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Value of HPV-DNA test in women with cytological diagnosis of atypical glandular cells (AGC)

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ABSTRACT

Objective: This study analyzed whether HPV (human papillomavirus) testing contributes towards defining histological abnormalities in women with atypical glandular cells (AGC) diagnosed at cervical cytology.

Study design: One hundred and eight women with conventional cervical cancer screening smears suggestive of AGC not otherwise specified (AGC-NOS) and favor neoplastic (AGC-FN) were consecutively enrolled. All women underwent colposcopic examinations and biopsy was performed according to the cytopathologic and/or colposcopic abnormalities present. All specimens were tested for high risk HPV genotypes by Roche's polymerase chain reaction reverse line blot assay. The chi-square test was used to evaluate the association between HPV findings and a diagnosis of high-grade pre-invasive or invasive disease (CIN 2 or worse) taking negative tests or CIN 1 as a reference. Odds ratios (OR) with their respective 95% confidence intervals (95%CI) were used to evaluate the magnitude of the association between HPV testing and CIN 2 or worse. Sensitivity, specificity and their respective 95% confidence intervals (95%CI), positive predictive values (PPV) and negative predictive values (NPV) were also calculated.

Results: Final diagnosis revealed a negative outcome in 80 cases (74%), cervical epithelial neoplasia 1 (CIN 1) in 13 cases (12%), CIN 2 or worse in 12 cases (11%) and glandular neoplasia in 3 (3%) cases. The overall detection rate of HPV was 21% (23/108). Neoplasia was significantly associated with positive HPV-DNA in women with AGC-NOS (OR = 15.21; 95%CI: 2.64–87.50); however, there was no significant association between a histological diagnosis of neoplasia and HPV positivity in women with AGC-FN (OR = 3.00; 95%CI: 0.36–24.92). The sensitivity, specificity, positive predictive value and negative predictive value of HPV-DNA testing for the detection of CIN 2 or worse in women with AGC-NOS were 71%, 86%, 29% and 97%, respectively. In women with AGC-FN, these values were 50%, 75%, 66% and 60%, respectively.

Conclusions: HPV testing at the time of colposcopy for patients with AGC in whom no colposcopic abnormality is found may be a powerful ancillary tool for identifying women at a high risk of underlying significant cervical lesions.

1. Introduction

Adenocarcinomas are the second most common type of malignant cervical neoplasm. Squamous cell carcinomas represent 75–85% of all cases, while adenocarcinomas occur in 11–25% and adenosquamous carcinomas in 2–3% of cases [1]. The natural history of the cervical adenocarcinoma is similar to that of the squamous cell carcinoma, particularly in relation to the existence of precursor lesions and their association with high-risk oncogenic human papillomavirus (HPV) infection [2,3]. Adenocarcinoma in situ (AIS) is known to be a precursor of invasive adenocarcinoma and it is considered to be the glandular counterpart of cervical intraepithelial neoplasia (CIN) 3. Similar HPV types have been demonstrated in most invasive adenocarcinomas and AIS [4].

Lesions less severe than AIS are not as well characterized epidemiologically or histologically [5,6]. Glandular lesions

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characterized as endocervical glandular dysplasias or low-grade glandular intraepithelial lesions have shown a significantly lower rate of detection of HPV-DNA and it is suggested that the majority of these diagnoses are unrelated to cervical carcinogenesis [4].

The Bethesda interpretation of atypical glandular cells defines an increased level of risk, as opposed to a specific neoplastic precursor entity. The changes made in the last revision (2001) classified endocervical glandular cell abnormalities less severe than AIS and invasive adenocarcinoma into two categories: atypical glandular cells (AGC) not otherwise specified (NOS) and AGC favor neoplastic (FN) because the risk of neoplasia associated with the latter is substantially higher [7–9].

The low prevalence of AGC in cervical cytology, the relative absence of findings at colposcopy and a broad spectrum of differential diagnoses are factors that pose significant diagnostic challenges to cytopathologists and clinicians [1–4]. Cervical neoplasia, principally of squamous origin, is the most frequent neoplastic diagnosis in women referred for glandular endocervical abnormalities, and the value of HPV testing in the clinical management of women with this cytological diagnosis has received attention in recent years [10–12].

High-risk HPV-DNA was detected by hybrid capture in 96% of women with biopsy-confirmed CIN 2 or CIN 3 and in 83% with adenocarcinoma in situ or invasive cervical adenocarcinoma [10]. Using PCR, high-risk HPV was detected in 82%, 100% and 80%, respectively, of biopsy-confirmed cases of AIS, high-grade squamous lesion and invasive adenocarcinoma [11]. The risk of cervical neoplasia associated with infection by individual HPV types has been examined to some extent. There are indications that the detection of HPV 16 in women with glandular abnormalities in cervical smears did not help differentiating squamous from glandular lesions. However, the detection of HPV 18 can predict glandular neoplasia as histologic diagnoses [12].

In fact, Castelsague et al. [2] conducted a multicenter study and found a clear association between types 16 and 18 and cervical adenocarcinoma, with odds ratios (OR) of 164.12 (95%CI: 76.09–354.0) and 410.32 (95%CI: 167.44–∞), respectively. Associations were also found with types 59 and 33 ($OR > 100$) and with types 35, 45, 51 and 58 ($OR > 18$). Nonetheless, it is important to emphasize the significance of the diversity that exists within HPV types, i.e., genomic differences with biological consequences related to viral types 16 and 18. Asian-American and European variants of HPV 16 are more prevalent in glandular and squamous cell neoplasias, respectively. In fact, a study conducted in Brazil showed that the Asian-American variant of HPV 16 was significantly associated with a histological diagnosis of glandular neoplasia [13].

The 2006 consensus guidelines of American Society for Colposcopy and Cervical Pathology (ASCCP) established that neither the use of HPV-DNA testing alone nor a program of repeat cervical cytology is acceptable as an initial screening test for all subcategories of AGC and AIS, and included HPV-DNA testing together with colposcopy and endometrial sampling in the initial workup [14]. The 2002 version of the consensus guidelines considered the data available for the assessment of the impact of HPV-DNA testing on AGC to be limited and consequently made no recommendations [15].

Recent epidemiological lines of evidence suggest that HPV-DNA testing may yield good sensitivity and specificity for the detection of significant cervical lesions in women with atypical endocervical glandular cells. There are some indications that endometrial abnormalities tend to be found in women with AGC and a negative HPV test, while squamous or glandular abnormalities of the cervix are more common in those with a positive HPV test [16–18]. These data suggest that HPV testing may help determine the area in which the initial workup should be focused: in the cervix or in the endometrial/uterine canal. The present study was therefore designed to examine the relationship between HPV-DNA testing and pathological outcomes in women referred because of AGC-NOS or AGC-FN at cervical cytology.

2. Materials and methods

2.1. Patient selection and clinical samples

The study's protocol was approved by the Institution's Internal Review Board and all selected women voluntarily signed an informed consent form prior to enrollment. One hundred and eight women with conventional cervical cancer screening smears suggestive of endocervical glandular abnormalities (AGC-NOS or AGC-FN) were enrolled consecutively to this study. These women were recruited at the colposcopy clinics of the State University of Campinas, Brazil, between March 2002 and March 2005. AGC-NOS was diagnosed in 92 women and AGC-FN in 18 women. Thirty-five cases of AGC with high-grade squamous intraepithelial lesion (HSIL) and 14 cases of AIS were previously excluded from the study because of the well-established association of these types of cytological diagnoses with HPV infection. All the cervical smears were analyzed by the same cytopathologist in accordance with the 2001 Bethesda System (TBS) [4].

Following enrollment, all women were subjected to a thorough pelvic examination, including the collection of samples for a second cervical smear and polymerase chain reaction (PCR) and genotyping, colposcopy and directed punch biopsy in accordance with the cytopathologic and/or colposcopic abnormalities present. Punch biopsy was taken when a suspicious image was completely identified. Women with a suspicious image penetrating in the cervical canal, or an unsatisfactory colposcopy but with a second abnormal cervical smear underwent cervical conization.

All women were also subjected to pelvic ultrasound examinations, and whenever endometrial abnormalities were suspected, uterine curettage was performed. Women with invasive cervical or endometrial carcinoma were treated according to the clinical guidelines. Samples for histology were obtained from punch, cone biopsies or hysterectomy specimens and in cases in which the woman had undergone more than one histological examination the most severe diagnosis was the one considered.

Biopsies were performed in 81 of the 110 women initially recruited for the study. In the remaining 29 cases, colposcopy was negative, a second cervical smear was negative and both clinical and ultrasonographic evaluations of the pelvis were normal; therefore, the final diagnosis was negative for neoplasia. Four-monthly follow-up visits were scheduled for these 29 women. Since all of them had negative cervical smears after two follow-up visits, they were considered free of neoplasia and were included in this study together with the other women whose histological diagnosis was negative for neoplasia. β-globin, a reaction internal control, could not be detected in two cases of women submitted to biopsy resulting in a sample of 108 women for HPV-DNA testing.

2.2. HPV-DNA testing

HPV detection and typing were performed using Roche line blot assays. This assay involved the hybridization of a 450-nucleotides PCR amplicon generated by the PGMY primer set to a nylon strip containing immobilized probes. The strip contained 2 levels of β-globin control probes, 18 high-risk HPV (HR-HPV 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 55, 56, 58, 59, 68, 73, 82, and 83) probes and 9 low-risk HPV (LR-HPV probes 6, 11, 40, 42, 53, 54, 57, 66, and 84) The primers PGMY09 and PGMY11 (14), adapted from primers MY09 and MY11, detect genital HPV types at a higher rate than

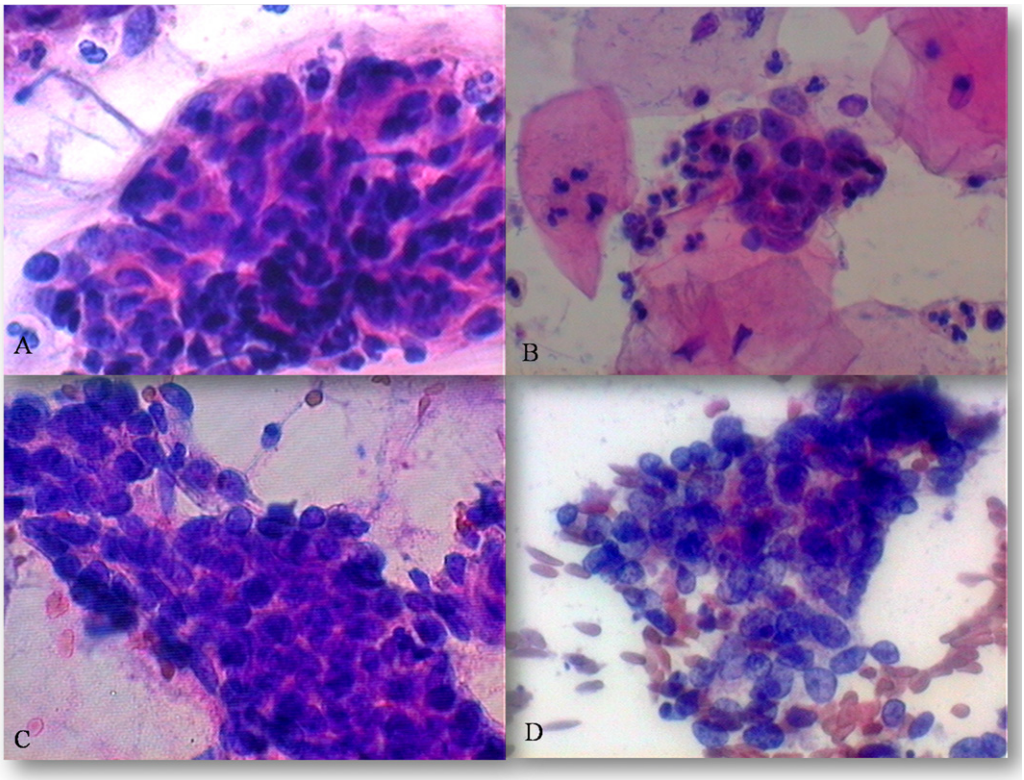

Fig. 1. (A) Atypical glandular cells not otherwise specified (AGC-NOS), HPV positive. Histological follow-up showed CIN 3 (Pap stain, 400×). (B) Atypical glandular cells not otherwise specified (AGC-NOS), HPV negative. Histological follow-up showed CIN 3 (Pap stain, 400×). (C) Atypical glandular cells favor neoplastic (AGC-FN), HPV positive. Histological follow-up showed CIN 3. (Pap stain, 400×). (D) Atypical glandular cells favor neoplastic (AGC-FN), HPV negative. Histological follow-up showed endometrial adenocarcinoma (Pap stain, 400×).

primers MY09 and MY11 [19,20]. Hybrid capture is the standard HPV detection method utilized in many countries, but there are indications that the Roche Linear Array is the assay is the most sensitive, as it was able to reveal the HPV type present in the specimens [21].

2.3. Histopathology

The specimens were reviewed according to the WHO criteria [22] and classified as: CIN 1, CIN 2, CIN 3, invasive squamous carcinoma, in situ adenocarcinoma, invasive cervical adenocarcinoma, endometrial adenocarcinoma and synchronous gynecological adenocarcinomas that included endocervical, endometrial, tubal and ovarian origin (Fig. 1). "No Neoplastic Diagnosis" included cervicitis, squamous metaplasia, tubal metaplasia, tunnel cluster hyperplasia, microglandular hyperplasia and polyps. All histological analyses were carried out at the same laboratory of pathology and diagnosed by the same pathologist, who was unaware of the cytological diagnoses

2.4. Statistical analysis

The chi-square test was used to evaluate the association between HPV findings and a diagnosis of high-grade pre-invasive or invasive disease (CIN 2 or worse) taking negative tests or CIN 1 as a reference. Odds ratios (OR) with their respective 95% confidence intervals (95%CI) were used to evaluate the magnitude of the association between HPV testing and CIN 2 or worse. Sensitivity, specificity and their respective 95% confidence intervals (95%CI), positive predictive values (PPV) and negative predictive values (NPV) were also calculated. The Mann–Whitney test was used to evaluate the difference of woman's age at final diagnosis.

3. Results

Final diagnosis revealed a negative outcome in 80 cases (74%), CIN 1 in 13 cases (12%), CIN 2 or worse in 12 cases (11%) and glandular neoplasia in 3 cases (3%). The women with glandular neoplasia are older than the women with the other final diagnosis.

The women with glandular neoplasia were significantly older than those women with the other final diagnosis and this difference was statistically significant. The overall HPV detection rate was 21% (23/108) and all infections were by high risk HPV types. HPV-DNA testing was positive in 9.6% and 15.3% of the women whose results at follow-up consisted of an absence of malignancy or CIN 1, respectively. Conversely, 9 women (75%) with a result of CIN 2 or worse tested positive for HPV-DNA. All the cases of glandular neoplasia detected were found in HPV-DNA-negative women with AGC-FN (Table 1).

Women with AGC-NOS were detected with CIN 2 or worse in 7.6% (7/92) of the cases. Of these, 71% (5/7) were HPV-DNA-positive. Of 75 HPV-DNA-negative cases, only two harbored CIN 2 or worse. There were no cases of endocervical or endometrial adenocarcinomas, or adenocarcinomas at any other site, in the women with AGC-NOS. Thirty-one percent (5/16) and 19% (3/16) of women with AGC-FN were detected, respectively, with squamous neoplasia (CIN 2 or worse) and invasive adenocarcinoma. HPV-DNA testing was positive in 50% of the women who had clinically significant lesions. Neoplasia was significantly associated with a positive HPV-DNA test in women with AGC-NOS (OR = 15.21; 95%CI: 2.64–87.50). However, there was no significant association between the histological diagnosis of neoplasia and HPV positivity in women with AGC-FN (OR = 3.00; 95%CI: 0.36–24.92) (Table 2).

The sensitivity, specificity, positive predictive value and negative predictive value of HPV-DNA testing for the detection

Table 1
Final diagnosis in women with AGC.

Final diagnosis	AGC-NOS	AGC-FN	Total	HPV+/Total final diagnosis	Mean age
	n (%)	*n* (%)	*n* (%)	*n* (%)	
Negative	73 (79)	7 (44)	80 (74)	12/80 (9.6)	42.8 (17–76)
CIN 1	12 (13)	1 (6)	13 (12)	2/13 (15.3)	37.3 (18–52)
CIN 2 or worse	7 (8)	5 (25)	12 (11)	9/12 (75.0)	42.1 (28–56)
Glandular neoplasia	0	3 (25)	3 (3)	0/3 (0)	66 (57–71)
Total	92 (100)	16 100)	108 (100)	23(100)	42.7 (17–74)

Negative or non neoplastic diagnosis, CIN – cervical intraepithelial neoplasia.
The Mann–Whitney TEST showed that the women with glandular neoplasia are older than those women with the other final diagnosis.

of CIN 2 or worse in women with AGC-NOS were 71%, 86%, 29% and 97%, respectively. In women with AGC-FN these values were 50%, 75%, 66% and 60%, respectively. The accuracy of HPV testing for the detection of CIN 2 or worse was higher in women with AGC-NOS compared to women with AGC-FN (Table 3).

3.1. Comments

The findings of the present study suggest that the probability of detecting a significant cervical lesion, either squamous or glandular, in women with AGC-NOS and a negative HPV-DNA test is low. On the other hand, HPV-DNA testing does not appear to add any significant clinical information in cases of women with AGC-FN, since the likelihood of a glandular lesion, especially of endometrial origin, is higher in these cases, and is not dependent on the result of the HPV-DNA test. It should be considered that a sample of 18 women referred for AGC-FN has a low statistical power and, therefore, it is not possible to show statistically an association, even if one exists. Irrespective of this fact, however, the findings of the present study support the ASCCP recommendation that indicate colposcopy with endocervical sampling for women with all subcategories of AGC and suggest the high-risk HPV-DNA testing as an additional guide to follow-up after initial colposcopic evaluation and endocervical sampling and to help detect small or difficult-to-sample neoplastic cervical lesions [14].

Table 2
Association of HPV positivity and severity of histopathological diagnosis.

Cytological diagnosis	Final diagnosis		
	CIN 2 or worse	Negative/CIN 1	OR (95%CI)
	n (%)	*n* (%)	
AGC-NOS			
Age (years)			
≥45	2 (29)	34 (40)	0.6 (0.11–3.27)
≤44	5 (71)	51 (60)	
Total	7 (100)	85 (100)	
HPV status			
HPV+	5 (71)	12 (14)	15.21 (2.64–87.50)
HPV−	2 (29)[a]	73 (86)	
Total	7 (100)	85 (100)	
AGC-FN			
Age (years)			
≥45	6 (75)	4 (50)	3.00 (0.36–24.92)
≤44	2 (25)	4 (50)	
Total	8 (100)	8 (100)	
HPV status			
HPV+	4 (50)	2 (33)	3.00 (0.36–24.92)
HPV−	4 (50)[b]	6 (77)	
Total	8 (100)	8 (100)	

AGC-NOS – Atypical glandular cells not otherwise specified, AGC-FN – Atypical glandular cells favor neoplastic.
[a] One case diagnosed as CIN 2 and one case diagnosed as CIN 3.
[b] Three cases of adenocarcinoma, two endometrial and one synchronous gynecological adenocarcinomas that included endocervical, endometrial, tubal and ovarian origin.

In this study, the overall prevalence of HPV in women referred for AGC was similar to that observed in other reports. The total prevalence of HPV has been reported to range from 24.3% to 30.4% in two large series [16,17]. In women with AGC of presumed cervical origin, the prevalence of HPV was 20.2% in one report [18]. Considering the subclassifications of AGC diagnosis, the prevalence of HPV in women with AGC-NOS and AGC-FN was, respectively, 18,4% and 37.%. Chen and Yang [18] detected prevalence of HPV of 17% in women with atypical endocervical cells not otherwise specification (AEC-NOS), but the HPV prevalence in women with atypical endocervical cells favor neoplastic (AEC-FN) was higher (86%) when compared with those observed in this study. This is probably due to the fact that all cases of endometrial carcinoma, obviously HPV negative had been diagnosed in women referred for AGC-NOS in this study.

The accuracy of HPV testing in detecting CIN 2 or worse was higher in women with AGC-NOS compared to that in women with AGC-FN in this study. A literature search indicated that the HPV testing had an overall 90% sensitivity, 79% specificity, 53% positive predictive value and 97% negative predictive value [23]. Schantz et al. [16] observed that the sensitivity of HPV testing in women with AGC for HPV-associated disease was 81.3%. Chen and Yang [18] reported similar rates of sensitivity, specificity, positive predictive value and negative predictive value (respectively, 91.0%, 91.2%, 62.5% and 98.4%).

Several studies have demonstrated that the HPV positivity is higher in women with significant cervical lesions [7,9–12]. In fact, Schnatz et al. [16] showed that the HPV-associated disease among cases testing positive for HPV was 40% compared with 4% among HPV-negative cases. In the present study, HPV-DNA testing was positive in the majority of women with AGC-NOS and clinically significant lesions. However, 50% of the women with a clinically significant histological lesion who were referred for AGC-FN were found to be HPV-DNA-negative. Chen and Yang [18] detected HPV positivity in 55.8% of women with AEC-NOS and with significant cervical lesions. The frequency of HPV positivity in women referred with AEC-FN and with significant cervical lesions was 91.7%.

It has been established that neither HPV-DNA testing nor repeat cervical cytology is sensitive enough to be used alone as an initial screening test for women with AGC. HPV testing has limitations even considering its high sensitivity for the detection of cervical lesions [10,12,18]. In fact, in this study, 2.6% of the women with AGC-NOS and a negative HPV-DNA test harbored a clinically significant lesion (CIN 2 or CIN 3). Of 251 women with AEC and a negative HPV test, Chen and Yang [18] found one case (0.4%) of CIN 2 and 3 cases (1.2%) of adenocarcinoma in situ. HPV-DNA testing also can obviously miss non-HPV associated neoplasia arising in the endometrium or the fallopian tube. In this study, two endometrial and one multiple HPV-DNA-negative adenocarcinomas were detected in women with AGC-FN. On the other hand, Chen and Yang [18] detected a significant number of endometrial abnormalities in women referred for AEC-NOS. In fact, correctly classifying the cell origin on cervical cytology specimens is challenging for most practicing cytopathologists. These findings

Table 3
Sensitivity, specificity, positive and negative predictive values of HPV testing in women referred with AGC for the clinical detection of significant lesions (CIN 2 or worse).

	AGC-NOS		AGC-FN	
	Percentage	95%CI	Percentage	95%CI
Sensitivity	71%	38–105%	50%	15–85%
Specificity	86%	78–93%	75%	78–93%
Positive predictive values	29%		66%	
Negative predictive values	97%		60%	
Accuracy	85%		63%	

AGC-NOS – Atypical glandular cells not otherwise specified, AGC-FN – Atypical glandular cells favor neoplastic, 95%CI – 95% Confidence interval.

support the ASCCP 2006 guidelines regarding the endometrial evaluation in women aged ≥35 years and in women referred because of endocervical AGC-NOS or -FN.

Age is a key factor in determining the frequency and type of neoplasia found in women with AGC. There is a higher risk of CIN 2, 3 and AIS in premenopausal women compared to postmenopausal women, premenopausal women with AGC having a lower risk of endometrial hyperplasia or cancer [18–22]. In this context, age and clinical presentation rather than an HPV-DNA test result should dictate appropriate management (i.e., endometrial sampling) in older women, since this is the age-group at greater risk for endometrial and metastatic neoplasms [7,18]. In fact, in the present study, all the cases of adenocarcinoma were detected in women over 50 years of age, and in all cases these women were HPV-DNA-negative. These data are in agreement with other studies that showed that the HPV-negative lesions are more common in women aged >50 years [16,24].

This study showed that 79% (73/92) of the women with a cytological diagnosis of AGC-NOS could theoretically have been managed conservatively based on their negative HPV-DNA test. Several other studies have also indicated that the HPV testing may be useful in women with AGC [16–18,24,25]. Chen and Yang [18] reported that up to 80% of women with a cytological diagnosis of atypical endocervical cells (AEC) could be managed conservatively with either cytological follow-up or further HPV testing. Saqi et al. [25] suggested that HPV-DNA testing may constitute a reliable alternative to colposcopy and endocervical sampling for the management of initial diagnoses of AGC. Considering that not all patients with AGC have significant pathological lesions and that glandular lesions are subtle and often located high in the endocervical canal, these authors believe that such lesions may remain undetected, resulting in false-negative reports at initial colposcopic examinations. Therefore, physicians could confidently manage women with positive HPV tests aggressively with colposcopy and endocervical sampling, while HPV-negative patients could be monitored conservatively with repeat cytology.

The present results suggest that HPV-DNA testing at the time of colposcopy in patients with AGC and normal colposcopy may constitute a powerful tool for identifying women at risk of significant cervical lesions high in the cervical canal. HPV-DNA testing in these situations may reduce the number of unnecessary colposcopies and endocervical curettages in women with asymptomatic benign cervical abnormalities. However, attention should always be paid to potential lesions of a glandular nature.

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