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ORIGINAL ARTICLE

Age cutoff for reporting of benign-appearing endometrial cells in Papanicolaou specimens; should it be raised? A 10-year retrospective study from a large county hospital

Stacy Hinson, MD, Kyle Molberg, MD, Mariam Mir, MD, Melinda Flores, MD, Wenxin Zheng, MD, Elena Lucas, MD*

Department of Pathology, University of Texas Southwestern Medical Center, Dallas, Texas

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Introduction The recommendation for reporting benign-appearing endometrial cells in Papanicolaou specimens was increased from 40 to 45 years in the 2014 edition of The Bethesda System. Recent studies suggest that increasing the reporting age to 50 years would have no significant negative impact. Reporting of benign endometrial cells may trigger unnecessary procedures and increase the cost of patient care. The goal of our study was to perform cytohistologic correlations and determine an optimal age cutoff for reporting endometrial cells in cervical cytology specimens.
Materials and methods The pathology database was searched between 2006 and 2015 for Papanicolaou tests with benign-appearing endometrial cells that were followed by endometrial sampling within 1 year of the cytology result in women ≥45 years. In cases where more than one follow-up surgical specimen was available, only the most significant result was included. Endometrial carcinoma or atypical hyperplasia was considered a significant histologic result. The data were organized into 4 age groups, 45 to 49, 50 to 54, 55 to 59, and ≥60 years.
Results Among 453,420 Papanicolaou specimens, 1121 cases reported endometrial cells in women ≥45 years. Of these, 588 (52%) had an endometrial biopsy/curettage or hysterectomy. Benign diagnosis was reported for 558 (95%) and 12 (2%) samples were insufficient for diagnosis. Significant histologic findings were present in 18 (3%) of cases, of which all were endometrial carcinoma. The difference was statistically significant between the age groups 45 to 54 and ≥55 (1.5% versus 17% of cases had significant endometrial pathology, $P < 0.05$).
Conclusions Increasing the current reporting age appears safe and may improve efficiency and cost savings.

Introduction

Cytologically benign-appearing endometrial cells (BEC) are commonly found in cervical cytology specimens. They may appear in Papanicolaou specimens during the first half of the

*Corresponding author: Elena Lucas, MD, Department of Pathology, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390. Tel.: (469) 419-1538; Fax: (469) 419-3021.
E-mail address: Elena.Lucas@UTSouthwestern.edu (E. Lucas).

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menstrual cycle or with abnormal vaginal bleeding. The question remains as to whether their identification in an otherwise unremarkable Papanicolaou specimen is physiologic or a sign of an underlying endometrial pathology, and whether groups of patients can be delineated in which their reporting is unnecessary.[1]

For historical perspective, the reporting of BEC has evolved quite considerably over the last 3 decades. The Bethesda System (TBS) 1991 recommended reporting cytologically benign-appearing endometrial cells in postmenopausal women to indicate the possibility of endometrial pathology.[2] Because the clinical information on the menstrual/menopausal status, hormone therapy, and other risk factors are not always readily available to the pathologist, the 2001 TBS version modified the recommendations by introducing a 40 years or older age threshold for reporting of BEC.[3,4] This age was felt to be a safe cutoff point that would increase the test sensitivity by capturing all postmenopausal women while leaving clinical correlation to the clinician's discretion.[5,6] Since this change, several studies have demonstrated that although the reporting of BEC in Papanicolaou specimens and histologic follow-up increased,[7,8] the positive predictive value for detection of significant endometrial pathology remained low.[9,10] Despite the recommendations of the American Society of Colposcopy and Cervical Pathology regarding the management of these patients on a case-by-case basis exercising clinical judgment,[11] many patients continued to undergo unnecessary endometrial sampling, which has potential risks including bleeding, infection, and, rarely, uterine perforation. In addition, the procedure may cause patient anxiety and drives up health care cost.

The 2014 TBS attempted to address this problem by raising the age for reporting of BEC to $\geq$45 years. In addition, it suggested including an educational note, which should emphasize that endometrial evaluation be done only in postmenopausal women or in cases of abnormal uterine bleeding.[6] No further endometrial evaluation was recommended for asymptomatic women. Although these new recommendations were designed to help reduce unnecessary endometrial biopsies, in routine clinical practice, such comments and patient management vary widely among institutions and practitioners.

Since the TBS 2014 guidelines were published, several studies further investigated the best strategy for reporting of BEC and questioned 45 years as an optimal threshold.[12-15] In light of the need for further clarification of the best cutoff age that would reflect a balance between sensitivity and specificity, we undertook a retrospective study. Our primary goal was to perform cytohistologic correlations and determine optimal age threshold for reporting endometrial cells in Papanicolaou specimens. We also performed correlation of BEC in Papanicolaou samples with clinical parameters and histopathologic characteristics of endometrial preneoplastic and neoplastic lesions. This is one of the largest studies of this kind to date with a focus on patients from a large county hospital.

Materials and methods

Case selection

A retrospective study was approved by the institutional review board of the University of Texas Southwestern Medical Center. Cervical cytology cases accessioned between January 2006 and December 2015 with a diagnosis of endometrial cells in women aged $\geq$40 years that had concurrent or subsequent endometrial sampling within 1 year were selected from the pathology database of Parkland Health and Hospital System. This institution is a county safety-net hospital and clinic system with one of the largest obstetric and gynecologic services in the nation. Between 2006 and 2015, 35,000 to over 45,000 Papanicolaou tests were collected annually within the Parkland system. In our study, all specimens were liquid-based cytology (Hologic, Inc, Bedford, MA) prepared according to the manufacturer's instructions. Because it is now established by multiple studies that the change of the reporting of BECs from age $\geq$40 to $\geq$45 years has had no significant impact on detection of significant endometrial lesions, patients younger than 45 years were not analyzed in our study. Endometrial sampling included endometrial biopsy, curettage, or hysterectomy.

Data recording

The patient's age at the time of Papanicolaou diagnosis, the time between the Papanicolaou and endometrial sampling, the type of surgical specimen, histological diagnosis, menstrual history, clinical symptoms, and indication for the endometrial sampling were extracted from the medical and pathology records. Endometrial carcinoma or atypical endometrial hyperplasia/endometrial intraepithelial neoplasia (EIN) was considered a significant histologic result. In cases where more than 1 follow-up surgical specimen was available, only the most significant result was included. These significant surgical results and the correlating Papanicolaou cytology were reviewed by two authors (EL and KM) to confirm the diagnoses. No discrepancies were discovered in the cases available for review. The patients were stratified into 4 age groups, 45 to 49, 50 to 54, 55 to 59, and $\geq$60 years.

Statistical analysis

The Fisher exact test was used to evaluate differences between age groups in frequencies of significant endometrial pathology. P values < 0.05 were considered significant.

Results

A total of 453,420 Papanicolaou specimens were reviewed during the study period, and 1121 (0.25%) cases reported BEC in women $\geq$45 years. Of these, 588 (52%) had

Table 1 Papanicolaou specimens with BEC in women aged 45 to 60+ years from 2006 to 2015.

Results, n (%)	Age group			
	45 to 49 years	50 to 54 years	55 to 59 years	≥60 years
Number of Papanicolaou tests with BEC, n	735	278	51	57
Number with histologic follow-up	378 (51.4)	151 (54.3)	30 (59)	29 (51)
Insufficient for diagnosis	5 (1.3)	6 (4)	1 (3.3)	0 (0)
Benign histologic findings	368 (97.4)	142 (94)	24 (80)	24 (82.8)
Endometrial carcinoma	5 (1.3)	3 (2)	5 (16.7)	5 (17.2)

Abbreviation: BEC, benign-appearing endometrial cells.

subsequent endometrial sampling. Procedures for endometrial sampling included endometrial biopsy/endometrial curettage or hysterectomy. If the patient had both a hysterectomy and an endometrial biopsy or curettage, the pathology result of the hysterectomy was used in this study. For those cases with multiple endometrial biopsies or curettages, only the most significant result was used in this study.

A total of 558 (95%) follow-up endometrial samplings had benign diagnoses and 12 (2%) were insufficient for diagnosis. Benign findings included normal cycling endometrium (proliferative, secretory or menstrual), disordered proliferative endometrium, anovulatory bleeding, endometrial polyps, chronic endometritis, and atrophy. We also placed hyperplasia without cytologic atypia into the benign category, as it is currently not considered a precancerous lesion. Significant histologic findings were present in 18 (3%) of cases, of which all were endometrial carcinomas. Results are summarized in Table 1 and Fig. 1. As seen in Table 2, the difference was most statistically significant between the age groups 45 to 54 and all groups ≥55 (1.5% versus 17% of cases had significant endometrial pathology, $P < 0.0001$).

The mean age of patients with significant endometrial histology is 54.3 years (range: 46 to 66). Eight (44%) of the patients were premenopausal and 10 (56%) were postmenopausal. Analysis of clinical history revealed that all patients with significant endometrial pathology had reported abnormal vaginal bleeding. This appears to be the main indication for endometrial sampling in these patients. The clinical-pathologic findings are summarized in Table 3.

Discussion

Gynecologic cytology is designed for screening of cervical lesions. Its success in reducing the incidence and mortality of cervical cancer is indisputable. In contrast, endometrial cancer, the most common malignancy of the gynecologic tract (6% of all cancers in women), lacks an effective and comparable screening test. According to the National Cancer Institute statistics, there will be more than 63,230 new uterine cancer cases in 2018, with an estimated 11,350 women expected to die of the disease. Endometrial cancer is primarily a disease of postmenopausal women, with a mean age at diagnosis of 60 years. Although it is generally accepted that Papanicolaou cytology is an ineffective tool for screening of endometrial pathology, endometrial cells are a common finding on routine Papanicolaou smears and pathologists must therefore assess cytological features,

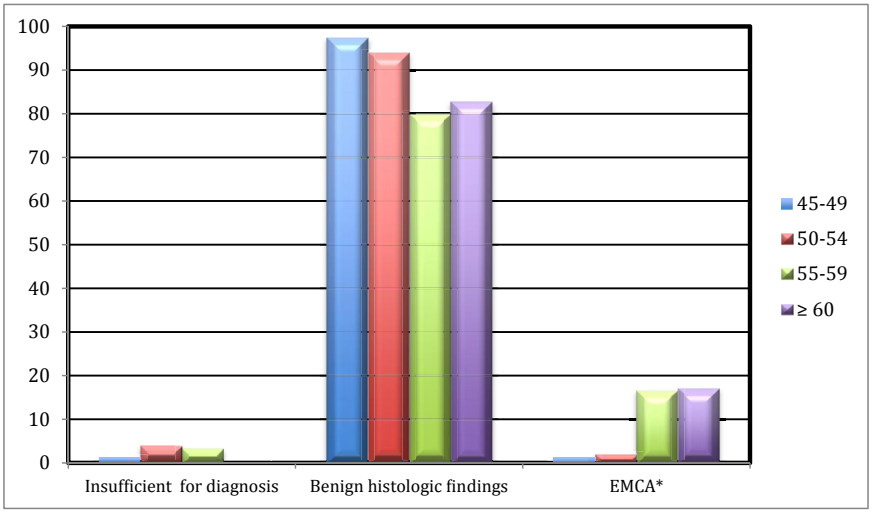

Figure 1 Comparison of the percentages of different histologic diagnostic groups in patients with benign-appearing endometrial cells in Papanicolaou specimens stratified by age groups. *EMCA, endometrial carcinoma.

Table 2 *P* value for comparison of PPV among age groups.

Age group, years	50 to 54 years	55 to 59 years	≥60 years
45 to 49	0.6920	0.0003[a]	0.0003[a]
50 to 54		0.0036[a]	0.0036[a]
55 to 59			1.0000

[a]Statistically significant difference (two-sided Fisher exact test).

assign the potential clinical significance, and decide on reporting this finding. An annual well-woman exam and Papanicolaou test is an opportunity for the physician to potentially detect an early precancerous or cancerous endometrial lesion.

BEC can be seen in Papanicolaou smears in association with various benign, premalignant, and malignant endometrial lesions, including anovulatory bleeding, atrophy, leiomyoma, polyps, atypical and non-atypical endometrial hyperplasia, and carcinoma. The controversy exists regarding their value in Papanicolaou reports. Association of BEC with endometrial hyperplasia and cancer in both asymptomatic and symptomatic postmenopausal women has been previously documented by a number of correlational studies,[16-24] although a few two-arm studies demonstrated no association with significant pathology when compared to the control group of patients whose Papanicolaou reports did not include benign endometrial cells.[25-27] Some investigators documented that there is no additional value of reporting BECs in Papanicolaou tests because all patients had clinical symptoms triggering endometrial sampling.[28] Overall, although the sensitivity of BEC in Papanicolaou tests is low, the accumulated data show that their presence has enough specificity to justify follow-up in postmenopausal and premenopausal women who are not actively menstruating. To reduce the number of unnecessary investigations, the 2014 TBS raised the age for reporting BEC from 40 years to ≥45 years; the optimal age threshold is still a matter of debate, however. In this study we analyzed whether the threshold for reporting of BEC can be raised even further without compromising sensitivity.

Table 3 Clinical-pathological correlation of cases with BEC and endometrial carcinoma.

Clinical-pathologic parameters	
Menopausal status, n (%)	
Premenopausal	8 (44)
Postmenopausal	10 (56)
Mean days to endometrial sampling	73
Histologic diagnosis (most significant pathology), n	
Endometrial carcinoma	18
High-grade serous carcinoma	1
Endometrioid carcinoma, FIGO grade 1	9
Endometrioid carcinoma, FIGO grade 2	4
Endometrioid carcinoma, FIGO grade 3	4

Abbreviation: FIGO, International Federation of Gynecology and Obstetrics.

Our results demonstrated that BEC in cervical cytology specimens of women aged ≥45 years are associated with significant endometrial pathology in a small proportion (3%) of women. In women ≥55 years of age there was a statistically significant increase in the proportion of cases with malignancy when compared with the 45 to 54 years age group (17% versus 1.5%). There was no statistically significant difference when the following age groups were compared: 45 to 49 and 50 to 54 years; or 55 to 59 and ≥60 years. Additionally, when all the endometrial carcinoma cases were analyzed for clinical symptoms, 100% of patients reported postmenopausal or abnormal uterine bleeding, which was the primary indication for endometrial sampling. In our cohort, we did not identify any cases of BEC associated with atypical hyperplasia/EIN. We found 8 cases of hyperplasia without atypia; we did not include them in our calculations because currently hyperplasia without atypia is not considered a precancerous lesion and has a low probability to progress to cancer.

Results of our study are similar to results of several recent studies that assessed the impact of TBS 2014 on significance of BEC and demonstrated that increasing the reporting age to >45 years has little effect of detection of significant endometrial pathology and that raising the cutoff age further likely will improve the test specificity without a negative effect on sensitivity. Weiss et al analyzed the incidence of endometrial hyperplasia and carcinoma in 138 patients with BEC in Papanicolaou specimens of patients who had histologic follow-up. The authors found no carcinoma or atypical hyperplasia in patients aged ≤50 years, whereas 8.6% of patients had endometrial carcinoma and one patient had atypical hyperplasia in the >50 years group.[12]

Coletti et al analyzed 159 women older than 40 years who had follow-up and found women aged >47 years to have higher odds (5.38) of having significant endometrial lesions, which predominantly were seen in women aged >50 years.[14] Fischer et al analyzed 155 patients with BEC and histologic follow-up. In women aged ≥50 years they found 7.6% malignancies and 9.1% cases of hyperplasia without atypia. None of women in 45 to 49 years age group had malignancy, and 4.5% had hyperplasia without atypia.[15] In their large cohort study, Grada et al demonstrated no cases of endometrial carcinoma and 2 cases of hyperplasia in a group of women aged <50 years whereas 5.5% of women aged ≥50 years had carcinoma or hyperplasia with statistically significant difference.[29] Yu et al calculated the negative predictive values (NPVs) in a large cohort (n = 3331) of patients aged >40 years with BEC and histologic follow-up and demonstrated that NPV of BEC in women aged 40 to 44 years and 45 to 49 years were not significantly different (99.5% and 99.3%, respectively). NPVs for patients aged 50 to 54 years, 55 to 59 years, and ≥60 years were statistically lower than the NPV for patients aged 40 to

49 years. Also, asymptomatic patients in all age groups were shown to have an overall very low risk for subsequent endometrial carcinoma or atypical hyperplasia, although patients ≥50 years had slightly higher risk compared with patients <50 years.[13]

In summary, our results, which cover an entire decade, are in agreement with previous studies. We demonstrated that the reporting of normal endometrial cells in cervical cytology specimens has limited significance as all patients in our study had symptomatic vaginal bleeding, which alone should trigger endometrial sampling. Reporting of BEC may create a management dilemma for clinicians and cause unnecessary procedures in premenopausal patients. We agree with other investigators who have concluded that increasing the current reporting age of ≥45 years appears safe and may improve efficiency and cost savings. Although our data indicated that 55 years might be the safe age cutoff, data from other similar studies reported 50 years to be an optimal threshold. Accumulation of a greater data volume from additional studies would help define reporting guidelines. On the clinical side, adherence to American Society of Colposcopy and Cervical Pathology guidelines and interpreting of Papanicolaou cytology results in conjunction with clinical symptoms and menstrual status remains the best practice in managing these patients.

Declaration of interest

None.

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None.

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