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Original Research Article

Correlation of the HPV genotype with the degree of dysplasia in patients with cervicouter cancer in the General Hospital Naval of high specialty

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ABSTRACT

Background: Cervical-uterine cancer (CaCu) is the second leading cause of death in women worldwide and the first in developing countries. It has been correlated to human papillomavirus (HPV) genotype with cancerous lesions reported in histopathological studies, which tells us about the prognosis of the patients. Objective of present study was to correlate the genotype of HPV to the histopathological result evaluated in these patients at the Naval Hospital of High Specialty.

Methods: A total of 316 women attended at the Naval General High Marine Hospital from 2015 to 2016 with HPV diagnosis were included, the histopathological report was correlated with the HPV genotype determined by the chain reaction of the polymerase (PCR). Statistical tests were applied for Smirnov and Kolmogorov, Chi square, OR, Anova-Kruskal Wallis. Data were processed using the SPSS software version 19 and a P <0.05 was taken as statistical significance.

Results: The mean age was 36.0±10.2. The detection of cervical cancer was reported in 3.8% and stage CIN III 2.5%; the highest proportion of patients were in the CIN I stage (51.3%), while the CIN II was 9.2%, and up to 30.7% were classified as HPV infection; only 2.5% were normal. The types of HPV prevalent by PCR were those at high risk different from 16 and 18 with a rate of 34.8%, then 16 at 5.1% and 18 at 0.3%. More than half of the cases (54.4%) were negative for the serotypes analyzed. In general terms, CaCu and CIN III were observed in 15% of the type 16, 0% in type 18, 25% in other high risk and 60% in negative PCR.

Conclusions: In this study, we obtained essential data that tells us that this population could be treated with low-risk HPV types associated with CaCu.

Keywords: Cervical dysplasia, Human papilloma virus, Polymerase chain reaction, Uterine cervical cancer

INTRODUCTION

Cervical cancer is the second most common cancer among women worldwide.¹ It is the second leading cause of mortality due to malignant neoplasia in women, producing up to 11 deaths per day affecting the age group

of 25-69 years and only is outweighed by breast cancer.² In Mexico, human papillomavirus infection is the cause of a large percentage of cervical cancer; is one of the main public health problems, with an incidence of 15.5% and a mortality of 12.8%.³ It has been identified that there are differences in the prevalence of type of HPV.⁴

Cervical cancer is caused by oncogenic HPV infection. More than 100 HPV genotypes have been described, of which approximately 40 are responsible for genital infection.⁵ HPV is classified as low or high risk based on its association with premalignant and malignant lesions, respectively. Low-risk HPVs include 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, and 81. Of these types, 6 and 11 cause 90% of cases of anogenital warts and low grade in cervical cells.^{6,7} High risk types include 16, 18, 31, 33, 35, 45, 52, and 58, of which 16 and 18 cause approximately 70% of all cases of invasive cervical cancer.⁸ Some authors have suggested geographical differences in the distribution of HPV can have an impact on the effectiveness of the HPV vaccine in different populations.⁹ In 2005, the International Agency for Research on Cancer reported the worldwide distribution of HPV types in women with cervical cytology normal. The most frequent serotype is HPV 16 followed by HPV 42, 58, 31, 18, 56, 81, 35, 33 and 45.¹⁰ In Mexico, HPV 16, 18, 31, 33, 39, 45, 53, 58 and 59 have frequently been found in normal cervical samples.¹¹⁻¹⁷ In the year 2015 in the United States they report that the most common high-risk human papillomavirus is serotype 16, associated with precancerous lesions in the cervix and conferring greater risk of disease of high-grade lesions; also reported that 50% of adenocarcinoma in situ and 50% of cases of invasive cancer were attributable to HPV infection 18.¹⁸

METHODS

The patients with cervical alterations between 2015 and 2016 were 316 with histopathological report, HPV genotyping by polymerase chain reaction, colposcopy surveillance, with cervical cytology; as well as a history and risk factors for CaCu were reviewed.

According to the results of pathology, the cases were classified according to histological types diagnosed in patients with HPV as follows: normal, changes associated with HPV infection, CIN I, CIN II, CIN III and cervical cancer. From the HPV PCR report the cases of agreement were classified as follows: 16, 18, other high risk and negative. Colposcopies were determined, which were classified as follows: normal, abnormal and CaCu; as to the cytologies were classified as: normal, low grade, high grade and CaCu. The records were searched with a complete medical history and specified risk factors for CaCu such as age, menarche, onset of active sex life, nulliparity, smoking, sexually transmitted diseases and menopause. Subsequently with the collected data a database was made for statistical analysis. The present study was approved by the Ethics and Local Research Committee, which granted approval with document number 2S.1.798 / JP373 / 16.

Statistical analysis

The description of the sample was carried out using descriptive statistics with measures of central trend and dispersion, as well as frequency counting, proportions

and percentages. For the bivariate and multivariate analysis, inferential statistics were applied, including analysis of variance of one and two factors to compare means and to evaluate the interactions; the Chi square test was applied to compare ratios and Student's t-test to compare two averages of samples with normal distribution. A p equal to or less than 0.05 was considered significant to reject null hypotheses. The data were analyzed with the SPSS package ver 17.0 for Windows, with a significance value of $p < 0.05$.

RESULTS

The mean age with its respective standard deviation was 36.0 ± 10.2 in the range of 17 to 71 years. The average menarche was at 12.6 ± 1.6 with 7 years the lowest until 19 the highest. The onset of active sexual life fell in 18.5 ± 2.9 years with an interval of 11 to 32. Only 17.4% were in the menopause, 42.1% referred to sexually transmitted diseases, approximately 40% were positive to alcoholism and 24.1% to smoking. A little more than half were nulliparous (50.6%) and 3.5% were diagnosed as cervical cancer by colposcopy, but up to 93.4% were reported with abnormal results; only 5 cases (1.6%) were reported as cervical cancer, 8.5% had high-grade lesions, 66.1% were low-grade, and 23.7% were normal.

By the gold standard the identification of cervical cancer reached a rate of 3.8% and in stage CIN III 2.5%; (Figure 1) showed that the highest proportion of patients were in the CIN I stage (51.3%), while the CIN II was 9.2%, and up to 30.7% were classified as HPV infection, only 2.5% were normal.

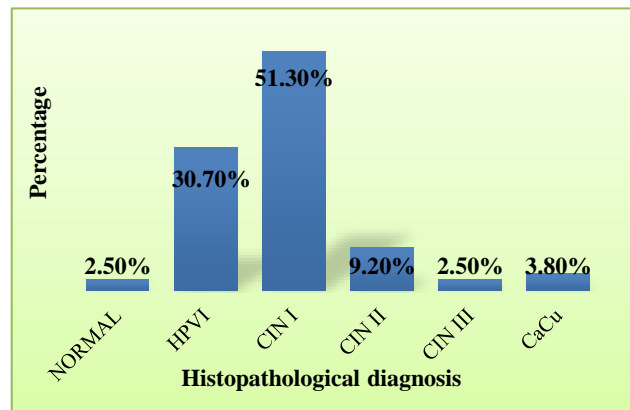


Figure 1: Histopathological diagnoses of cases.

The HPV types prevalent by PCR were those of high grade different to 16 and 18 with a rate of 34.8%, then 16 in 5.1% and 18 in 0.3%; the combination of 16 plus other high risk were 4.1% and the combination of 18 plus other high risk were barely 1.3%. In general, type 16 (only or combined) amounted to 9.2%, 18 (only or combined) was present in 1.6% of the total. It should be noted that more than half of the cases (54.4%) were negative for the serotypes analyzed (Figure 2).

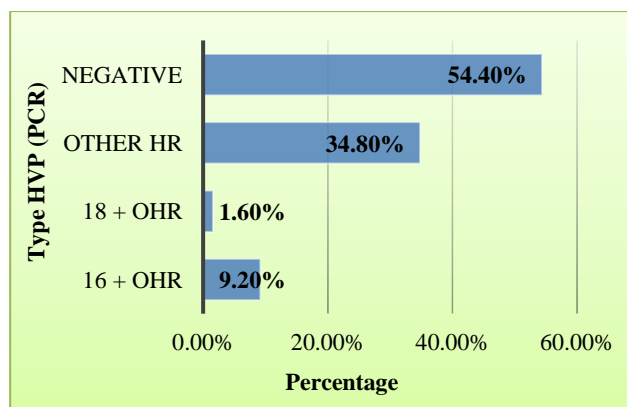


Figure 2: Prevalence of HPV types identified by PCR.

Bivariate and multivariate analysis

As can be observed (Table 1), the cases of CIN 3-Cacu had a significantly higher mean age than the patients in the other strata of the histopathological diagnosis ($p = 0.0001$ according to the analysis of variance of one factor = ANOVA ONE WAY); On the contrary, normal cases started menarche at a significantly higher age than the other diagnostic strata ($p = 0.02$ ANOVA ONE WAY); it is also easy to observe in the same table 1 that up to 65% of the cases classified as CIN 3-Cacu were in the menopause whereas in the other diagnostic strata the proportions of patients in menopause did not exceed 41% ($p = 0.0001$ according to Chi square test). It is also noticeable that, so many cases classified as CIN 1-2 and

those with HPV1, had higher proportions of nulliparous patients ($p = 0.02$). Finally, it should be noted that serotype 16 (alone or in combination with other high-grade) was distributed in a significantly higher proportion of cases of CIN 3-Cacu (15%) versus 12.5% in normal cases, 9.9% in CIN1-2 and 6.2% in the HPV1, note that when the age analysis according to the distribution of serotype 16, the cases of CIN 3-Cacu decreased the age to 33.3 average years, while the cases of IVPH with serotype 16 increased the average age to 43.1 years; serotypes 18 (alone or combined with high grade) were only concentrated in the cases of CIN1-2 and between the normal ones, both with very similar average ages (32.5 years vs 34.0); the other high-grade serotypes were identified mainly in the normal classified cases (62.5%) and in the cases CIN 1-2 (37.2%) but an outstanding fact is that the age of CIN 3-Cacu patients simultaneously carrying serotypes of high levels different to 16 and 18 rises to an average of 52.4 years, that is to say, almost 20 years more than the average of the carriers of the serotype 16 whose age was 33.3 years, also, note that the average age of the cases normal is raised to 43.0 or 13 years longer than normal but carriers of serotypes 16; However, negative cases of serotypes studied were distributed in greater proportion within the diagnoses of HPV1 (63.9%) and within the CIN 3-Cacu (60.0%), and in both strata the age was higher (39.3 for HPV1 vs 47.0 for CIN 3-Cacu) to that of the other two strata or normal and CIN 1-2. ($p = 0.04$ when comparing the proportions of the HPV serotype according to the histopathological diagnosis according to the Chi square test).

Table 1: Analysis of sociodemographic factors with histopathological report.

Factors	Histopathological diagnosis				p
	Normal (n = 8)	HPV1 (n = 97)	CIN I-II (n = 191)	CIN 3-CaCu (n = 20)	
Age	38.5 ±9.2	38.1 ±11.0	33.8 ±8.3	46.3 ±14.4	0.0001
Menarche	14.0 ±2.3	12.3 ±1.7	12.6 ±1.5	12.9 ±1.1	0.02
IVSA	18.8 ±1.8	18.9 +7- 3.1	18.4 ±2.6	18.3 ±4.6	0.58
Menopause	3 (37.5%)	24 (24.7%)	15 (7.9%)	13 (65.0%)	0.0001
STDs	3 (37.5%)	40 (41.2%)	77 (40.3%)	13 (65.0%)	0.19
Nuliparity	3 (37.5%)	44 (45.4%)	108 (56.5%)	5 (25.0%)	0.02
Type of HPV					
16+other HR	1 (12.5%)	6 (6.2%)	19 (9.9%)	3 (15.0%)	P type of HPV=0.04
Age	29.9±9.6	43.1±3.9	32.8±2.2	33.3±5.5	
18+other HR	1 (12.5%)	-	4 (2.1%)	-	
Age	34.0±9.6	-	32.5±4.8	-	
Other HR	5 (62.5%)	29 (29.9%)	71 (37.2%)	5 (25.0%)	
Age	43.0±4.2	34.5±1.7	33.6 ±1.1	52.4±4.2	
Negative	1 (12.5%)	62 (63.9%)	97 (50.8%)	12 (60.0%)	
Age	30.0±9.6	39.3±1.2	34.1±0.9	47.0±2.7	
P for age	0.38	0.03	0.93	0.02	

To close the description of Table 1, it should be noted that when comparing the means of age according to

serotype within each diagnosis the differences are significant within the HPV1 ($p = 0.03$) and within those of CIN 3-Cacu ($p = 0.02$); this means that the serotypes

are distributed differently according to the age within each diagnosis, for example, in the HPV16 the average ages were: 43.1 for the 16; 34.5 for the other high-grade and 39.3 for the negative cases ($p = 0.03$); in the cases of CIN 3-Cacu the corresponding ages were 33.3 for the 16; 52.4 for high grade and 47.0 for negative ($p = 0.02$) overall and according to the analysis of variance of two factors there is a significant interaction ($p = 0.03$) between the histopathological diagnosis and the serotype for age.

If we analyze the relationship between the STDs strata (SI and NO), note that in the stratum of positive STDs ($n = 133$) the differences in the proportions of the serotypes are not significant ($p = 0.43$ Chi squared) and that in the stratum of negative STDs ($n = 183$) the differences between the proportions of the serotypes according to the histopathological diagnosis are very broad ($p = 0.009$ Chi squared). It should be noted that the mean age of the stratum with STD is 35.7 vs 36.3 years of the stratum

without STD ($p = 0.61$) so that the difference between strata is not explained by age. What is distinctive is that, on the one hand, other high-grade serotypes are widely distributed among the diagnoses of both strata and on the other hand it should be noted that serotype 16 is distributed in greater proportion in cases of CIN 3-CaCu, but of stratum without STDs.

In relation to nulliparity, the differences between the serotypes according to diagnosis are not significant ($p = 0.33$) in the nulliparous stratum ($n = 160$ but whose average age is 32.1 years versus 40.1 years of the 156 nulliparous ones: $p = 0.0001$ t of Student). In the non-nulliparous stratum within normal cases there are no negative serotypes and 80% correspond to other high-grade serotypes and one case with serotype 18, contrasting within the cases of HPV16, CIN1-2 and CIN 3-Cacu Negativity rates exceed 50% with serotypes 16 in very low proportions ($p = 0.01$ Chi square plausibility ratio).

Table 2: Sociodemographic factors related to HPV type.

Factors	Type of HPV				P
	16 (n = 29)	18 (n = 5)	OHR (n = 110)	Negative (n = 172)	
Age	34.9±10.6	32.8±7.7	35.1±9.6	36.9±10.5	0.4
Menarche	12.8±1.6	12.8±0.8	12.7±1.6	12.4±1.4	0.41
IVSA	17.6±2.1	18.4±7- 2.1	19.1±3.1	18.4±2.9	0.07
Menopause	5 (17.2%)	0	12 (10.9%)	38 (22.1%)	0.04
STDs	15 (51.7%)	2 (40.0%)	44 (40.0%)	72 (41.9%)	0.72
Alcoholism	7 (24.1%)	4 (80.0%)	46 (41.8%)	69 (41.9%)	0.08
Smoking	6 (20.7%)	2 (40.0%)	22 (20.0%)	46 (26.7%)	0.47
Nuliparity	17 (58.6%)	4 (80.0%)	59 (53.6%)	80 (46.5%)	0.24

Finally, for ethyl alcohol, the differences between the proportions of serotypes according to histopathological diagnosis are only significant ($p = 0.009$ Chi squared) in the stratum of cases with positive alcoholism, whose $n = 126$ and with a mean age of 34.4 years vs 37.1 years negative cases of alcoholism with $n = 190$ so that age again seems to be a strong confounding factor ($p = 0.02$ for the difference of means of age according to Student's t). In normal cases with positive efficacy serotypes 18 and others of high degree were detected and that in the opposite end the cases of CIN 3- CaCu within the same stratum of positive alcoholism were only serotypes 16 and the rest were negative serotypes; ($p = 0.27$ Chi squared), all the diagnoses shared similar distributions of serotypes 16 and others of high grade (without any case of serotypes 18).

Close the analysis of the data emphasizing that the serotypes were independently related with significant differences in their proportions according to menopause and with significant differences (without being

significant) according to age of IVSA and ethylism; (Table 2) that, in the presence of menopause, the rate of negative serotypes is proportionally greater than the proportions of serotype 16 and others of high grade ($p = 0.04$).

On the other hand, the IVSA age of patients with other high-grade phenotypes was higher in comparison to those of serotypes 16 and 18 and of negative ones ($p = 0.07$), and, finally, a relevant data is that 4 of 5 cases (80.0%) of serotype 18 were identified in patients with positive efficacy whereas within this same stratum of positive efficacy serotype 16 was only identified in 24.1%, other high grade types in 41.8% and negative serotypes in the 40.1% ($p = 0.08$).

Performance of diagnostic methods

Compared with the gold standard (histopathological diagnosis), colposcopy reveals a sensitivity of 55% and a specificity of 12.5%, as measured by diagnostic yield as

reasons for probability to be observed (Table 3) that cases reported as normal by colposcopy remain in the CaCu area discarded; while those reported as abnormal are only 0.46 times more likely to correspond to CaCu, obviously all cases reported as CaCu by colposcopy enter the confirmation zone.

In Table 4, the distribution of HPV types by colposcopy and gold standard results are mentioned.

Table 3: Probabilistic comparison of diagnosis by colposcopy and histopathological diagnosis.

Colposcopy	Histopathological diagnosis of CaCu		Probability ratio of CaCu
	Yes	No	
Normal	0	10 (3.4%)	Discarded
Abnormal	9 (45.0%)	286 (96.6%)	0.46
CACU	11 (55.0%)	0	Confirmed
Total	20	296	

Table 4: Distribution of HPV types according to colposcopy and presence or absence of CaCu.

Colposcopy	Type HPV (PCR)		CaCu		Total
			With	Without	
Normal	Type HPV (PCR)	16 +other HR		1(10%)	1 (10%)
		Other HR		2 (20%)	2 (20%)
		Negativos		7 (70%)	7 (70%)
	Total		10 (100%)	10 (100%)	
Abnormal	Type HPV (PCR)	16 +other HR	1 (11.1%)	25 (8.7%)	26 (8.8%)
		18+other HR	0 (0%)	5 (1.7%)	5 (1.7%)
		Other HR	3 (33.3%)	103 (36%)	106 (35.9%)
		Negative	5 (55.6%)	153 (53.5%)	158 (53.6%)
	Total		9 (100%)	286 (100%)	295 (100%)
CaCu	Type HPV (PCR)	16 +other HR	2 (18.2%)		2 (18.2%)
		Other HR	2 (18.2%)		2 (18.2%)
		Negative	7 (63.6%)		7 (63.6%)
	Total		11 (100%)		11 (100%)

For cytology the sensitivity is 25.0% with 20% specificity; however, measured the diagnostic yield as a likelihood ratio see (Table 5) that a normal cytology report equals a probability of 0.83 that corresponds to CaCu, if it is reported low-grade the probability is 0.07 times that it is CaCu, but if it is reported as high-grade it is 8.70 times more likely to correspond to CaCu.

Table 5: Probabilistic comparison of: diagnosis by cervical cytology and histopathological diagnosis.

Cytology	Histopathological Diagnosis of CaCu		Probability ratio of CaCu
	Yes	No	
Normal	4 (20.0%)	71 (24.0%)	0.83
Low grade	1 (5.0%)	208 (70.3%)	0.07
High grade	10 (50.0%)	17 (5.7%)	8.7
CaCu	5 (25.0%)	0	Confirmed
Total	20	296	

DISCUSSION

The incidence of cervical cancer in young women continues to increase; in this study with a mean age for CaCu of 46.3±14.4; very similar to that reported in the United States with a mean age at diagnosis of 48 years.¹⁹ In Mexico there is an incidence of 15.5% and a mortality

of 12.8%.³ A detection rate of 3.8% for CaCu and 2.5% for CIN III has been reported in this study. A low ratio of CaCu with HPV 16 and 18 was found to be different from what is currently reported in the literature and different population; in general the CaCu and CIN III were observed 15% in type 16, 0% in type 18; 25% in others at high risk and 60% in negative PCR reports, which makes us think that they could be low risk HPV; which differs to studies where it is mentioned that up to 70% of cases of CaCu are mainly caused by types 16 and 18.

Of the patients diagnosed with CaCu (n = 20), 65% (13) reported having undergone sexually transmitted diseases, which coincides with that reported in the literature, where STDs are considered a risk factor for CaCu.

The average age for initiation of active sexual life in cancer patients was 18.3±4.6; it is worth remembering that it is considered a risk factor if the first sexual relation is 21 years; the risk is approximately 1.5 times in 18 to 20 years and double for those under 18 years of age.²⁰ Although smoking is considered a risk factor for presenting CaCu; there was no statistical significance in relation to it, as in other literature where smoking is not associated with a significantly higher risk of cervical cancer compared to nonsmokers.²⁰⁻²²

In the studied population, 3.5% were diagnosed as cervical cancer by colposcopy, but up to 93.4% were reported with abnormal results; so that in this analysis we found a sensitivity of 55% and specificity of 12.5% in comparison with the gold standard (histopathology); it should be mentioned that colposcopy using the criteria of the International Federation of Cervical Pathology and Colposcopy of 2011 reports a sensitivity of 86 percent and a specificity of 30 percent, which differs in our study. Only 5 cases (1.6%) were reported as cervical cancer, 8.5% with high grade lesions, 66.1% low grade and 23.7% normal, with a sensitivity of 25% and specificity of 20%; In a systematic review, sensitivity and specificity varied significantly, sensitivity ranged from 30% to 87% and specificity ranged from 86% to 100%, for which it is mentioned that it is a dependent operator study; even so in this analysis, these values are reported below expectations.^{23,24}

CONCLUSION

Cervical cancer continues to be one of the pathologies of higher morbidity and mortality in the female population. In our population with detection of invasive CaCu of 3.8% and cancer in situ of 2.5%; despite the advances in screening, treatment and follow-up, it has not been possible to modify the natural course of the disease. The mean age of patients with cervical cancer was 46 years, ranging from 17 to 71 years; so, it is recommended that patients with risk factors should be considered for a broader follow-up, thus avoiding diseases of advanced stages, their complications and decreasing the quality of life of patients.

Compared to the gold standard (histopathological), cytology presented a sensitivity of 25% and specificity of 20%; colposcopy had a sensitivity of 55% and specificity of 12.5%; so, it is recommended to perform more than one screening study for further detection.

In this study we are reporting some interesting data on the risk factors and the presence of HPV genotypes with respect to the histopathology report present in our study population; which could be very useful to give an earlier detection of the disease and to be able to carry out the ideal treatment for each patient, with less complications; in this study we can conclude that the knowledge of HPV genotype as well as risk factors are data that could be applied in clinical practice in order to give an overview of the pathology, thus reducing institutional costs by giving preventive management and even timely treatment.

Concluding that, in our population, patients who were diagnosed with cervical cancer or cervical dysplasia, reported a negative PCR for high-risk HPV; which would make us think of including a broader PCR in which low risk HPV is detected and more specific for high risk HPV; which could be present in our population.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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