# Age Influences the Clinical Significance of Atypical Glandular Cells on Cytology

KATRIN CHRISTINE ASCIUTTO[1], EMIR HENIC[1], OLA FORSLUND[2], KAJ BJELKENKRANTZ[3] and CHRISTER BORGFELDT[1]

*Departments of [1]Obstetrics and Gynaecology, and [2]Clinical Virology, and [3]Regional Cancer Centre South, Skane University Hospital, Lund, Sweden*

**Abstract.** *Aim: To evaluate women with atypical glandular cells (AGC) or adenocarcinoma in situ (AIS) on cytology. Patients and Methods: Population-based data of cervical smears taken between 2008-2012 were analyzed. Results: Cancer was diagnosed in 107 out of 199 patients (54%) with AGC or AIS; 30 with cervical adenocarcinoma and 77 with endometrial cancer. All women with endometrial cancer were 50 years or older. In women younger than 50 years, cervical pre-cancerous lesions were found in 44 (47%) and cervical adenocarcinoma in 24 out of 92 cases (26%). High-risk HPV infection was found in 62 out of 103 women (60%). The detection rate of high-risk HPV at finding histopathological AGC, AIS, low-grade squamous intraepithelial lesions, high-grade squamous intraepithelial lesions or cervical cancer was 98% (95% confidence interval=0.903-1.000) (54/55). Conclusion: AGC or AIS indicates endometrial neoplasia in women 50 years or older and pre-cancerous or invasive glandular cervical lesions in younger women. HPV testing seems to identify underlying cervical adenocarcinoma and high grade squamous intraepithelial lesions.*

Cervical cancer is the second most frequent female malignancy worldwide, with 80% of cases occurring in developing countries. Although squamous cell cancer (SCC) and its precursors account for the majority of cervical carcinomas, a significant number of lesions are associated with glandular findings on cytology (1, 2). The diagnosis of glandular cells on cytology is often associated with underlying histological abnormalities such as low- or high-grade squamous intraepithelial lesion (LSIL or HSIL) but also with adenocarcinoma of the cervix (AC) in about 40% (3, 4).

Since the proportion and incidence rates of adenocarcinoma, which accounts for 20-25% of all cervical cancers, have been rising in high-income countries for the last two decades, the presence of atypical glandular cells (AGC) has become of increasing interest. The increased proportion of adenocarcinoma in cervical cancer is particularly evident among females under 40 years of age and is probably related to a decreasing incidence of SCC due to effective screening programs (5, 6)

Persistent human papilloma virus (HPV) infection is the cause of SCC and AC, with HPV types 18 and 45 known to be the predominant types for AC (7-9).

According to literature, AGCs are an uncommon diagnosis, with a reported screening incidence between 0.08 and 2.1% (10). This variation in reported incidence is mainly due to the challenging identification of cells with abnormal glandular features on cytology, while detecting squamous lesions can be considered as relatively simple. Furthermore the cytological features of different grades of glandular abnormalities are still not clearly defined and are often subject to inter-observer variability (11).

AGCs on cytology are still the subject of many investigations due to their clinical importance. Several studies have already highlighted the high percentage of cases associated with underlying high-grade disease of the lower uterine tract in women referred for AGC or adenocarcinoma *in situ* (AIS) in cytology (12-16).

As the associated tissue lesions normally comprise of a wide spectrum of different pre-invasive and invasive lesions of either squamous or glandular character, earlier studies also attempted to determine if patient-related factors, such as age or HPV status, could be helpful in predicting the character of the underlying histological condition (17-19).

Despite the fact that some studies are limited by small patient numbers, the reported correlation with significant histological findings ranging from 0% to 83% underlines the

*Correspondence to:* Christine Asciutto MD, Department of Obstetrics and Gynaecology, Skåne University Hospital, Lund University, SE-22185 Lund, Sweden. Tel: + 46 46171000, Fax: + 46 46157868, e-mail: christine.asciutto@yahoo.com

*Key Words:* Cervical cancer, atypical glandular cells, Pap smear, adenocarcinoma *in situ*, clinical population study.

need for clinical evaluation in women with Pap-smear findings of AGC or AIS (20).

The aim of this study was to compare the final histopathological diagnoses in women referred for Pap-smear findings of AGC or AIS in a well-defined population over five consecutive years.

## Patients and Methods

The Southern Swedish Regional cervical screening register was used in this population-based study which includes all women from whom a cervical smear had been taken between the 1st January 2008 and the 31st December 2012. The register includes data in the region from all women having a cervical smear taken, all histopathological reports and also all HPV types identified if HPV analyses are requested. The cytological samples were obtained using the liquid-based ThinPrep or SurePath device and analyzed at the four cytological laboratories in the Skåne region.

In our study period, a total of 224 women were consecutively diagnosed with either AGC or AIS in cytology, with histological findings available in 199 cases.

HPV testing was performed on the residual fluids of 103 patients (n=52%), including all women within the age group younger than 50 years and 11 women older than 50 years.

All HPV analyses were performed at the viral laboratory in Malmö. For HPV-DNA amplification, polymerase chain reaction (PCR) with modified GP5+/6+ (MGP) primers was used (21). After PCR amplification, Luminex-based HPV genotyping was used to identify HPV types (22). The technique allows the detection of 38 HPV genotypes of which 18 are high-risk HPV type genotypes: 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73 and 82; five are probable high-risk type genotypes: 26, 53, 66, 67 and 69; and 19 are low-risk HPV genotypes: 6, 11, 30, 40, 42, 43, 54, 61, 62, 70, 74, 81, 83, 86, 87, 89, 90, 91 and 114. The Luminex assay also includes two broadly reactive "universal" probes; HPV-DNA in samples positive only for a universal probe was typed by DNA sequencing. Potential HR-HPV types were classified as HR-HPV types.

The histological results were defined as: LSIL (cervical intraepithelial neoplasia (CIN) 1, HSIL (CIN 2 or 3), glandular dysplasia, endometrial hyperplasia, adenocarcinoma *in situ* of glandular (AIS) or squamous origin (CIS), and invasive carcinoma of the cervix or corpus uteri. Colposcopy findings were classified as normal or abnormal. In women with more than one documented histological result, only the worst result was taken into consideration for statistical analysis.

Most diagnostic specimens were obtained at the time of colposcopy, including endocervical curettage in all 168 women examined and additional cervical biopsy in 68 cases.

Endometrial biopsies were performed in 184 cases, mostly due to bleeding symptoms (n=131) or due to abnormal findings on transvaginal ultrasound.

The study was approved by the Regional Ethical Board, University of Lund (DNR 390:2013). All women having a cervical smear have the option not to be included in the Cervical screening register both when the smear is taken and later on request.

Chi-square or Fisher's exact tests were used to compare the different groups. When appropriate, tests were based on the binomial distribution and the exact confidence intervals (CI) are given.

Table I. *Histopathological diagnoses in relation to atypical glandular cells (AGC)/adenocarcinom in situ (AIS) in cervical smear and age.*

| | Cytological findings | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | <50 years | | | ≥50 years | | | | |
| Pathology | AGC | AIS | AIS (%) | AGC | AIS | AIS (%) | Total (n) | Total (%) |
| Normal | 19 | 4 | 17.3 | 13 | 3 | 18.7 | 39 | 19.5 |
| Glandular atypia | 1 | 5 | 83.3 | 2 | 0 | - | 8 | 4 |
| AIS | 5 | 11 | 68.7 | 0 | 3 | 100 | 19 | 9.5 |
| LowSIL | 1 | 3 | 75. | 1 | 0 | - | 5 | 2.5 |
| HighSil | 11 | 7 | 38.8 | 0 | 0 | - | 18 | 9 |
| Cervical cancer | 6 | 18 | 75 | 2 | 4 | 66.6 | 30 | 15 |
| Endometrial hyperplasia | 0 | 1 | 100 | 0 | 2 | 100 | 3 | 1.5 |
| Endometrial cancer | 0 | 0 | 0 | 11 | 66 | 85.7 | 77 | 40 |
| Total | 43 | 49 | 53.2 | 29 | 78 | 72.8 | 199 | 100 |

SIL: Squamous intraepithelial lesion

Table II. *Histopathological diagnoses in relation to bleeding symptoms and age.*

| | Bleeding as symptom | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | <50 Years | | | | ≥50 Years | | | |
| Pathology | No | Yes | Yes (%) | Total | No | Yes | | Total |
| Normal | 19 | 4 | 17.3 | 23 | 7 | 9 | 56.2 | 16 |
| Glandular atypia | 4 | 2 | 33.3 | 6 | 2 | 0 | - | 2 |
| AIS | 6 | 10 | 62.5 | 16 | 2 | 1 | 33.3 | 3 |
| LowSIL | | | | | | | | 1 |
| HighSil | 11 | 7 | 38.9 | 18 | 0 | 0 | - | 0 |
| Cervical cancer | 6 | 18 | 75 | 24 | 5 | 1 | 16.6 | 6 |
| Endometrial hyperplasia | 0 | 1 | 100 | 1 | 0 | 2 | 100 | 2 |
| Endometrial cancer | 0 | 0 | - | 0 | 1 | 76 | 98.7 | 77 |
| Total | 50 | 42 | 45.6 | 92 | 18 | 89 | 83.2 | 107 |

AIS: Adenocarcinom *in situ*; SIL: squamous intraepithelial lesion.

Spearman's rank correlation was used. All comparisons were two-sided and *p*-values less than 0.05 were considered statistically significant. Statistical analysis was performed using SPSS version 21.0 (IBM Corp., Amonk, NY, USA).

Table III. *Histopathological diagnoses in relation to colposcopy findings.*

| Pathology | Colposcopy findings | | | | |
|---|---|---|---|---|---|
| | Normal | Non conclusive | Pathologic | Pathological colposcopy (%) | Total |
| Normal | 29 | 1 | 3 | 9.1 | 33 |
| Glandular atypia | 2 | 0 | 6 | 75 | 8 |
| AIS | 3 | 2 | 13 | 72.2 | 18 |
| LowSIL | 2 | 1 | 1 | 25 | 4 |
| HighSil | 0 | 1 | 17 | 94.4 | 18 |
| Cervical cancer | 2 | 0 | 27 | 93.1 | 29 |
| Endometrial hyperplasia | 1 | 0 | 1 | 50 | 2 |
| Endometrial cancer | 49 | 1 | 6 | 10.7 | 56 |
| Total | 88 | 6 | 74 | 44 | 168 |

AIS: Adenocarcinoma *in situ*; SIL: sqamous intraepithelial lesion.

Table IV. *Histopathological diagnoses in relation to high risk human papillomavirus (HR-HPV) type.*

| Pathology | HR HPV (n) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | No. HR HPV (n) | 16 | 18 | 31 | 33 | 53 | 16+18 | Total HR HPV (n) |
| Normal | 16 | 4 | 0 | 1 | 0 | 2 | 0 | 7 |
| Glandular atypia | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 3 |
| AIS | 1 | 5 | 5 | 0 | 0 | 0 | 0 | 10 |
| LowSIL | 0 | 1 | 1 | 0 | 1 | 0 | 0 | 3 |
| HighSil | 0 | 7 | 5 | 0 | 0 | 0 | 0 | 12 |
| Cervical cancer | 0 | 12 | 12 | 0 | 0 | 0 | 3 | 27 |
| Endometrial cancer | 23 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Endometrial hyperplasia | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total (n) | 41 | 29 | 26 | 1 | 1 | 2 | 3 | 62 |
| Percentage | 100% | 46.7% | 41.9% | 1.6% | 1.6% | 3.2% | 5% | 100% |

AIS: Adenocarcinoma *in situ*; SIL: squamous intraepithelial lesion.

## Results

Between 2008-2012, in the region of Skåne, located in the southern part of Sweden, with a population of 1.25 million, a total of 224 women were diagnosed with AGC or AIS on cervical smear, which was 0.05% of all cervical smears taken in this time period.

In 199 women, the final histological diagnosis and documented follow-up were found and used for further analyses. Among these women, cells with cytological criteria of AIS were found in 126 cases, while the cytological diagnosis of AGC was established in the remaining 73 patients (Table I).

A total of 92 women (46%) with cytological findings of AGC or AIS were 50 years of age or younger, while 107 patients (54%) were older than 50 years.

Eleven women with either AGC or AIS on cervical cytology who had already been diagnosed with advanced cancer of ovarian or tubal origin were not suitable for further investigation as they were receiving palliative oncological treatment. The remaining 14 women refused diagnostic follow-up.

Invasive cancer was found in 107 (54%) women, arising in 30 cases from the cervix and in 77 patients from the endometrium. All cervical carcinomas were adeno-carcinomas, and no SCC was found. Abnormal lesions on histopathology were found in 53 additional women (26%), while a benign condition was detected in 39 women (20%). All women with endometrial cancer were 50 years of age or older (Table II). Six women older than 50 years had cervical cancer. In women younger than 50 years, cervical pre-cancerous lesions of the squamous (LSIL, HSIL) or glandular (AGC, AIS) type were found in 44 (47%) cases and cervical adenocarcinoma was found in 24 out of 92 women (26%) (Table I).

Bleeding abnormalities were reported in 131 women (66%) and all except one woman with endometrial cancer had post-menopausal bleeding symptoms (Table II). The women with cervical cancer had bleeding disturbances in 19 out of 30 cases (63%).

In the overall study population, bleeding symptoms were associated with histologically-significant lesions ($p$=0.005 for women ≥50 years of age and $p$=0.002 for women <50 years of age).

Another 30 out of 68 patients (44%) who did not report clinical symptoms were diagnosed with HSIL, AIS or invasive cervical cancer.

Cytological findings defined as AIS were found to be significantly associated with the presence of pre-malignant or malignant lesions in 109 women (86%), arising from the cervical tissue or endometrium ($p$<0.005), while AGC on cytology were found in 32 women (43%) with benign histological findings ($p$<0.005) (Table I).

AIS was significantly associated with invasive endometrial carcinoma in women over 50 years of age (n=66, $p$<0.005).

In women younger than 50 years of age, AIS was found in 36 patients (73%) with pre-cancerous lesions or invasive adenocarcinoma ($p$<0.031), while AGC was correlated with findings of cervical neoplasia in 22 out of 43 women (51%) (Table I).

Abnormal colposcopy findings were found in 64 out of 73 patients (88%) with cervical lesions (Table III). In the younger age group (<50 years), 57 out of 60 women with severe colposcopic conditions were diagnosed with cervical pathology including HSIL, AIS and invasive adenocarcinoma ($p<0.005$).

Colposcopy abnormalities were found in 6 out of 56 women (10%) with endometrial cancer.

Loop electrosurgical excision procedure (LEEP) was performed in 47 patients (24%). Hysterectomy was performed as part of a staging operation due to endometrial cancer in 76 patients (>50 years) or cervical cancer in 25 patients (<50 years) and in total in 114 (57%) cases.

One patient with advanced endometrial cancer (International Federation of Gynecology and Obstetrics (FIGO) stage 3) and a total of five patients with advanced cervical tumours (>4 cm diameter FIGO stage IB2) were directly scheduled for neoadjuvant chemo- or combined chemo-radiation therapy.

HPV was analyzed in 103 cases and HR HPV infection was found in 62 women (60%) (Table IV). Fifty-four out of 55 women (98% CI=0.903-1.000) with histopathological findings of AGC, AIS, LSIIL, HSIL or cervical cancer were found to be positive for HR-HPV. HR-HPV was found in all tested women with AGC (n=3), squamous lesions (n=15) and cervical cancer (n=27), and in 10 out of 11 women with AIS (Table V). HR-HPV DNA types 16/18 were present in 90% of women with cervical adenocarcinoma (n=27), in 52% (n=10) of patients with AIS, and in 66% (n=12) of HSIL lesions. Association between preinvasive and invasive glandular lesions of the cervix for HVP type 18 was found ($p<0.005$).

## Discussion

This population-based study shows that more than 80% of women with a cervical smear finding of AGC or AIS had pathological findings which required for further treatment or follow-up. Furthermore, 54% had invasive cancer. AGCs have always been a challenging diagnosis for cytologists as the distinction from other reactive or benign glandular lesions or even pre-invasive glandular abnormalities remains problematic (11, 23).

To improve the interpretation of glandular cells, the Bethesda System underwent a revision in 2001 replacing the term atypical glandular cell of undetermined significance with the term atypical glandular cells. AGCs were defined as cells exhibiting either endometrial or endocervical differentiation and displaying nuclear atypia that exceeds reactive or reparative changes but does not exhibit the characteristic features of AIS or AC (24). While the cytomorphological criteria for AIS are clearly defined, all other glandular findings summarized under the term AGC still seem to be subject to interobserver variability (25-27).

Recent studies report a poor correlation between initial Pap-smear results of AGC or AIS and their corresponding findings on final histopathology (17, 20). Despite the difficulties in establishing the correct cytological diagnosis, glandular abnormalities in cytology are of great clinical interest due to the reported risk for pre-cancerous abnormalities in cervical or endometrial tissue and the resulting need for further histopathological evaluation procedures on both the cervix and endometrium (12-15, 20, 28).

Out of the younger women in this study, 39 cases were treated with fertility-sparing LEEP conisation. Histopathological examination revealed squamous lesions (LSIL, HSIL) in 14 women, while 16 patients were found to have AIS. The post-conization check-up for women with squamous abnormalities is scheduled according to an established follow-up protocol (colposcopy, Pap-smear and HPV testing) with appointments six and 12 months after treatment. On the other hand, the appropriate follow-up after conization for AIS is still not completely defined as these abnormalities have a potential risk of recurrence and undetected skip lesions. Normally hysterectomy is considered the standard treatment as the conization procedure can miss lesions located higher up in the cervical canal (29, 30).

Women of childbearing age are normally managed conservatively if there are negative conization margins and negative findings at endocervical sampling during the follow-up (29-31). However, all women should be informed about the need for a follow-up protocol including colposcopy, Pap-smear, endocervical sampling and HPV testing with a first check-up six months after the initial treatment procedure. Subsequent check ups are scheduled every half a year. (30, 32, 33). HPV analyses are already integrated into the follow-up schedule but the most efficient and safe follow-up algorithm needs further evaluation.

According to our results, the cytological diagnosis of AIS was correlated with the presence of severe glandular pathology in 96% of all women older than 50 years of age. Whether cytological screening for endometrial adenocarcinoma is a realistic benefit of cytological screening is a matter of debate (34). In the present study, only one woman with endometrial carcinoma was detected by AGC or AIS in the screening program during the five-year period. All other women with endometrial cancer had bleeding symptoms which led to diagnosis. According to this observation, cervical screening cytology should not be considered as a possibility for finding endometrial cancer. Atypical glandular cells in the Pap smear also detected three cases of pre-cancerous complex atypical endometrial hyperplasia.

Several investigators have noted that precise discrimination of the site of origin of AGC or AIS is often uncertain (10, 35, 36). According to the last Consensus Guidelines of the American Society for Colposcopy and Cervical Pathology, endometrial sampling is recommended in conjunction with

colposcopy and endocervical sampling in women 35 years of age and older with AGC or AIS in cytology (37). Our results can be compared to those of earlier studies reporting an association of AGCs in women older than 35 years with neoplastic changes of the endometrium, while women younger than 35 years were found to have pre-invasive or invasive cervical lesions of a squamous or glandular nature (15, 16, 38, 39).

The evaluation of colposcopy results in our study population revealed a significant correlation between pathological findings on colposcopy and the presence of underlying cervical lesion on final tissue specimen, especially in women younger than 50 years of age.

The interpretation of glandular abnormalities found on colposcopy has always been considered a challenge as these lesions have the tendency to extend high into the cervical canal and to develop skip lesions making colposcopic accessibility and identification a critical issue (40). The relatively high frequency of visible lesions in our patient cohort can be explained by the fact that glandular atypia or AIS sometimes coexisted with HSIL, or were found next to early invasive adenocarcinoma. According to the literature, glandular and squamous lesions coexist in 50-70% of all cases of AIS and it is mostly the squamous component which is identified on colposcopy (39, 41).

Among the tested women, HR HPV was found in 98% of cases with significant cervical lesions needing further evaluation. The results of our study are comparable to those of recent publications (17, 18, 28, 42). We found HR-HPV types 16 and 18 to be the most predominant types (94%). HPV infection has by some authors been found to be more difficult to detect in glandular than in squamous lesions as the glandular epithelium does not support productive viral infection, resulting in a relative absence of more easily accessible episomal DNA copies (7, 43, 44). In contrast, recent data from four studies imply that HPV-based screening provides a 60-70% greater protection against invasive cervical carcinomas compared to cytology. There was a higher protection for adenocarcinoma than for SCC (45).

In the present study, only one woman (AIS) out of 54 with cervical pathology had negative HPV test, supporting the notion that HPV test is able to identify cervical adenocarcinoma.

This is a population-based study with a high number of included patients with AGC or AIS compared to other single-Institutional studies (2, 17, 46). The histopathological follow-up was achieved in 94% of the women and 92% underwent an endometrial biopsy, which is according with the guidelines. HPV testing was started as a routine procedure in patients with AGC and AIS in 2010. Because of this, HPV testing was not performed for all included patients.

## Conclusion

A cervical smear with AGC or AIS in the organized screening program or performed due to symptoms needs further histopathological examination and also evaluation of the endometrium since more than 80% of uses have histopathological abnormities and a high proportion have invasive cancer.

AGC or AIS in cytology indicates the presence of endometrial neoplasia in post-menopausal women. In women younger than 50 years of age, AGC and AIS findings indicate pre-cancerous abnormalities or invasive adenocarcinoma of the cervix. HPV testing seems to identify cervical adenocarcinoma in the cervix and HSIL to a very high extent.

## Conflicts of Interest

None of the Authors of this article has any conflict of interest.

## References

1 Derchain SF, Rabelo-Santos SH, Angelo-Andrade LA, Sarian LO, Oliveira E and Zeferino LC: Atypical glandular cells and adenocarcinoma *in situ* according to the Bethesda 2001 classification: cytohistological correlation and clinical implications. Eur J Obst Gyn Reprod Biol *139*: 79-85, 2008.

2 Diaz-Montes TP, Farinola MA, Zahurak ML, Bristow RE and Rosenthal DL: Clinical utility of atypical glandular cells (AGC) classification: cytohistologic comparison and relationship to HPV results. Gynecol Oncol *104*: 366-371, 2007.

3 http://www.cancerscreening.nhs.uk/cervical/cervical-cancer.html. Last accessed 17th April, 2014.

4 www.asccp.org/edu/practice/cervix/colposcopy/indications.html. consensusguidelinesbytheamericansocietyforcolposcopyandcervicalpathology Last accessed 17th April, 2014.

5 Zaino RJ: Symposium part I: adenocarcinoma *in situ*, glandular dysplasia, and early invasive adenocarcinoma of the uterine cervix. Int J Gynecol Pathol *21*: 314-326, 2002.

6 Young RH and Clement PB: Endocervical adenocarcinoma and its variants: their morphology and differential diagnosis. Histopathol *41*: 185-207, 2002.

7 Pirog EC, Kleter B, Olgac S, Bobkiewicz P, Lindeman J, Quint WG, Richart RM and Isacson C: Prevalence of human papillomavirus DNA in different histological subtypes of cervical adenocarcinoma. Am J Pathol *157*: 1055-1062, 2000.

8 Zielinski GD, Snijders PJ, Rozendaal L, Daalmeijer NF, Risse EK, Voorhorst FJ, Jiwa NM, van der Linden HC, de Schipper FA, Runsink AP and Meijer CJ: The presence of high-risk HPV combined with specific p53 and p16INK4a expression patterns points to high-risk HPV as the main causative agent for adenocarcinoma *in situ* and adenocarcinoma of the cervix. J Pathol *201*: 535-543, 2003.

9 Andersson S, Rylander E, Larson B, Sigurdardottir S, Backlund I, Sällström J and Wilander E: Types of human papillomavirus revealed in cervical adenocarcinomas after DNA sequencing. Oncol Rep *10*: 175-179, 2003.

10 Cangiarella JF and Chhieng DC: Atypical glandular cells–an update. Diagn Cytopathol *29*: 271-279, 2003.
11 Lee KR, Darragh TM, Joste NE, Krane JF, Sherman ME, Hurley LB, Allred EM and Manos MM: Atypical glandular cells of undetermined significance (AGUS): Interobserver reproducibility in cervical smears and corresponding thin-layer preparations. Am J Clin Pathol *117*: 96-102, 2002.
12 Meath AJ, Carley ME and Wilson TO: Atypical glandular cells of undetermined significance. Review of final histologic diagnoses. J Reprod Med *47*: 249-252, 2002.
13 Kennedy AW, Salmieri SS, Wirth SL, Biscotti CV, Tuason LJ and Travarca MJ: Results of the clinical evaluation of atypical glandular cells of undetermined significance (AGCUS) detected on cervical cytology screening. Gynecol Oncol *63*: 14-18, 1996.
14 Burja IT, Thompson SK, Sawyer WL, Jr. and Shurbaji MS: Atypical glandular cells of undetermined significance on cervical smears. A study with cytohistologic correlation. Acta Cytol *43*: 351-356, 1999.
15 Zhao C, Austin RM, Pan J, Barr N, Martin SE, Raza A and Cobb C: Clinical significance of atypical glandular cells in conventional Pap smears in a large, high-risk U.S. West coast minority population. Acta Cytol *53*: 153-159, 2009.
16 DeSimone CP, Day ME, Tovar MM, Dietrich CS, 3rd, Eastham ML and Modesitt SC: Rate of pathology from atypical glandular cell Pap tests classified by the Bethesda 2001 nomenclature. Obstet Gynecol *107*: 1285-1291, 2006.
17 Derchain SF, Rabelo-Santos SH, Sarian LO, Zeferino LC, de Oliveira Zambeli ER, do Amaral Westin MC, de Angelo Andrade LA and Syrjänen KJ: Human papillomavirus DNA detection and histological findings in women referred for atypical glandular cells or adenocarcinoma *in situ* in their Pap smears. Gynecol Oncol *95*: 618-623, 2004.
18 Castle PE, Fetterman B, Poitras N, Lorey T, Shaber R and Kinney W: Relationship of atypical glandular cell cytology, age, and human papillomavirus detection to cervical and endometrial cancer risks. Obstet Gynecol *115*: 243-248, 2010.
19 Sharpless KE, O'Sullivan DM and Schnatz PF: The utility of human papillomavirus testing in the management of atypical glandular cells on cytology. J Low Genit Tract Dis *13*: 72-78, 2009.
20 Levine L, Lucci JA, 3rd and Dinh TV: Atypical glandular cells: new Bethesda Terminology and Management Guidelines. Obstet Gynecol Surv *58*: 399-406, 2003.
21 Soderlund-Strand A, Carlson J and Dillner J: Modified general primer PCR system for sensitive detection of multiple types of oncogenic human papillomavirus. J Clin Microbiol *47*: 541-546, 2009.
22 Schmitt M, Bravo IG, Snijders PJ, Gissmann L, Pawlita M and Waterboer T: Bead-based multiplex genotyping of human papillomaviruses. J Clin Microbiol *44*: 504-512, 2006.
23 Davey DD, Neal MH, Wilbur DC, Colgan TJ, Styer PE and Mody DR: Bethesda 2001 implementation and reporting rates: 2003 practices of participants in the College of American Pathologists Interlaboratory Comparison Program in Cervicovaginal Cytology. Arch Pathol Lab Med *128*: 1224-1229, 2004.
24 Solomon D, Davey D, Kurman R, Moriarty A, O'Connor D, Prey M, Raab S, Sherman M, Wilbur D, Wright T Jr and Young N: Forum Group Members; Bethesda 2001 Workshop: The 2001 Bethesda System: terminology for reporting results of cervical cytology. JAMA *287*: 2114-2119, 2002.
25 Davey DD, Woodhouse S, Styer P, Stastny J and Mody D: Atypical epithelial cells and specimen adequacy: current laboratory practices of participants in the college of American pathologists interlaboratory comparison program in cervicovaginal cytology. Arch Pathol Lab Med *124*: 203-211, 2000.
26 Soofer SB and Sidawy MK: Atypical glandular cells of undetermined significance: clinically significant lesions and means of patient follow-up. Cancer *90*: 207-214, 2000.
27 Raab SS, Isacson C, Layfield LJ, Lenel JC, Slagel DD and Thomas PA: Atypical glandular cells of undetermined significance. Cytologic criteria to separate clinically significant from benign lesions. Am J Clin Pathol *104*: 574-582, 1995.
28 Ronnett BM, Manos MM, Ransley JE, Fetterman BJ, Kinney WK, Hurley LB, Ngai JS, Kurman RJ and Sherman ME: Atypical glandular cells of undetermined significance (AGUS): cytopathologic features, histopathologic results, and human papillomavirus DNA detection. Hum Pathol *30*: 816-825, 1999.
29 DeSimone CP, Day ME, Dietrich CS, 3rd, Tovar MM and Modesitt SC: Risk for residual adenocarcinoma *in situ* or cervical adenocarcinoma in women undergoing loop electrosurgical excision procedure/conization for adenocarcinoma *in situ*. J Reprod Med *56*: 376-380, 2011.
30 Wright TC Jr, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ and Solomon D: 2006 American Society for Colposcopy and Cervical Pathology-sponsored Consensus Conference. 2006 consensus guidelines for the management of women with cervical intraepithelial neoplasia or adenocarcinoma *in situ*. Am J Obstet Gynecol *197*: 340-345, 2007.
31 Muntz HG, Bell DA, Lage JM, Goff BA, Feldman S and Rice LW: Adenocarcinoma *in situ* of the uterine cervix. Obstet Gynecol *80*: 935-939, 1992.
32 Denehy TR, Gregori CA and Breen JL: Endocervical curettage, cone margins, and residual adenocarcinoma *in situ* of the cervix. Obstet Gynecol *90*: 1-6, 1997.
33 Lea JS, Shin CH, Sheets EE, Coleman RL, Gehrig PA, Duska LR, Miller DS and Schorge JO: Endocervical curettage at conization to predict residual cervical adenocarcinoma *in situ*. Gynecologic oncology *87*: 129-132, 2002.
34 Kipp BR, Medeiros F, Campion MB, Distad TJ, Peterson LM, Keeney GL, Halling KC and Clayton AC: Direct uterine sampling with the Tao brush sampler using a liquid-based preparation method for the detection of endometrial cancer and atypical hyperplasia: a feasibility study. Cancer *114*: 228-235, 2008.
35 Chhieng DC and Cangiarella JF: Atypical glandular cells. Clin Lab Med *23*: 633-657, 2003.
36 Cohen JM: Endometrial cancer. N Engl J Med 303: 522, 1980.
37 Massad LS, Einstein MH, Huh WK, Katki HA, Kinney WK, Schiffman M, Solomon D, Wentzensen N and Lawson HW: 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. J Low Genit Tract Dis *17*: S1-S27, 2013.
38 Daniel A, Barreth D, Schepansky A, Johnson G, Capstick V and Faught W: Histologic and clinical significance of atypical glandular cells on Pap smears. Int J Gynaecol Obstet *91*: 238-242, 2005.
39 Sharpless KE, Schnatz PF, Mandavilli S, Greene JF and Sorosky JI: Dysplasia associated with atypical glandular cells on cervical cytology. Obstet Gynecol *105*: 494-500, 2005.

40 Schnatz PF, Pattison K, Mandavilli S, Fiel-Gan M, Elsaccar OA, O'Sullivan DM and Sharpless KE: Atypical glandular cells on cervical cytology and breast disease: What is the association? J Low Genit Tract Dis *15*: 189-194, 2011.
41 Moritani S, Ioffe OB, Sagae S, Dahmoush L, Silverberg SG and Hattori T: Mitotic activity and apoptosis in endocervical glandular lesions. Int J Gynecol Pathol *21*: 125-33, 2002.
42 Zhao C, Florea A and Austin RM: Clinical utility of adjunctive high-risk human papillomavirus DNA testing in women with Papanicolaou test findings of atypical glandular cells. Arch Pathol Lab Med *134*: 103-108, 2010.
43 Park JS, Hwang ES, Park SN, Ahn HK, Um SJ, Kim CJ, Kim SJ and Namkoong SE: Physical status and expression of HPV genes in cervical cancers. Gynecol Oncol *65*: 121-129, 1997.
44 Stoler MH, Rhodes CR, Whitbeck A, Wolinsky SM, Chow LT and Broker TR: Human papillomavirus type 16 and 18 gene expression in cervical neoplasias. Hum Pathol *23*: 117-128, 1992.
45 Ronco G, Dillner J, Elfström KM, Tunesi S, Snijders PJ, Arbyn M, Kitchener H, Segnan N, Gilham C, Giorgi-Rossi P, Berkhof J, Peto J and Meijer CJ: Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. Lancet *383*: 524-532, 2014.
46 Ajit D, Gavas S, Joseph S, Rekhi B, Deodhar K and Kane S: Identification of atypical glandular cells in pap smears: Is it a hit and miss scenario? Acta Cytol *57*: 45-53, 2013.

*Received October 6, 2014*
*Revised November 5, 2014*
*Accepted November 10, 2014*