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Human Papilloma Virus genotypes in Type III cervical intraepithelial neoplasia. Cuenca–Ecuador, 2013-2017

Genotipos del virus del papiloma humano en neoplasias intraepiteliales tipo III; Cuenca-Ecuador, 2013-2017

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Abstract

Cervical cancer is one of the most common cancers in female population worldwide in underdeveloped countries, and in Ecuador it stands out in second place. This research focuses on HPV-genotype description in type III-intraepithelial neoplasms. The study type was analytical, retrospective and cross-sectional. The sample was 195 patients with NIC III diagnosis, from 20 to 60 years old, who were in the data system of "Sociedad de Lucha Contra el Cáncer" Cuenca–Ecuador, 2013-2017 term. It was established that HPV-16 genotype was in 32.9% (n 51) of all cases; factors like sociodemographic variables, tobacco use, infection, hormonal contraceptives use, more than one sexual partner, age of start of active sex life equal or less than 20 years old, didn't show a relationship with HPV infection; on the other hand, IUD use and HPV-16 infection had a statically significant relationship (OR 2,75; CI 95% 1,21-6,26; p 0,01). HPV genotype HPV-16 was the most common, and IUD use was a risk factor to get HPV infection.

Keywords: carcinoma in situ, uterine cervical dysplasia, papanicolaou test.

Resumen

El cáncer de cuello uterino, es uno de los cánceres más frecuentes en la población femenina a nivel mundial en países subdesarrollados, y en Ecuador ocupa el segundo lugar. Esta investigación se sitúa en la descripción de los genotipos del VPH en neoplasias intraepiteliales tipo III. El tipo de estudio fue analítico, retrospectivo y transversal. La muestra fueron 195 pacientes con diagnóstico de NIC III, de 20 hasta los 60 años de edad, que se encontraba en el sistema informático de la "Sociedad de Lucha Contra el Cáncer", Cuenca – Ecuador, periodo 2013 - 2017. Los datos fueron procesados a través del software SPSS 23.00. Se determinó que el genotipo VPH-16 estuvo en el 32,9% (n 51) de los casos; las variables sociodemográficas, consumo de tabaco, infecciones, uso de anticonceptivos hormonales, más de una pareja sexual, IVSA igual o menor de 20 años no presentaron relación a la infección por VPH; pero, el uso de DIU e infección por VPH-16 tuvo una relación estadísticamente significativa (OR 2,75; IC 95% 1,21-6,26; p 0,01). El genotipo de VPH-16 fue el más frecuente, y el uso de DIU fue un factor de riesgo para adquirir la infección por el VPH.

Palabras claves: carcinoma in situ, displasia del cuello del útero, prueba de papanicolaou.

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Introduction

Cervical cancer is one of the most prevalent cancer types in female population worldwide, particularly in third-world countries, there are many factors that are related to disease development, and one of them is human papilloma virus infection (HPV), infection that stands out as one of the most common in our field. This virus acts altering epidermis' and mucous' cells. Within this infection, many virus genotypes have been sorted, of which the high-risk ones are the most commonly related to lesion evolution prevalence (1,2).

This has led many studies to focus on virus' infection early diagnosis, some of them finding that cytology and colposcopy, which are the diagnostic methods in our field, have not had a big influence in cervix cancer's prevalence-and-death rates, since they detect cervix lesions in advanced stages (3).

In 2008, it was estimated that 4.8% of the 12.7 million cancer cases that were diagnosed worldwide, were related to HPV infection (4). For this reason, many studies have aimed to show HPV virus as a big factor in the development of premalignant and malignant lesions in cervix, esophagus, anal region, etc (5,6). The most important relationship is with cervical cancer, whom according to World Health Organization (WHO), in a non-immunocompromised woman could develop cancer in 15 to 20 years, and in an immunocompromised woman cancer could develop in 5 to 10 years (7).

As expressed above, for this research is appropriate to recognize human papilloma viruses-infection current prevalence in our field and contextualize these results according to world literature; knowledge will let us detect this issue's control and measures to take.

The objective of this study was to determine the prevalence and risk factors for infection by the genotypes of human papilloma virus in cervical intraepithelial neoplasia Type III, classified by the Bethesda System, in patients 20 to 60 years of age, users of the hospital SOLCA of Cuenca; period 2013 - 2017.

Methods

Investigation design: non-experimental analytical, cross sectional and retrospective study was done.

Population and sampling: the universe and sample of the study was formed by 195 female patients, with an III-intraepithelial neoplasms diagnosis, in ages between 20 and 60 years old, who were examined in external medical gynecology area in "Sociedad de Lucha contra el Cáncer" SOLCA in Cuenca - Ecuador. Inclusion criteria were: patients with NIC III confirmed results through cytology or biopsy, patients with infection evidence caused by one or more HPV genotypes, patients with complete medical records.

Methodology: according to protocol, samples were taken through cervical brushing, and then processed through DNA amplification through polymerase chain

reaction and hybrids capture. DNA amplification was done in Gene-Amp DNA PCR System 9700 and hybrids capture through Hibri-Max DNA HHM-2. For genotyping "37 HPV GenoArray Diagnostic Kit" was used, which has a primer, "HybriMem", which is a membrane that reacts according to different genotypes that feature in the sample, determines 37 different HPV genotypes (15 high risk, 6 low risk and 16 probably low risk); results are interpreted through a diaphragm which shows the exact place that must react and change its color. Quality control is according to ISO certification, through HybriBio's quality management system; besides each kit has quality control methods: an external one which controls each test lot, an internal one in each membrane which has a biotin control to examine all hybridization process, and a beta-globin one which shows the DNA-amplification's efficiency due to polymerase chain reaction.

Data collection: information was taken through forms for both sociodemographic variables and age, place of residence, marital status, education level and occupation, also aspects like gynecological background, sexually-transmitted-disease background and HPV genotyping were added.

Statistical analysis: data was entered in SPSS version 23.00 program. Recordings were made and results analysis was done with descriptive statistic according to frequency tables and percentages for qualitative variables and through average calculation and standard deviation for quantitative variables. For association, Pearson's square Chi and Odds Ratio were used with a 95% confidence interval, statistical significance was determined with a $p < 0,05$ value.

Bioethical aspect: in our country, physician's duty is to promote and ensure patient's health, wellness and rights, including those who take part in medical research; therefore, physician's knowledge and awareness must subordinate to that duty's accomplishment. Current research is ruled according to Helsinki's agreement and our country's laws, to give further protection to this study's participants.

All taken data will be used solely for this study, will have absolute confidentiality and will take respect for participants and their rights. Besides, through an ethical commitment letter with the Committee on bioethics of the Catholic University, the author of this study commits to use patient's taken data in an appropriate way.

Results

In sociodemographic parameters (Table 1), it was demonstrated that most of them were from urban areas (146), also a bigger portion is married (106), they predominantly had an elementary (78) and secondary (71) education level, regarding occupation there are more patients who do only housework.

Among study group's clinical characteristics features that patient's average number of sexual partners is 2,

additionally, sexual initiation's average age was 18 years old (Table 2).

Regarding related factors (Table 3), most patients did not consume tobacco (146); 27 women had a STD at some point in their lives, being Candidiasis the most common (13); about used contraceptive method, hormone use was the most common one (99); besides that, of the 195 patients with a diagnosis of type III-intraepithelial lesions, 159 had HPV infection and 42 had coinfection with 2 or 3 subtypes.

Table 1. Sociodemographic characteristics of SOLCA's female patients with a diagnosis of NIC III intracervical lesion; 2013-2017.

Variable	n (%)
Average age 39,4 ± 9 (DS)	
Origin	Rural 49 (25,1)
	Urban 146 (74,9)
Marital status	Single 42 (21,5)
	Married 106 (54,4)
	Widow 8 (4,1)
	Divorced 20 (10,3)
	Consensual union 19 (9,7)
Education Level	None 16 (8,2)
	Elementary 78 (40)
	Secondary 71 (36,4)
Occupation	Postsecondary 30 (15,4)
	Employed 87 (44,6)
	Housework 105 (53,8)
	None 3 (1,5)

Table 2. Clinical characteristics of SOLCA's patients with a diagnosis of NIC III intracervical lesion; 2013-2017.

Variable	Average	SD
Number of sexual partners	2	1,3
Age of sexual initiation	18	3

Table 3. Factors related to HPV infection of SOLCA's patients with a diagnosis of NIC III intracervical lesion; 2013-2017.

Variable	n (%)
195 (100)	
Cigarette smoking	Yes 47 (24,1)
	No 146 (75,9)
Sexually-transmitted diseases	Candidiasis 13 (6,7)
	Vaginosis 5 (2,6)
	Trichomoniasis 3 (1,5)
	Syphilis 3 (1,5)
	HIV 3 (1,5)
Contraceptive Method	None 168 (86,2)
	Hormonal 99 (50,8)
	IUD 28 (14,4)
	Tubal ligation 22 (11,3)
	Condom 14 (7,2)
HPV Infection	Rhythm 10 (5,1)
	None 22 (11,3)
	Yes 159 (81,5)
	No 7 (3,6)
HPV Coinfection	Undone test 29 (14,9)
	Yes 42 (21,5)
	No 124 (63,6)
	Undone test 29 (14,9)

Table 4 show genotype distribution in SOLCA's patients with a diagnosis of NIC III intracervical lesion; 155 of the 195 patients had HPV infection, in 29 of them the test was not performed, 4 were negative for HPV infection, and in 4 patients that were diagnosed positive for infection, HPV subtypes could not be found because they were out of the analysis spectrum regarding what is performed in the hospital. Of the high-risk genotypes, genotype 16 was found in 51 patients being the most common one, without considering the subtypes that are related to other subtypes, meanwhile low risk ones were rarely found, being genotype 71 the main subtype.

Table 4. Detected genotypes in SOLCA's patients with a diagnosis of NIC III intracervical lesion; 2013-2017.

Variable	n (%)
	155 (100)
	16 51 (32,9)
	31 18 (11,6)
	58 12 (7,7)
	33 5 (3,3)
	52 5 (3,3)
	16,52 4 (2,5)
	49 3 (1,9)
	31,58 3 (1,9)
	39 3 (1,9)
	16,45 3 (1,9)
	71 3 (1,9)
	35 2 (1,2)
	66 2 (1,2)
	16,33 2 (1,2)
	16,54 2 (1,2)
	6,1 1 (0,6)
	56 1 (0,6)
	43,31 1 (0,6)
	58,16 1 (0,6)
Genotypes	31,16,6,11 1 (0,6)
	18 1 (0,6)
	42,58 1 (0,6)
	16,52,58 1 (0,6)
	16,56 1 (0,6)
	33,35 1 (0,6)
	31,33 1 (0,6)
	59 1 (0,6)
	15,35,56 1 (0,6)
	35,58 1 (0,6)
	6,31 1 (0,6)
	6,52 1 (0,6)
	51,58 1 (0,6)
	16,68 1 (0,6)
	16,51,58 1 (0,6)
	51 1 (0,6)
	59,68 1 (0,6)
	6,16,45,51 1 (0,6)
	16,18 1 (0,6)
	53 1 (0,6)
	Other 15 (9,6)

Altogether, 42 coinfection cases with 2 or more HPV genotypes were found, the 16, 52 genotype-association was the most common; also genotype 16 is the most correlated with another genotype, being present in more than 10 of all possible associations (Table 5).

Risk factors like: cigarette smoking, hormone use as a contraceptive method, 2 or more sexual partners in the last

6 months, less-than-20-year-old age of sexual initiation, sexually-transmitted-disease background, and a marital status of singleness or consensual union, did not have a statistically significant relationship with human papilloma virus' genotype 16 infection; however, copper T type-IUD use as a contraceptive method was a related factor to this genotype's infection (OR 2.75; CI 95% 1,21–6,26; p 0,013) (Table 6).

Table 5. Found genotypes in SOLCA's patients with various-HPV subtypes' coinfection with a diagnosis of NIC III intracervical lesion; 2013-2017.

Variable	n (%)
	42 (100)
	16, 52
	31, 58
	16,45
	16, 33
	16, 54
	6, 31
	43, 31
	58, 16
	31, 16, 6, 11
	42, 58
	16, 52, 58
Coinfection	16, 56
Genotypes	33, 35
	31, 33
	15, 35, 56
	35, 58
	6, 31
	6, 52
	51, 58
	16, 68
	16, 51, 58
	59, 68
	6, 16, 45, 51
	16, 18

Table 6. Risk factors related to genotype 16 HPV infection, in study patients, SOLCA Hospital; 2013–2017.

Related Factors	Genotype 16		OR	CI 95% LI - LS	p Value
	Yes n (%) 77 (39,5)	No n (%) 118 (60,5)			
Age > 29 years old	Yes	72 (36,9)	1,9	0,66–5,62	0,21
	No	5 (2,5)			
Cigarette Smoking	Yes	18 (9,2)	0,9	0,48–1,84	0,84
	No	59 (30,2)			
Hormone Use	Yes	34 (17,4)	0,6	0,34–1,11	0,10
	No	43 (22)			
Sexual partners ≥ 2	Yes	44 (22,5)	0,9	0,47–1,52	0,59
	No	33 (16,9)			
Start of active sex life < 20 years old	Yes	54 (27,6)	0,6	0,39–1,16	0,12
	No	23 (11,7)			
Infection	Yes	11 (5,6)	0,59	0,72–1,27	0,17
	No	66 (33,8)			
IUD Use	Yes	17 (8,7)	2,75	1,21–6,26	0,013
	No	11 (5,6)			
Single or Consensual union	Yes	25 (12,8)	1,09	0,59–2,03	0,77
	No	52 (26,6)			

Discussion

Garcia et al., in 2017 (8), through a quantitative, observational, descriptive, cross-sectional, retrospective study, in 190.203 25-to-64-year-old women in Spain; determined that HPV prevalence is directly proportional to detected cytological lesion, affecting 90% of patients with a NIC III lesion. Likewise, Aguilar-Lemarroy et al. (9), through a 2015-Mexico-accomplished-studies meta-analysis formed by 822 patients with ages between 18-87 years old, demonstrated that 100% of type III-intracervical lesion patients had HPV infection. On this side, our study's results vary because it was determined that 81% of all population had an HPV infection.

De la Fuente et al., in 2013 (10), through an observational, cross-sectional, prospective and comparative analytical study where 343 Mexico City's women were studied, demonstrated that VPH infection's most prevalent age was 40 years old, which slightly differs with our study's found data (age average 39,4 years old ± 9).

Cabrera-Gaytan et al. (11), through a descriptive retrospective study, performed in Mexico in 2014, in a 299 women sample, demonstrated that variables like singleness or consensual union mean a slight risk for HPV infection regarding other marital status (RM = 1.214 CI 95% p= 0.548). It differs from our study because we could not find an association between a marital status of singleness or consensual union and a genotype 16-HPV infection.

Drolet et al. (12), through a meta-analysis performed in Canada in 2013 with a 953-patient sample, demonstrated that 38,5% of VPH-infected patients had accomplished secondary education, which differs with our study, because most of our patients finished elementary education.

Melo et al. (13), through their retrospective descriptive study made in Chile in 2016, in which a 151 18-to-24-year-old-university-student sample was used, they determined that more than half of the studied population (58,3%) with HPV infection said to having had three or more partners in the last three years; it is important to underline that most of them had high risk HPV genotypes (71,4%), besides that, they determined that HPV infection prevalence increased proportionally according to the number of sexual partners: 15,1% (one partner), 33,3% (two partners) and 51,5% (three or more partners) (13). This matches with our study, because it was proved that most women who had HPV infection had more than one sexual partner.

In their study, De la Fuente et al. (10), determined that start of active sex life showed an age average of 19,9 years old in HPV infected patients, unlike this, our study determined that start of active sex life is a year less, being 18 years old the average age for women with HPV infection.

Sánchez, in 2012 (14), through an observational, descriptive and retrospective study made in Malaga in a 111-patient sample, it determined that there was no statistically significant relationship between tobacco use

and HPV infection, however, an important percentage (52,1%) of HPV infected patients and with a diagnosis of type II and III intracervical lesions had a tobacco-use habit at the time of the study; what we beared out in our research, because an association between HPV infection and tobacco use was demonstrated.

Additionally, in the same study, Sanchez (14) demonstrated that 36% of hormonal-contraceptive using patients had type II or III intracervical lesions, but did not show a statistically significant relationship between HPV infection and referred contraceptives; in our study, it was demonstrated that a lesser number of patients used hormonal contraceptive method and had HPV infection, which represents 17% of all patients.

Rodríguez et al. (15), in their research named "Human papilloma virus infection in middle-aged women and related factors", a descriptive cross sectional study made in Cuba in 2014, which includes 177 patients, demonstrated that 31,1% of HPV infected patients did not have sexually-transmitted-disease background, and most of the patients with STD background were related to trichomoniasis cases (38,5%). It differs from our study, because we could demonstrate a bigger prevalence of candidiasis in 6.7% of all cases.

Flores-Miramontes et al. (16), in their research "HPV-genotype prevalence in Mexico and worldwide detected through Linear Array", which is a meta-analysis that consists of 12 studies made in Mexico, United States, Canada, Brazil, Sweden, Tanzania, Saudi Arabia and Australia, with 5.294 patients, in 2015 they demonstrated that infection in high-grade-intracervical lesions in homogeneous, due to a bigger-HPV-16 incidence, followed by HPV -31, -18, -52 and -51. This was beared out by Paredes through a cross-sectional study made in Spain in 2017 (17), with a 595-patient sample in which HPV-16 was the most prevalent genotype, found in 30,08% of HPV-infected women, besides that, a bigger coinfection incidence was noticed in less-than-34-year-old women. In our study HPV-16 was found to be the most common genotype in infected patients with a 32.9% percentage, likewise followed by HPV-31, but the following genotypes vary, with HPV-58 and HPV-32 featuring in third and fourth place according to their incidence.

In regard to coinfection, Aguilar-Lemarroy et al. (17), demonstrated that HPV-16 was the most common genotype related to other genotypes, and those other genotypes related to HPV-16 in women with malignant lesions were 18, 39 and 70; Paredes et al., demonstrated that less-than-34-year-old women are more likely to have a multiple infection. In our study it was proved that HPV-16 is the most related genotype to other genotypes, being related to more than 10 of possible relations to other genotypes, besides that, the most common relations of coinfection incidence were: 16,52; 31,58; 16,45; 16,33.

Averbach et al. (18), through a prospective-type research in 2017, in San Francisco, included 591 women who did not use IUD and 85 women that used IUD, the study's approach was on proving a relationship between HPV infection and IUD use as a contraceptive method,

and it could not be able to find a statistically significant relation between IUD use and HPV infection (OR: 0.50; CI: 95% 0.20-1.23; p = 0,13) or a decrease of HPV infection (OR: 1.44; CI: 95% 0.76-2.72; p= 0.26) . On the other side, this research demonstrated that 14,4% of studied patients used IUD as a contraceptive method, showing a statistically significant relationship (OR: 2,75; CI: 95% 1,21-6,26; p=0,013).

Salazar (19), through an analytical cross-sectional study, in 2016, made in indigenous women from 3 ecuatorian provinces, in which a 396-random-women sample was used, it was demonstrated a relationship between being more than 29 years old and having intracervical lesions without HPV, but in our study, this demonstrated relationship between older-than-29 age and HPV infection did not have a statistically significant value.

The prevalence of human papilloma virus infection in patients with type III-intraepithelial-lesion diagnosis was high. The sociodemographic profile showed by most of this study's patients, was 32-to-42-year-old patients, from urban origin, who have accomplished an elementary education level, married, whose occupation is housework.

Regarding gynecologic-obstetric characteristics found in most study's patients, were 2-or-more-sexual-partner patients, whose start of active sex life was at 18 years old. High-risk-HPV-16 genotype was the most common in study's group. Besides that, it was demonstrated that most patients have coinfection by two or more HPV genotypes, HPV-16 genotype was also regarded as the most common in referred coinfections, being the most related to other genotypes.

Bedoya et al., (20). In Ecuador, 166 samples were analyzed, including 57 and 95 cases of cervical intraepithelial neoplasia type 1 (CIN 1) and type 2/3 (CIN 2/3) respectively, and 14 cases of cancer. HPV DNA was found in 54.4% of the CIN 1 sample, 74,7% on the CIN 2/3 sample and 78.6% of the cancer sample. The types HPV 16 (38.9%) and HPV 58 (19.5%) were the most frequent. The risk factors for the development of cervical lesions / cancer were or more pregnancies (OR: 4.3) and HPV infection (OR: 3.7 for high-risk HPV, OR: 3.5 for HPV 16) among others.

The only related factor to HPV-16 infection that had a statistically significant value was IUD use. Variables like: more-than-29-year-old age, cigarette smoking, hormone use as a contraceptive method, two-or-more sexual partners, less-than-20-year-old start of active sex life and sexually-transmitted-disease background, did not have statistically significant values.

This research provides relevant information about the genotypes of human papilloma virus of the south-central region of Ecuador. These results may relate to the genotypes that cover the currently existing vaccines against HPV.

Conflict of Interest

Authors declare to have no conflict of interest.

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Study Limitations

There were no limitations for this study, because it is working with the total population.

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Authors Contribution:

TSPS: Information collection and bibliographic review. **STZK:** methodological analysis. **CDFR:** content analysis. **AHKA, EML:** contribution of methodological design and statistical processing, **EHM:** statistical and results analysis.