **66**, 72, 81, **82**, 83	16	--	6, **16**, **18**, **31**, **33**, **45**, **52**, **53**, 61, **66**, **68**, 71, 72, **82**, 83, 89
Reactive change	0	1	--	0	0	--
ASC-US	3	2	**16**, **31**, 61	2	2	**16**, **45**, **53**, **58**
ASC-H	0	1	--	1	0	**35**, **45**, **53**
LSIL	2	1	**18**, 54, 62, 84	5	4	**16**, **56**, **58**, 61, 62, **69**
HSIL	0	0	--	0	0	--
Cancer	0	0	--	0	0	--
Unsatisfactory	5	3	**31**	1	5	--
Total samples	50	50	--	49	49	--

ASC-H, atypical squamous cells, cannot exclude HSIL; ASC-US, atypical squamous cells of undetermined significance; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; NILM, negative for intraepithelial lesion or malignancy; --, not applicable.
Note: [a] HPV testing was performed on the first sample; high-risk HPV genotypes in bold type.
Source: Prepared by the authors based on the study data.

TABLE 4. Occurrences of low-risk and high-risk HPV genotypes in 54 samples positive for HPV

HPV genotype	Risk level	Number of women
6	Low	1
16	High	6
18	High	2
31	High	3
33	High	1
35	High	1
45	High	4
52	High	3
53	High	7
54	Low	1
56	High	1
58	High	3
61	Low	13
62	Low	6
66	High	4
68	High	1
69	High	1
71	Low	2
72	Low	4
81	Low	2
82	High	3
83	Low	4
84	Low	2
89	Low	1

Source: Prepared by the authors based on the study data.

self-sampling was easy to use and 79 of 97 (81%) found the procedure comfortable. Overall, 93 of 94 women (99%) would recommend self-sampling. The most commonly reported problem with the self-sampling device was not knowing the location of the cervix or the correct depth to insert the applicator. Of the 10 pairs of samples with one or more inadequate samples, nine (90%) were self-samples. This suggests that the instructions for using the self-sampling device could be improved by helping women to better recognize the cervix location and the proper insertion depth.

DISCUSSION

Our study confirmed the adequacy, agreement, and acceptability of cervical self-sampling in cytology and identifying HPV genotypes compared to physician-sampling in asymptomatic women in Grenada. While high-risk HPV 16 and 18 were found, HPV 53 was the most common genotype identified using both sampling methods, detected in 7 of 29 (24%) women with high-risk HPV. A majority of women expressed satisfaction with the self-sampling device and recommended it. Our results align with the CASSIS study which compared cytology and HPV obtained by self-screening and physician-sampling, and documented a preference for self-sampling (17). Our study adds to the literature supporting self-sampling, by use of the iSelf-Screen™. High acceptance of self-sampling among Caribbean women can also conserve resources, increase screening, as recommended by De la Hoz Restrepo et al. (32), and facilitate the identification of HPV genotypes.

Cytology performed on both self-collected and physician-collected specimens identified abnormal cervical cytology in 14 women: ASC-US, ASC-H, and LSIL. No HSIL or cancer was identified. Interestingly, high-risk HPV genotypes were associated with ASC-US and LSIL cytology, which are normally caused by low-risk HPV. High-risk HPV 16, 31, 45, 53, and 58 were expressed in ASC-US; HPV 35, 45, and 53 in ASC-H; and HPV 16, 18, 56, 58, and 69 in LSIL. In women with normal cytology, 46% carried oncogenic HPV with probable high-risk HPV 53 being the most common.

The bivalent, quadrivalent, and 9-valent vaccines all prevent high-risk HPV 16 and 18, which were detected in 8 of 29 (28%) high-risk HPV-positive women in our study. Oncogenic HPV genotypes in Grenada that were uncommon in other Caribbean islands were HPV 53, our most frequent genotype, identified only in Cuba; HPV 56, noted by Scott-Williams et al. (2) but not in our review of HPV in the Caribbean; and HPV 82, not previously reported. In Grenada, oncogenic genotypes HPV 35, 56, 69, 82 and probable oncogenic HPV 53 and 68 are not prevented by any current HPV vaccine. Given the broad range of high-risk genotypes identified, the available vaccines would provide full protection for 22 of 40 (55%) of the occurrences of high-risk genotypes in our study. Despite some cross-protection (34, 35) the lack of full protection against HPV in the Caribbean is a concern, as HPV-infected women may not receive sufficient vaccine prophylaxis for the genotypes they may be exposed to, but may believe that they are fully protected. Physicians, nurses, healthcare teams, public health, and community educators should continue to advise regular screening and "safe sex" practices for all.

Our findings indicate the need for further research into the oncogenic strains identified in the Caribbean, their persistence, and virulence. Further studies in the Caribbean identifying both high- and low-risk genotypes from biopsies, loop electrosurgical excision procedure (LEEP), cone biopsy, and hysterectomy would better inform decision-making, vaccine strategies, and advance care of women.

The limitations of this study include its being a convenience sample; therefore, the results only apply to the women enrolled in the study. Participants were assigned to alternating groups based on their arrival at the clinic, but all women in this research were seeking care. Most participants were from the most densely populated parish in Grenada. We did not survey comfort during the standard physician-obtained cytology. The limited sample size also makes it difficult to conclusively associate the high-risk HPV as causative of the low-grade lesions. These observations concur with evidence of HPV coinfection and the predisposition from high-risk HPV in developing higher-grade cervical neoplasia or cancer. The presence of high-risk HPV with low-grade cytology raises concern that Caribbean women with low-grade lesions may warrant increased surveillance.

Conclusion

Our results show the adequacy, agreement, and acceptability of self-collection for cervical cancer screening and HPV identification. HPV results in Grenada revealed additional non-16, non-18 HPV genotypes that differed from those reported as most common in the literature. Although HPV 16 was a predominant genotype, HPV 18 was not, as it was identified in only 2 of 101

specimens tested for HPV. Unexpectedly, HPV 53 was the major genotype, followed by HPV 16, 45, and 66. Furthermore, our results showed high-risk genotypes in women with ASC-US and LSIL cytology, usually not associated with low-risk lesions. The persistence and oncogenicity of non-16, non-18 HPV circulating strains among asymptomatic women requires further study of HPV genotypes identified in pathological specimens from LEEP, cone biopsy, and hysterectomy specimens of women with cervical neoplasia and particularly with invasive cervical cancer. Caribbean investigators (24–25) have expressed the need for knowledge on HPV distribution as important to provide a baseline and evaluate the effect of vaccination on cervical disease in specific populations. The preliminary identification of HPV genotypes in asymptomatic women in Grenada provides new information for the region and the need for further study of true oncogenicity of these high-risk HPV genotypes.

Author contributions. ESM and FMcG designed and implemented the work. FMcG, ESM, and JL implemented the clinical study. RB, KP, SL, PJF, AB-Y, and FMcG analyzed the HPV and cytology data. TJ-B maintained and analyzed the database and comfort survey and created the tables. PJF performed and documented the statistical analysis. ESM, RB, KP, JL, TJ-B, SL, AB-Y, PJF, and FMcG actively contributed to the writing of the manuscript and the literature review. AB-Y, PJF, and FMcG revised the work critically for intellectual content. FMcG was the lead for the entire project. All authors reviewed and approved the final version of the manuscript.

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Conflict of interest. None declared.

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REFERENCES

1. World Health Organization, International Agency for Research on Cancer. GCO Cancer Today. Cancer factsheets. Lyon: IARC; 2022 [cited 31 October 2023]. Available from: https://gco.iarc.fr/today/en/fact-sheets-cancers.
2. Scott-Williams J, Hosein A, Akpaka PE, Venkata CRA. Epidemiology of cervical cancer in the Caribbean. Cureus. 2023;15(11):e48198. https://doi.org/10.7759/cureus.48198.
3. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–249. https://doi.org/10.3322/caac.21660.
4. Burd EM. Human papillomavirus and cervical cancer. Clin Microbiol Rev. 2003;16(1):1–17. https://doi.org/10.1128/cmr.16.1.1-17.2003.
5. Muñóz N, Bosch FX, de Sanjosé S, Herrero R, Castellsagué X, Shah KV, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med. 2003;348(6):518–527. https://doi.org/10.1056/nejmoa021641.
6. de Sanjosé S, Quint WG, Alemany L, Geraets DT, Klaustermeier JE, Lloveras B, et al. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncol. 2010;11(11):1048–1056. https://doi.org/10.1016/s1470-2045(10)70230-8.
7. Toliman PJ, Badman SG, Gabuzzi J, Silim S, Forereme L, Kumbia A, et al. Field evaluation of Xpert HPV Point-of-Care test for detection of human papillomavirus infection by use of self-collected vaginal and clinician-collected cervical specimens. J Clin Microbiol. 2016;54(7):1734–1737. https://doi.org/10.1128/jcm.00529-16.
8. Ragin CC, Watt A, Marković N, Bunker CH, Edwards RP, Eckstein S, et al. Comparisons of high-risk cervical HPV infections in Caribbean and US populations. Infect Agent Cancer. 2009;4(Suppl 1):S9. https://doi.org/10.1186/1750-9378-4-s1-s9.
9. Bruni L, Albero G, Serrano B, Mena M, Collado JJ, Gómez D, et al. Human papillomavirus and related diseases in the world. Barcelona: ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre); 2022 [cited 8 December 2023]. Available from: https://hpvcentre.net/statistics/reports/XWX.pdf.
10. Glasgow L, Lewis R, Charles S. The cancer epidemic in the Caribbean region: Further opportunities to reverse the disease trend. Lancet Reg Health Am. 2022;13:100295. https://doi.org/10.1016/j.lana.2022.100295.
11. Giorgi Rossi P, Fortunato C, Barbarino P, Boveri S, Caroli S, Del Mistro A, et al. Self-sampling to increase participation in cervical cancer screening: an RCT comparing home mailing, distribution in pharmacies, and recall letter. Br J Cancer 2015;112(4):667–675. https://doi.org/10.1038/bjc.2015.11.
12. Nelson EJ, Maynard BR, Loux T, Fatla J, Gordon R, Arnold LD. The acceptability of self-sampled screening for HPV DNA: a systematic review and meta-analysis. Sex Transm Infect. 2017;93(1):56–61. https://doi.org/10.1136/sextrans-2016-052609.
13. Racey CS, Gesink D, Burchell A, Trivers S, Wong T, Rebbapragada A. Randomized Intervention of Self-Collected Sampling for human papillomavirus testing in Under-Screened Rural Women: Uptake of screening and acceptability. J Womens Health (Larchmt). 2016;25(5):489–497. https://doi.org/10.1089/jwh.2015.5348.
14. Singla AA, Komesaroff P. Self-collected Pap smears may provide an acceptable and effective method of cervical cancer screening. Health Sci Rep. 2018;1(5):e33. https://doi.org/10.1002/hsr2.33.
15. Gupta S, Palmer C, Bik EM, Cárdenas JP, Nuñez H, Kraal L, et al. Self-sampling for human papillomavirus testing: increased cervical cancer screening participation and incorporation in international screening programs. Front Public Health. 2018;6:77. https://doi.org/10.3389/fpubh.2018.00077.
16. Gottschlich A, Rivera-Andrade A, Grajeda E, Álvarez C, Mendez Montano C, Meza R. Acceptability of human papillomavirus self-sampling for cervical cancer screening in an Indigenous community in Guatemala. J Glob Oncol. 2017;3(5):444–454. https://doi.org/10.1200/jgo.2016.005629.
17. El-Zein M, Bouten S, Louvanto K, Gilbert L, Gotlieb W, Hemmings R, et al. Validation of a new HPV self-sampling device for cervical

cancer screening: The Cervical and Self-Sample In Screening (CASSIS) study. Gynecol Oncol. 2018;149(3):491–497. https://doi.org/10.1016/j.ygyno.2018.04.004.
18. Recio FO, Spoo LE, Crawford P, Slager TJ, Maleck JM, Migliozzi JA, et al. Self-Administered Pap Smear, Selfpap ® : an acceptable and effective cervical cytology sampling method. Jacobs J Gynecol Obstet. 2014;2(4):23.
19. Perkins RB, Wentzensen N, Guido RS, Schiffman M. Cervical cancer screening. JAMA. 2023;330(6):547–558. https://doi.org/10.1001/jama.2023.13174.
20. Ortíz AP, Romaguera J, Pérez CM, Otero Y, Soto-Salgado M, Méndez K, et al. Human papillomavirus infection in women in Puerto Rico: agreement between physician-collected and self-collected anogenital specimens. J Low Genit Tract Dis. 2013;17(2):210–217. https://doi.org/10.1097/lgt.0b013e318260e312.
21. Lewis-Bell K, Luciani S, Unger ER, Hariri S, McFarlane SR, Steinau M, et al. Genital human papillomaviruses among women of reproductive age in Jamaica. Rev Panam Salud Publica. 2013;33(3):159–165. Available from: https://iris.paho.org/handle/10665.2/9205.
22. Soto Y, Torres G, Kourí V, Limia CM, Goicolea A, Capó V, et al. Molecular epidemiology of human papillomavirus infections in cervical samples from Cuban women older than 30 years. J Low Genit Tract Dis. 2014;18(3):210–217. https://doi.org/10.1097/lgt.0b013e3182a7bb89.
23. Gaëte S, Auguste A, Bhakkan B, Péruvien J, Herrmann-Storck C, Socrier Y, et al. Frequent high-risk HPV co-infections excluding types 16 or 18 in cervical neoplasia in Guadeloupe. BMC Cancer. 2021;21(1):281. https://doi.org/10.1186/s12885-021-07940-3.
24. Andall-Brereton G, Brown E, Slater S, Holder Y, Luciani S, Lewis M, et al. Prevalence of high-risk human papillomavirus among women in two English-speaking Caribbean countries. Rev Panam Salud Publica. 2017;41:e41. Available from: https://iris.paho.org/handle/10665.2/33997.
25. Ward JM, Schmalenberg K, Antonishyn NA, Hambleton IR, Blackman EL, Levett PN, et al. Human papillomavirus genotype distribution in cervical samples among vaccine naïve Barbados women. Cancer Causes Control. 2017;28(11):1323–1332. https://doi.org/10.1007/s10552-017-0959-y.
26. Ragin CC, Wheeler VW, Wilson JB, Bunker CH, Gollin SM, Patrick AL, et al. Distinct distribution of HPV types among cancer-free Afro-Caribbean women from Tobago. Biomarkers. 2007;12(5):510–522. https://doi.org/10.1080/13547500701340384.
27. Guilarte-García E, Soto-Brito Y, Kourí-Cardellá V, Limia-León CM, Sánchez-Alvarez ML, Rodríguez-Díaz AE, et al. Circulation of human papillomavirus and chlamydia trachomatis in Cuban Women. MEDICC Rev. 2020;22(1):17–27. Available from: https://pubmed.ncbi.nlm.nih.gov/32327618/.
28. Bahadoor-Yetman A, Riley L, Gibbons A, Fields PJ, Mapp-Alexander V, Hage R, et al. Prevalence of cervical cancer and associated mortality in Grenada, 2000-2010. Rev Panam Salud Publica. 2016;39(4):194–199. Available from: https://iris.paho.org/handle/10665.2/28409.
29. World Health Organization. WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention. 2nd edition. Geneva: WHO; 2021. Available from: https://iris.who.int/handle/10665/342365.
30. American College of Obstetrics and Gynecology. Practice Bulletin No. 168: Cervical cancer screening and prevention. Obstet Gynecol. 2016;128(4):e111–e130.
31. Markowitz LE, Unger ER. Human papillomavirus vaccination. N Engl J Med. 2023;388(19):1790–1798. https://doi.org/10.1056/nejmcp2108502.
32. De la Hoz Restrepo F, Alvis-Guzmán N, De la Hoz Gomez A, Ruiz C. Policies and processes for human papillomavirus vaccination in Latin America and the Caribbean. Rev Panam Salud Publica. 2017;41:e124. https://doi.org/10.26633/rpsp.2017.124.
33. Solomon D, Davey D, Kurman R, Moriarty A, O'Connor D, Prey M, et al. The 2001 Bethesda System: terminology for reporting results of cervical cytology. JAMA. 2002;287(16):2114–2119. https://doi.org/10.1001/jama.287.16.2114.
34. Wheeler CM, Castellsagué X, Garland SM, Szarewski A, Paavonen J, Naud P, et al. Cross-protective efficacy of HPV-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by non-vaccine oncogenic HPV types: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. Lancet Oncol. 2012;13(1):100–110. https://doi.org/10.1016/s1470-2045(11)70287-x.
35. Tsang SH, Sampson JN, Schussler J, Porras C, Wagner S, Boland J, et al. Durability of cross-protection by different schedules of the bivalent HPV vaccine: the CVT trial. J Natl Cancer Inst. 2020;112(10):1030–1037. https://doi.org/10.1093/jnci/djaa010.

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Investigación de los genotipos de virus del papiloma humano infranotificados en mujeres de Granada mediante automuestreo para el tamizaje del cáncer cervicouterino

RESUMEN

Objetivo. Comparar la idoneidad, concordancia y aceptabilidad de la prueba de Papanicolaou (citología) para el tamizaje del cáncer cervicouterino mediante la comparación de muestras obtenidas con automuestreo y muestras tomadas por personal médico en Granada, en el Caribe. Asimismo, en el estudio se identifican los genotipos del virus del papiloma humano (VPH) existentes en las mujeres asintomáticas con un resultado positivo en las pruebas del VPH, la causa etiológica del cáncer cervicouterino.

Métodos. Las participantes se dividieron en dos grupos y se tomaron dos muestras cervicouterinas de las mujeres de cada grupo: una muestra tomada por la propia paciente y una muestra tomada por personal médico. Se realizó un examen citológico y una prueba de detección del VPH en las muestras. En las muestras positivas, se determinó el genotipo del VPH.

Resultados. Las muestras tomadas por las propias pacientes fueron adecuadas y concordaron con las obtenidas por el personal médico, sin que se observaran diferencias entre ambos métodos de muestreo. Se identificaron genotipos de VPH de alto riesgo oncogénico en muestras cervicouterinas positivas para células escamosas atípicas y lesiones intraepiteliales escamosas de grado bajo. Los genotipos de VPH de alto riesgo encontrados, en especial VPH 45 y 53, diferían de los notificados con mayor frecuencia. Aunque se encontraron los genotipos de alto riesgo habituales 16 y 18 del VPH, también se encontraron los genotipos 31, 33, 35, 52, 66, 68 y 82.

Conclusiones. El uso del automuestreo facilitó la detección de genotipos inesperados del VPH en mujeres asintomáticas de Granada. Estos resultados agregan nueva información a la bibliografía sobre el tamizaje de las neoplasias y el cáncer cervicouterino, así como sobre los genotipos del VPH, en el Caribe. Esta información sobre el genotipo puede repercutir en la vigilancia de las mujeres con lesiones de bajo grado, en la elección de la vacuna contra el VPH y, posiblemente, en las ulteriores investigaciones sobre vacunas. Es necesario investigar la presencia del VPH en muestras anatomopatológicas de neoplasias y cánceres cervicouterinos en el Caribe.

Palabras clave Virus del papiloma humano; infecciones por papillomavirus; prueba de Papanicolaou; neoplasias del cuello uterino, diagnóstico; detección precoz del cáncer; servicios de salud comunitaria; región del Caribe; Grenada.

Investigação de genótipos subnotificados de papilomavírus humano em mulheres de Granada por meio de autoamostragem para rastreamento de câncer do colo do útero

RESUMO

Objetivo. Comparar a adequação, o nível de concordância e a aceitabilidade do exame de Papanicolau (citologia) para o rastreamento do câncer do colo do útero usando amostras autocoletadas em comparação com amostras coletadas por médicos em Granada, no Caribe. Além disso, o estudo identifica os genótipos de papilomavírus humano (HPV) presentes entre as mulheres assintomáticas com resultado positivo para HPV, a causa etiológica do câncer do colo do útero.

Métodos. As participantes foram divididas em dois grupos, e duas amostras cervicais foram coletadas das mulheres de cada grupo: uma amostra autocoletada e uma amostra coletada por um médico. As amostras cervicais foram submetidas a exames citológicos e de HPV. A genotipagem do HPV foi realizada nas amostras positivas.

Resultados. As amostras autocoletadas eram adequadas e compatíveis com as amostras coletadas por médicos, não havendo diferença entre os dois métodos de amostragem. Foram identificados genótipos de HPV de alto risco oncogênico em amostras cervicais positivas para células escamosas atípicas e lesões intraepiteliais escamosas de baixo grau. Os genótipos de HPV de alto risco encontrados, principalmente HPV 45 e 53, não correspondiam aos genótipos registrados com mais frequência na literatura. Embora os genótipos de alto risco HPV 16 e 18, que são frequentemente registrados, tenham sido observados, também foram detectados os genótipos 31, 33, 35, 52, 66, 68 e 82.

Conclusões. O uso da autocoleta facilitou a detecção de genótipos inesperados de HPV entre mulheres assintomáticas em Granada. Esses achados adicionaram novas informações à literatura sobre o rastreamento de neoplasias e câncer do colo do útero e sobre os genótipos de HPV no Caribe. Essas informações genotípicas podem afetar a vigilância de mulheres com lesões de baixo grau, a seleção da vacina contra o HPV e, possivelmente, futuras pesquisas sobre vacinas. É necessário pesquisar o HPV em amostras patológicas de neoplasias cervicais e câncer do colo do útero no Caribe.

Palavras-chave Papillomavirus humano; infecções por papillomavirus; teste de Papanicolaou; neoplasias do colo do útero, diagnóstico; detecção precoce de câncer; serviços de saúde comunitária; região do Caribe; Granada.