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The usefulness of high-risk HPV hybrid capture in patients with squamous cell atypia in cervical cytological examination

A utilidade da captura híbrida para o HPV de alto risco em pacientes com atipia de células escamosas na colpocitologia

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ABSTRACT

Introduction: The cervical cytological examination and the investigation of high-risk human papillomavirus (HPV) deoxyribonucleic acid (DNA) are well-known valuable tools for screening of cervical lesions, since they allow the early diagnosis of cancer and its precursor lesions. **Objective:** This study aimed to evaluate the ability of high-risk HPV DNA detection by hybrid capture to predict intraepithelial lesions and cancer in patients with initial cervical cytological diagnosis of atypical squamous cells (ASC). **Method:** Retrospective analysis of histological or cervical cytological results after one-year follow-up from hybrid capture for high-risk HPV DNA research in patients with previous ASC diagnosis. Sensitivity, specificity and positive and negative predictive values of hybrid capture were calculated in relation to the identification of squamous intraepithelial lesions. **Results:** Among the 163 patients previously diagnosed with ASC and absence of high-risk HPV DNA, nine (5.5%) showed low-grade (LSIL) or high-grade squamous intraepithelial lesion (HSIL) during the follow-up. On the other hand, among the 110 patients presenting ASC and high-risk HPV DNA positivity, 43 (39%) showed cervical lesions within one year. Sensitivity and specificity values and positive and negative predictive values applied to hybrid capture for the identification of squamous intraepithelial lesions were 82.3%, 69.3%, 38.1%, and 94.4%, respectively. **Conclusion:** Our results showed a high negative predictive value of hybrid capture for cervical lesions detection, in patients with previous diagnosis of ASC, when the high-risk HPV DNA research was negative.

Key words: cervical squamous cells of the atypia; early detection of cancer; cervical intraepithelial neoplasia; cervical squamous intraepithelial lesions; papillomavirus infections; Brazil.

RESUMO

Introdução: *O exame colpocitológico e a investigação do ácido desoxirribonucleico (DNA)-papilomavírus humano (HPV) de alto risco são ferramentas bem conhecidas para o rastreamento das lesões cervicais, pois permitem o diagnóstico precoce do câncer e suas lesões precursoras.* ***Objetivo:*** *Este estudo tem o objetivo de avaliar a capacidade da detecção do DNA-HPV de alto risco pela captura híbrida em predizer lesões intraepiteliais e câncer em pacientes com diagnóstico colpocitológico inicial de atipia de células escamosas (ASC).* ***Método:*** *Análise retrospectiva de resultados histológicos e colpocitológicos após um ano de seguimento a partir da captura híbrida para pesquisa de DNA-HPV de alto risco em pacientes com diagnóstico prévio de ASC. Sensibilidade, especificidade e valores preditivos positivo e negativo da captura híbrida foram calculados em relação à identificação de lesões intraepiteliais escamosas.* ***Resultados:*** *Entre as 163 pacientes com diagnóstico de ASC prévio e ausência do DNA-HPV de alto risco, nove (5,5%) apresentaram lesões intraepiteliais escamosas de baixo grau (LIEBG) ou alto grau (LIEAG) durante o acompanhamento. Por outro lado, das 110 pacientes com ASC e positividade para o DNA-HPV de alto risco, 43 (39%) apresentaram lesões cervicais em até um ano. Os valores de sensibilidade e especificidade e os valores preditivos positivo e negativo aplicados à captura híbrida*

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para a identificação de lesões intraepiteliais escamosas foram 82,3%, 69,3%, 38,1% e 94,4%, respectivamente. ***Conclusão:*** *Nossos resultados mostraram alto valor preditivo negativo da captura híbrida para detecção de lesões cervicais em pacientes com diagnóstico prévio de ASC, quando a pesquisa do DNA-HPV de alto risco foi negativa.*

Unitermos: *atipia de células cervicais escamosas; detecção precoce de câncer; neoplasia intraepitelial cervical; lesões intraepiteliais escamosas cervicais; infecções por papilomavírus; Brasil.*

RESUMEN

Introducción: *La colpocitología y la investigación del ácido desoxirribonucleico (ADN) del virus del papiloma humano (VPH) de alto riesgo son herramientas bien conocidas para la detección de lesiones cervicales, puesto que permiten el diagnóstico precoz del cáncer y sus lesiones precursoras.* ***Objetivo:*** *El objetivo de este estudio es evaluar la capacidad de detección del ADN-VPH de alto riesgo por captura híbrida en predecir lesiones intraepiteliales y cáncer en pacientes con diagnóstico colpocitológico inicial de atipia de células escamosas (ASC).* ***Método:*** *Análisis retrospectivo de resultados histológicos y citológicos después de un año de seguimiento desde la captura híbrida para investigación de ADN-VPH de alto riesgo en pacientes con diagnóstico previo de ASC. Se calcularon sensibilidad, especificidad y valores predictivos positivo y negativo en relación con la identificación de lesiones intraepiteliales escamosas.* ***Resultados:*** *Entre las 163 pacientes con diagnóstico de ASC previo y ausencia de ADN-VPH de alto riesgo, nueve (5,5%) presentaron lesiones escamosas intraepiteliales de bajo grado (LEIBG) o alto grado (LEIAG) durante el seguimiento. Por otra parte, entre las 110 pacientes con ASC y positividad para ADN-VPH de alto riesgo, 43 (39%) presentaron lesiones cervicales en un plazo de un año. Los valores de sensibilidad y especificidad y los valores predictivos positivo y negativo empleados en la captura híbrida para identificar lesiones escamosas intraepiteliales fueron 82,3%, 69,3%, 38,1% y 94,4%, respectivamente.* ***Conclusión:*** *Nuestros resultados demostraron alto valor predictivo negativo de la captura híbrida para detectar lesiones cervicales en pacientes con diagnóstico previo de ASC, cuando la investigación de ADN-VPH de alto riesgo ha sido negativa.*

Palabras clave: *atipia en células escamosas del cuello uterino; detección precoz del cáncer; neoplasia intraepitelial cervical; lesiones intraepiteliales escamosas del cuello uterino; infecciones por papillomavirus; Brasil.*

INTRODUCTION

According to the World Health Organization (WHO), in 2014, cervical cancer was among the five most frequent neoplasms in the female population[1] and is the second leading cause of death in women aged 20-39 years according to the American Cancer Society[2, 3]. It is the second most common type of cancer among women in countries that do not have access to screening programs[2].

The causal relation between human papillomavirus (HPV) and cervical cancer and its precursor lesions is well established in the literature. It is recognized that most of the female genital tract infections caused by different types of HPV have a transient nature. However, the persistence of high-risk HPV infection is a *sine qua non* for the development of intraepithelial cervical neoplasms. The integration of viral deoxyribonucleic acid (DNA) into the cellular genome is a necessary event for triggering the process of carcinogenesis. Notably, the overexpression of oncogenic E6 and E7 viral proteins leads to changes in the cell cycle due to mutations in the genes encoding the tumor suppressor proteins p53 and Rb (retinoblastoma). Messenger RNA (mRNA) levels corresponding to the expression of oncogenic E6 and E7 proteins are closely related to cervical lesions, and are directly proportional[4-8].

Cytological screening is an effective method that has a positive impact on the early diagnosis of cervical cancer. However, some studies suggest that tests for the detection of high-risk HPV exhibit greater sensitivity compared to cytology[5, 7-10]. According to Sauter *et al*. (2014)[4], cervical cytology as a single screening method presents around 73% sensitivity in the detection of high-grade intraepithelial lesions (HSIL) or carcinomas, while Barut *et al*. (2015)[11] observed sensitivity and specificity corresponding to 57% and 76%, respectively, for colpocytology as a single method. In turn, Mustafa *et al*. (2016)[7] observed rates of 43%-94% for sensitivity and 78%-98% for specificity attributed to cervical cytological examination. In contrast, the sensitivity of

the hybrid capture method to high-risk HPV DNA is approximately 96% and 95.3% for high-grade intraepithelial lesions (CIN2) and high grade 3 (CIN3), respectively[4].

Thus, several studies suggest that molecular tests for the detection of high-risk HPV may be an alternative to cytological study in the detection of low-grade intraepithelial lesion (LSIL), HSIL and carcinomas of the cervix[2, 8, 10, 12, 13]. It is discussed the possibility of adopting the hybrid capture method as the primary screening tool for cervical cancer in order to replace cytology in the detection of cervical lesions, especially in women of over 30 years old. The hybrid capture has been progressively incorporated into screening programs in recent years, resulting in lower rates of invasive cancers in subsequent screening cycles[5, 12, 14].

The molecular method for the detection of HPV DNA is considered the "gold standard" worldwide; Hybrid Capture 2 (digene HC2, QIAGEN Corporation, Gaithersburg, Maryland, USA) was approved by the US Food and Drug Administration (FDA) for the detection of thirteen high-risk HPV genotypes. According to the US guidelines, it is recommended to use it in the investigation of cervical cytology of squamous cells atypical of indeterminate significance (ASC-US) or atypical squamous cells of undetermined significance, and could not exclude high-grade intraepithelial lesion (ASC-H), in discordant diagnoses or in co-test with cytological investigation in women aged 30 years or older every 5 years[2, 7, 8, 10, 12, 14]. However, even in HSIL, virus screening may be negative, and this issue should be studied prior to the institution of hybrid capture as a primary and single screening method, with simultaneous screening (co-test) being the most recommended modality currently[12]. In Brazil, the current Ministry of Health (MOH) screening guidelines do not recommend routine use of HPV DNA screening[15].

In this context, the objective was to evaluate the ability of the hybrid capture method for high-risk HPV to predict the detection of squamous intraepithelial lesions and carcinoma in patients presenting atypical squamous cells in the cervical cytological analysis.

METHOD

This study consisted of a retrospective analysis of the results of examinations contained in a database of the Centro de Diagnósticos Anatomopatológicos (CEDAP), in Joinville, Santa Catarina, Brazil, conducted consecutively between November 2015 and May 2018.

The mean age of patients included in the study was 36 ± 10.1 years (18-77 years) and cervical cytological diagnosis of ASC-US or ASC-H, resulting in high-risk HPV DNA screening by the hybrid capture method (digene HC2, QIAGEN Corporation, Gaithersburg, Maryland, USA), performed as a co-test or a subsequent test following the manufacturer's instructions. Patients who had at least a histological or cervical cytology follow-up were considered up to the end of the first year after a cervical cytology with ASC-US or ASC-H associated with the hybrid capture test. Sensitivity, specificity and positive and negative predictive values of the hybrid capture were calculated against the identification of lesions in the period defined for the follow-up.

The diagnosis obtained in cervical cytology and histology were categorized according to the Bethesda System, stratified in normal/reactive, ASC, LSIL, and HSIL.

The data were tabulated and analyzed on a Microsoft® Excel spreadsheet for Windows 10. The chi-square test was used to compare the distribution of cases of lesions (LSIL and HSIL) and carcinoma identified at follow-up among groups of patients with positive and negative hybrid capture, and a significant difference was estimated when $p < 0.05$.

RESULTS

From the 273 ASC patients included in the study by colpocytology, 110 (40.3%) presented positive hybrid capture for high-risk HPV, as shown in **Figure 1**. Among these and over one year, 43 (39%) patients presented cervical lesions. Histology detected In 19 LSIL cases (five histological diagnoses and 14 cervical cytological diagnoses) were detected; 23 HSIL cases (19 histological diagnoses and four cervical cytological diagnoses),

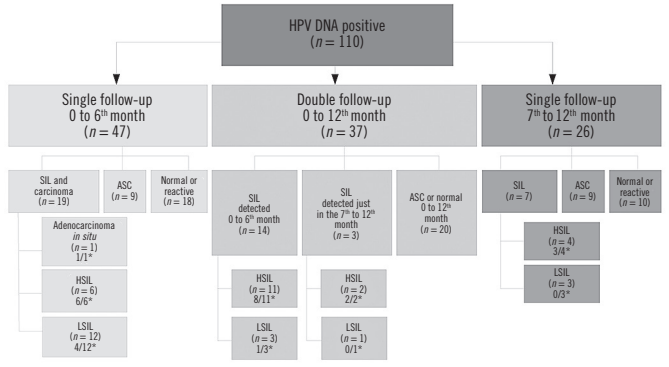

FIGURE 1 – *Distribution of HPV-positive by hybrid capture cases for histological or colposcopy evaluation outcome within one-year of follow-up after identification of atypical squamous cells*

*HPV: human papillomavirus; DNA: deoxyribonucleic acid; SIL: squamous intraepithelial lesions; ASC: atypical squamous cells; HSIL: high-grade intraepithelial lesion; LSIL: low-grade intraepithelial lesion; *number of cases with histology/total number of cases.*

and one case of adenocarcinoma *in situ* determined. From the 57 patients who underwent cervical cytological or histological evaluation within six months, 33 presented lesions, while 10 patients presented lesions in the second half of the 1-year follow-up.

The 163 (59.7%) cases that presented ASC diagnosis by cervical cytology and negative hybrid capture for high-risk HPV are analyzed in **Figure 2**. It was observed that nine (5.5%) patients presented a subsequent diagnosis of LSIL ($n = 7$), three histologically determined and the others by cervical cytology; or HSIL diagnosis ($n = 2$), of which one determined by histology and the other by cervical cytology. With the exception of one LSIL case, all others were detected within the first six months of the 1-year follow-up.

The cases of cervical lesion identified in the follow-up were significantly concentrated in patients who, in addition to presenting atypia, presented positive hybrid capture for high-risk HPV (39% vs 5.5%, $p < 0.05$). The sensitivity, specificity, positive and negative predictive values are shown in **Table**.

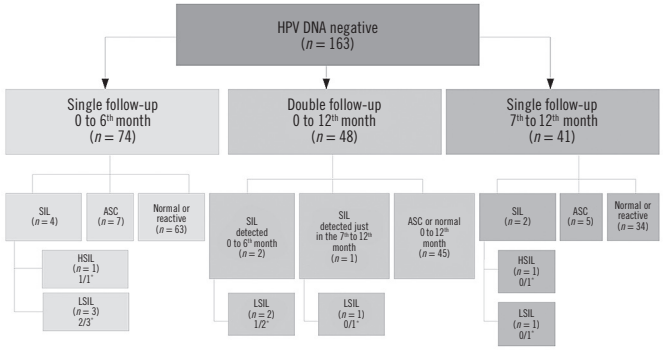

FIGURE 2 – *Distribution of HPV-negative by hybrid capture cases for histological or colposcopy evaluation outcome within one-year of follow-up after identification of atypical squamous cells*

*HPV: human papillomavirus; DNA: deoxiribonucleic acid; SIL: squamous intraepithelial lesions; ASC: atypical squamous cells; HSIL: high-grade intraepithelial lesion; LSIL: low-grade intraepithelial lesion; *number of cases with histology/total number of cases.*

TABLE – Sensitivity, specificity, positive and negative predictive values for HSIL and LSIL

Parameters (%)	HSIL	LSIL	Both
Sensitivity	92	73	82.3
Specificity	64	63.1	69.3
Positive predictive value	20.9	17.2	38.1
Negative predictive value	98.7	95.7	94.4

HSIL: high-grade intraepithelial lesion; LSIL: low-grade intraepithelial lesion.

DISCUSSION

The high negative predictive value (98.7%) obtained for the observation of HSIL within one year after diagnosis of ASC in the cervical cytology associated with negative hybrid capture for high-risk HPV indicates an advantage in associating the two methods as a screening tool for lesions in the uterine cervix. A high negative predictive value attributed to hybrid capture after the identification of ASC in colpocytology may help in the definition of subsequent conducts, insofar as it reassures the physician and patient and allows the reduction of the frequency of invasive procedures, such as colposcopy and biopsy[9,14]. According to Zeferino *et al.* (2018)[16], when high-risk HPV DNA is undetectable, the occurrence of precursor lesions or cervical cancer is very unlikely.

The relevance of a high negative predictive value attributed to hybrid capture is evident in the "Kaiser Permanente Northern California" (Oakland) study, which involved 315,061 women for more than 5 years. In those who showed negativity for high-risk HPV, the incidence of cervical cancer was extremely low (3.8 women per 100,000/year). This indicates that the absence of HPV DNA in the capture tests correlates with low rates of cervical lesions[5].

In ATHENA study (Addressing the Need for Advanced HPV Diagnostics) developed in 61 US medical centers, 47,208 women aged 21 years or older were subjected to screening for cervical cancer in the period between May 2008 and August 2009. From the total, 1,578 were diagnosed with ASC-US on cytology and submitted to high-risk HPV DNA and biopsy, simultaneously. The sensitivity, specificity, positive predictive value and negative predictive rates attributed to hybrid capture were as follows, respectively: 87.2% for CIN2 and 91.3% for CIN3; 71.1% for CIN2 and 70% for CIN3; 13.7% for CIN2 and 8.5% for CIN3; and 99.1% for CIN2; 99.6% for CIN3[9,14].

Arbyn *et al.* (2013)[17] evaluated the accuracy of the digene HC2 and APTIMA (Gen-Probe Incorp, San Diego, CA) methods for the detection of CIN2 and CIN3 lesions. Eight studies with 1,839 women diagnosed with ASC-US and 1,887 with LSIL cytology, all investigated for the presence of high-risk HPV, were analyzed. The sensitivity attributed to the methods for patients with initial ASC-US examination with CIN2 outcome ranged from 75% to 100% and patients with CIN3 outcome ranged from 93% to 100%. The specificity ranged from 20% to 81% for CIN2 and 38% to 81% for CIN3.

Sauter *et al.* (2014) studied 1,856 cervical cytological samples with ASC-US diagnosis, resulting in the hybrid capture of high-risk HPV by the HC2 method. The sensitivity rate attributed to hybrid capture in the co-test modality was 96.7% for CIN2 and 95.3% for CIN3. The sensitivity found for HSIL in our study was similar to those reported by the cited authors[4,5,12,14].

In a retrospective study, Fakhreldin and Elmasry (2016)[18] demonstrated that the high-risk HPV DNA detection test by polymerase chain reaction (PCR) followed by hybridization (HPV DNA) can predict two-thirds of cases of ASC-US that can progress to HSIL.

However, in our study, it was observed that 39% of patients diagnosed with ASC and providing positive hybrid capture for high-risk HPV showed LSIL and HSIL within one year of follow-up. That is, despite the high sensitivity in predicting the presence or development of neoplastic lesions of the cervix, the digene HC2 method has limited specificity.

According to the current Brazilian MOH guidelines for screening of cervical cancer, in 2016, women of over 30 years of age who present a diagnosis of ASC-US on cytological examination should repeat the cervical cytology investigation in six months. When presenting two subsequent negative cytology results, women should be advised to continue triennial cytological screening. However, if the result of repeat cytology is equal to or suggestive of intraepithelial lesion or cancer, the patient should be referred for colposcopy[15]. In the case of greater abnormal findings (suggestive of CIN2 or 3) or suspected invasion of colposcopy, a biopsy should be performed. Due to the non-requirement of biopsy after the detection of ASC, not all cases of our study were confirmed by histology. Regarding the use of hybrid capture for the investigation of high-risk HPV, the Brazilian MOH guidelines do not recommend its use routinely since it implies the use of a technology not widely available in the Brazilian Unified Health System (SUS) and does not dispense cytology[15].

Zeferino *et al.* (2018)[16] proposed a revision and update of the Brazilian Guidelines for Cancer Screening of the Uterine Cervical Cancer of the MOH of 2016. According to the authors, tests for DNA detection of high-risk HPV should be applied according to the resources of each Brazilian municipality and used in women older than 30 years. In the case of colposcopy with ASC-US or ASC-H, the capture could be used instead of the cytology at reassessment after six months. If positive for oncogenic types, the patient should be referred for colposcopy. In the case of negative cytology and positive HPV screening, the capture should be repeated in 12 months.

CONCLUSION

We conclude that the HC2 method for investigating the presence of high-risk HPV DNA has a high negative predictive value for LSIL and, especially, for HSIL. This may help in defining the follow-up of patients with ASC to colpocytology and reduce the costs associated with long-term screening for the potential reduction in the number of colposcopies and biopsies indicated for such patients.

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STATEMENT OF ETHICS

The study protocol was approved by the Research Ethics Committee of the Hans Dieter Schmidt Regional Hospital of Joinville (Approval no. 3016825).

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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AUTHOR CONTRIBUTIONS

Adorno FA and Lousada DCF contributed equally to the study conception and design, acquisition and analysis of data, statistical analysis, and drafting of the manuscript. Coelho KMPA and França PHC critically reviewed the manuscript for intellectual content, as well as performed complementary data analysis and final approval.

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