Clinical Follow-up of Cervical Sampling With the Ayre Spatula and Zelsmyr Cytobrush

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Objective: To determine if cervical smears obtained with an Ayre spatula and a cytobrush are better detectors of atypia and dysplasia than the modified Ayre spatula alone, as determined by a 2-year clinical follow-up study.

Method: Paired cervical samples were obtained, one using a modified Ayre spatula and the other a cytobrush. In those smears with any abnormality, follow-up after 2 years documented subsequent cytologic and/or histologic diagnosis. The statistical relationship between the screening tests and follow-up cytologic diagnosis was investigated.

Setting: Seven hundred ninety-two women, aged 18 years and older, who presented to a family practice residency clinic for Papanicolaou tests.

Results: The correlation coefficient for the diagnoses obtained using the modified Ayre spatula and the clinical follow-up was .40 (P=.0008), while the correlation coefficient between the cytobrush samples and the clinical follow-up diagnoses was .25 (P=.04). The κ statistics indicate statistically significant concordance only between the spatula and the follow-up diagnoses.

Conclusions: Cervical smears obtained with a modified Ayre spatula correlated significantly with the follow-up diagnoses. As cervical sampling tools emerge, they need to be evaluated on the basis of accurate identification of significant clinical disease, not only on the basis of obtaining endocervical cells to avoid unnecessary repetition of screening tests and diagnostic workups.

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THE GOAL of preventive medicine's Papanicolaou test effort has been to prevent the occurrence of carcinoma of the cervix. In the 1920s, Papanicolaou[1] first reported the detection of cervical cancer by directly observing cancer cells in smears of pooled vaginal secretions. In 1941, in a publication with Traut,[2] he further reported that cervical cancer could be detected in vaginal smears even when it was clinically unsuspected. Later in that decade, Ayre[3] demonstrated that directly sampling the cervix significantly improved the detection of cervical carcinoma. In that same article he also reported the development of a spatula to obtain samples from the squamocolumnar junction.

In the 1960s Richart and Vaillant[4] recommended sampling both the ectocervix and endocervical canal to improve the sampling of the cervix for detecting cancer. This recommendation for clinical practice was based on the observation that more than 95% of cervical cancers occur at the transformation zone.[5,6] As time and technology have progressed, we have become increasingly able to detect premalignant dysplastic conditions of the cervix. Nevertheless, the technical limits of the process continue to result in significant numbers of false-positive and false-negative Papanicolaou test results.

In the hope of improving the effectiveness of the Papanicolaou test, additional criteria have been developed to evaluate the quality of Papanicolaou smear sampling. During the 1980s the presence of endocervical cells evolved as one indicator of quality in a sampling from the cervix.[7-9] New sampling

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PATIENTS AND METHODS

All patients undergoing Papanicolaou tests between August 1985 and July 1986 at the Duluth (Minn) Family Practice Center were enrolled in this study. After patients agreed to participate, cervical samples were obtained. The first sample was obtained with a modified Ayre spatula and a second sample was obtained with a cytobrush. The samples were placed on separate slides and fixed with 2% carbowax. The physicians obtaining these samples consisted of 24 family practice residents equally divided between the 3 years of training. All physicians participating in this project received training in the method of collection and preparation of the slides, including sampling from the transformation zone.

The slides were read by one of two certified cytotechnologists who were blinded to the method of sampling. If the findings from the two slides differed, the report identified the findings from each slide according to whether the end of the slide was frosted (modified Ayre spatula) or clear (cytobrush).

Appropriate clinical follow-up was offered to patients with any detected abnormality. Two years after the study, medical records of patients with abnormalities in the 1985-1986 screening were reviewed to determine their clinical course. Medical records of those patients with normal smears on initial sampling were not reviewed. The most severe diagnosis detected during the 2-year follow-up was recorded. If only cytologic follow-up was used, that diagnosis was used. If histologic diagnosis was made from colposcopic-directed biopsy specimens, endocervical curettings, or conization, that diagnosis was used for the follow-up diagnosis.

The continuum of the diagnostic findings was as follows: normal, including inflammatory changes; atypia, including squamous atypia, atypical squamous metaplasia and marked hyperkeratosis; and dysplasia, including mild dysplasia, moderate dysplasia, severe dysplasia, and carcinoma in situ. The data were analyzed using frequencies and statistical correlations between the Papanicolaou test results and the follow-up findings. For a positive correlation to exist, the diagnoses needed to be identical.

Seven hundred ninety-two patients were entered during the 11-month study. The age distribution of the women reflected the ages cared for in our family practice setting. While 383 (48%) of the subjects were younger than age 30 years, 147 (18%) were in the postmenopausal age range. The range of ages was 18 to 94 years, with a mean age of 29 years. Of the 792 women in the study, 32% were married. How they paid for their health care is an indicator of their socioeconomic status. Thirty-nine percent were receiving medical assistance or Medicare, 50% were using private insurance, and 11% were self-payers or had no insurance.

tools have been developed to improve the accuracy of the Papanicolaou test. Many of these are evaluated on the basis of their ability to obtain endocervical cells.[10-13] However, clinical decisions are not made on the basis of endocervical cells, but rather on the cytologic disease that is identified.[14-16]

One of the recently developed tools is the cytobrush (Zelsmyr Cytobrush Cell Collector, International Cytobrush, Hollywood, Fla). An extensive literature review demonstrates the effectiveness of the cytobrush in obtaining endocervical cells.[10,11,13,15-17] However, none of this literature has examined the cytobrush sample's effectiveness in detecting atypical and dysplastic cells. The purpose of this study was to determine if cervical smears obtained with a cytobrush are better indicators of atypia and dysplasia than cervical smears obtained with the Ayre spatula, using a 2-year follow-up of clinical findings.

RESULTS

In the 1985-1986 screens, the detected abnormalities ranged from atypia to carcinoma in situ. The distribution of abnormalities is shown in **Table 1**. There were no cases of invasive carcinoma identified. There was a difference in how well the two methods detected the presence of abnormalities. The cytobrush and spatula samples agreed in their documentation of 65 (72%) of the 90 abnormalities. The κ reflects the agreement between the two sampling techniques. The κ was .83, with an SE of .033, which reflects the fact that this level of agreement is significantly different from what is expected by chance. More abnormalities were found in the spatula samples than in the cytobrush samples, although each method detected abnormalities not documented by the other.

Of the 90 patients (11%) who had some abnormality on first screening, 80 (10% of the 792 total patients) had follow-up care on record at our clinic; these cases were available for the rest of the analysis. Complete data were available for 66 patients, and their results are reported herein. The correlations of the Papanicolaou smear screening results with the follow-up diagnoses documented in the 2 years after the study are seen in **Table 2**. Remarkably strong correlations occurred between the results of the spatula screens and the follow-up diagnoses. In fact, the correlation of the spatula screens with the follow-up findings was .40 (P=.0008).

Table 1. Initial Screening Results*

	Cytobrush			
Spatula	Normal	Atypia	Dysplasia	Total
Normal	702	8	2	712
Atypia	8	31	1	40
Dysplasia	4	2	34	40
Total	714	41	37	792

*Data are numbers of screenings.

Table 2. Spearman Correlation Coefficients of Papanicolaou Smear Screening Results With Follow-up Diagnoses

	r	P	No. of Patients
Spatula only	.40	.0008	66
Cytobrush only	.25	.04	66
Spatula and cytobrush	.38	.001	66

Cytobrush screens had a .25 correlation, which was weakly statistically significant (P=.04).

Further evaluation of the follow-up data revealed that two of the patients with abnomalities only detected with the cytobrush proved to have disease on follow-up. Six of the patients with abnormalities detected only with the spatula had verified follow-up diagnoses. The combination of the original findings of the spatula and cytobrush had a correlation of .39 (P=.001) with the follow-up data; this correlation and its level of significance reflect the strength of the spatula data. The combination of the data sets weakens the overall correlations. The κ statistics also reflect this finding. The κ reflecting the amount of agreement between the spatula findings and the follow-up data is .18, with an SE of .07; this is statistically significant at P=.01. The κ with the cytobrush and follow-up data is .05, which is not statistically significant. The κ for the combined data sets is .11, which is also not significant.

COMMENT

The results of this study indicated that using an Ayre spatula for Papanicolaou smear sampling to screen for cervical cancer provided a better indicator of atypia and dysplasia than the cytobrush in a patient's subsequent 2-year clinical follow-up. The results also confirm what has been documented elsewhere: additional cases of cervical disease are detected using a second sampling, in this case, the cytobrush. However, it is also evident in the data presented herein that the results of Ayre spatula sampling are clearly correlated with the clinical findings and course for these women; the cytobrush samples did not show similar correlations.

One strength, as well as a limitation, of this study is that the spatula sampling was always the first sampling technique used. Studies have shown that when more than one sampling of the cervix is done, the first sampling results in a higher yield of abnormalities.[18,19] Beilby et al[19] found that a second sampling with an Ayre spatula increased the detection of abnormalities 19% after sampling with a wood Ayre spatula or Armovical spatula. Luthy et al[20] found that 26% of abnormalities in their study were identified with a second cervical sample after sampling with a wood Ayre spatula or plastic Milex spatula.

In the current study, the cytobrush increased identification by 12%, which is less than that in other published findings. The literature has thus documented that the majority of cervical abnormalities are found with the first sampling, regardless of the sampling tool. The purpose of this study was to determine whether the cytobrush adds significantly to the detection of cervical abnormalities, given its ability to sample endocervical cells. The findings herein indicate that the cytobrush identified two additional cases, but it did not add to the extent of other second sampling techniques or add in any other way, using the clinical course over 2 years as the outcome indicator.

A second limitation of this study may be related to the reliability of the follow-up findings. Others[21-24] have reported that 7% to 78% of cases of atypia or dysplasia diagnosed cytologically regress spontaneously. Knowing this, some of the false-positive results in the cases in this study may represent spontaneous regression of these conditions. However, since this should apply equally to cases identified with the cytobrush and the Ayre spatula, it does not bias the findings of this study.

A third limitation of this study is that the follow-up was limited to only those cases in which abnormalities were detected. This, however, still allows for an answer to the question of whether there is an advantage of using the cytobrush as a second sampling technique in improving the positive predictive value of the Papanicolaou test. Evaluation of all initially "normal" readings during the follow-up period would be necessary to determine the extent of the false-negative readings and allow for determination of the sensitivity and specificity of the screening techniques.

The incidence of cervical cancer has dropped significantly in the past 60 years; many authors attribute this to the use of the Papanicolaou test.[25] Nevertheless, concern about the effectiveness of screening for cervical abnormalities continues today. In analyzing the failures that occur in detecting cervical carcinoma, Koss[26] identified patient errors, physician errors, and laboratory errors as causes. The prevalent patient error was failure to participate in the suggested follow-up. The common physician error was failure to perform a pelvic examination and obtain a cervical smear. The laboratory error Koss cited was the significant false-negative error rate in interpreting smears. In a large follow-up study, the sensitivity of cervical screening for severe dysplasia or carcinoma in situ was 83%.[27] Experienced sample takers and cytotechnologists were important in achieving this level of sensitivity. In the current study, the spatula consistently was more effective in identifying mild abnormalities that were documented in follow-up.

Today, attention is directed toward detecting (and treating) premalignant conditions. Cervical cancer is viewed as a sexually transmitted disease with the human papillomavirus serving as the vector.[14,28] New tools for screening are continually being marketed to improve sampling techniques. Indirect measurements of sampling have evolved, with attention directed to endocervical cells as a marker of "quality sampling." Studies have been done indicating the importance of endocervical cells in the sampling procedure,

but they have not evaluated the disease detected.[7-9] For example, Beilby et al[19] evaluated an alternative sampling device (the Armovical spatula) that improved the yield of endocervical cells by 45%. There was, however, no increase in the yield of pathologic abnormalities. If the yield of endocervical cells is the indicator of a quality smear, the new device was clearly an improvement. However, since there was no corresponding increase in the diagnosis of abnormalities, the two sampling tools are equally effective.

Additional studies have addressed the diagnostic efficiency of the cytobrush in diagnosing advanced disease. Boon and others[29,30] have demonstrated that the cytobrush can diagnose cervical interepithelial neoplasia III and invasive carcinoma better than other sampling tools. The abnormalities in the current study were of a lower grade; atypia and mild dysplasia were the most frequent abnormal diagnoses. In these cases, the cytobrush added little to the diagnostic efficacy.

The literature is replete with studies indicating an improvement in the number of endocervical cells obtained with the use of a cytobrush. The clinical treatment of patients, however, is determined by the pathologic abnormalities detected with cervical sampling. In this study, the evidence does not support the position that the cytobrush adds significantly to the screening sample.

CONCLUSION

In this study we found that the results obtained with the modified Ayre spatula had a *higher* correlation with the follow-up diagnoses. The addition of a second sampling, in this case with the cytobrush, did detect two additional cases of verified cervical disease. However, based on the results of other studies, the improved detection documented here with the cytobrush was less than would be expected of a second sampling tool.

As other sampling tools emerge, evaluation of the effectiveness and efficiency of these tools needs to be adequately evaluated. In the course of this evaluation, indirect parameters (such as the presence or absence of endocervical cells) may be widely used. However, the real outcome we need to evaluate is the ability of the sampling technique to detect significant clinical disease. Endocervical cells are not indicators of disease.

Further studies need to evaluate our technical advancements based on clinically relevant outcomes to reduce the number of false-positive Papanicolaou test results that are then pursued at ever increasing expense. We need to change our behavior when the innovations are shown to help us in detecting significant disease.

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