Koilocytotic Atypia and Underlying Dysplasia

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Background. Several studies have examined the agreement between Papanicolaou smear cytology and subsequent biopsy results in the diagnosis of cervical dysplasia. However, few studies have focused specifically on koilocytotic (KC) atypia. Given the increasing frequency of reporting KC atypia on Papanicolaou smears, we sought to obtain more information on the relationship between Papanicolaou smears and subsequent colposcopically directed cervical biopsies.

Methods. Retrospectively, we compared the Papanicolaou smears and colposcopically guided biopsy results for 132 college women who had abnormal Papanicolaou smears (KC, cervical intraepithelial neoplasia [CIN], or reactive atypia [RA]). Data were compiled through systematic review of the charts of these women. The cervical biopsies were taken 6 months or less after the Papanicolaou smears.

Results. Of 99 women having only KC atypia on cytology, histology revealed concordance in 51 cases and underlying dysplasia in 16 cases. Only one biopsy revealed CIN III, and no biopsies showed invasive carcinoma. We also noted variation in the histologic results between the laboratories that analyzed the biopsy specimens. In comparing the biopsy results after one or two KC atypic Papanicolaou smears 6 months or less apart, we found no statistically significant difference.

Conclusions. These findings suggest that physicians who obtain an initial Papanicolaou smear read as KC atypia could obtain a second smear 3 months later to determine if there is persistent KC atypia before advising a patient to have cervical biopsy. In addition, physicians also should know the limitations of the laboratories providing them with information.

Key words. Cervix dysplasia; colposcopy; cytology.
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Physicians who routinely screen for cervical cancer may have noted recently a significant increase in the reported cytological diagnosis of koilocytotic (KC) atypia, also described as viral associated atypia or human papillomavirus (HPV) effect. Although investigators have studied the relationship between atypia and underlying dysplasia, only two articles have specifically discussed KC atypia and its association with underlying undetected dysplasia or cervical intraepithelial neoplasia (CIN).[1,2] These studies demonstrated that a high percentage of the women had underlying dysplasia. Bolger and Lewis[1] reported that 18 of the 29 (62%) women who had only KC atypia on Papanicolaou smears showed dysplasia on cervical biopsy, and 6 of the 29 (21%) had CIN III. Morrison et al[2] reported that 23% of their 47 cervical biopsies of women with KC atypia showed CIN, but only CIN I or II. A number of other investigators have compared Papanicolaou smear findings with biopsy findings, but they did not focus on KC atypia as a cytological finding.[3-6] In addition, several others have published data that identified more severe disease detected by histology than by cytology.[7-10] Thus, limited objective data exist to guide physicians in dealing with the cytological diagnosis of KC atypia.

We hypothesized that the previously reported incidence of dysplasia and cancer when the Papanicolaou smear showed only atypia overestimated the histologic diagnosis. Given the common nature of this problem and the need for further clarification, we reviewed the charts of women from a university student health center who had abnormal Papanicolaou smear results.

Methods

Subject Population

All patients (N = 155) who had abnormal Papanicolaou smear results with any type of atypia (RA or KC) or dysplasia (CIN) taken at the student health center at the University of Colorado between 1985 and 1989 were

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included in this study. Approximately 2300 Papanicolaou smears were performed yearly, with a 1.3% abnormal rate during the study period. Demographic information specific for the health center was not available, but all students attending the university were eligible for treatment.

The population attending the university during this period was 90% white. Although information about specific smoking habits was not recorded, students at the university level have been shown to smoke less than their nonstudent peers.[11] Information about age at first intercourse and prevalence of sexually transmitted disease was also not available. Most women were nonparous.

The records selected for this investigation were those having abnormal Papanicolaou smear results and a subsequent colposcopically directed biopsy that was confirmed with a written report (n = 132). Biopsies occurred between 1986 and 1989. No more than 6 months passed between the precolposcopy Papanicolaou smear and the biopsy.

Data Collection

The information extracted from the medical records included the dates of Papanicolaou smears, the number of Papanicolaou smears, the classification of the results by the laboratory, the date of biopsy, the results of biopsy, and the laboratory performing the histology. The colposcopic findings were not available for analysis. All Papanicolaou smears were read by the university's pathology laboratory. Forty-nine of 132 biopsies were reviewed at the university laboratory, and the remainder were sent to other pathology laboratories. Not all of the biopsies were obtained at the student health center since some patients returned to their personal family physicians or gynecologists for colposcopy.

Data Analysis

Simple frequencies were calculated for all variables. In addition, two-way frequency tables were used to examine the agreement between Papanicolaou smear and biopsy results. In some instances, the classifications were simplified by combining samples containing both KC atypia and dysplasia into a category with other samples of dysplasia only. Also, all levels of dysplasia were combined (with specific CIN noted). When examining the specificity of the Papanicolaou test in detecting KC atypia compared with a more severe condition (dysplasia), cases diagnosed at biopsy as normal or as reactive atypia (RA) were included.

Calculations concerning the utility of the Papanicolaou smear focused on the agreement between the Papanicolaou smear and the biopsy results. Because biopsies were performed only on patients having abnormal Papanicolaou smears, the traditional calculations of positive predictive value and negative predictive value could not be performed. Instead, we examined the degree to which the Papanicolaou smear could distinguish between KC atypia (a negative test) and more severe disease (a positive test). On the biopsy, any result classified as KC atypia or less severe was considered a negative result, while dysplasia or more severe disease was classified as a positive result. As such, the negative predictive value indicated the proportion of Papanicolaou smears showing KC atypia that were confirmed as KC atypia or a less severe disease on the biopsy. The positive predictive value indicated the proportion of Papanicolaou smears demonstrating diseases more severe than KC atypia that were confirmed on biopsy.

The negative predictive value (NPV) was compared for biopsies following one Papanicolaou smear and more than one Papanicolaou smear using chi-square analysis. In addition, a similar test was used to compare the two laboratory groups. In both cases, the test was used to determine whether the factor influenced the proportion of cases in which severe disease would go undetected by the Papanicolaou smear (1−NPV).

Results

The 132 women in the final sample averaged 23.3 years of age, with an age range of 18 to 47 years. Nine women were 31 to 39 years of age, and one woman was older than 40 years. Of the 155 charts of patients with abnormal Papanicolaou smears, we located written pathological reports for 132 (85%) cervical biopsies. One hundred ten of the 155 women (70%) had KC atypia alone, and another 30 (19.4%) had KC atypia with other abnormalities. Ninety-nine of the 110 women (90%) with KC atypia had a biopsy performed and, as noted in Table 1, 16 of the 99 (16%) had CIN and KC atypia, or CIN alone. On biopsy, 51 (51.5%) showed KC atypia only, while 22 (22.2%) of the biopsies revealed normal tissue. Only one of the 16 (6.2%) biopsies returned with CIN III, and no invasive carcinoma was found. Therefore, 84 of the 99 cases (84.8%) with KC atypia on Papanicolaou smear had biopsies with equivalent or less severe findings. Overall, the negative and positive predictive values for Papanicolaou smears distinguishing KC atypia from more severe disease were .84 and .64, respectively. With a sample size of 99, however, the power to detect a difference was only .45. To increase our power to .80 would have required 265 subjects.

Table 1. Relationship Between Papanicolaou Smears and Subsequent Colposcopically Directed Biopsy Results

Smear Type	*n*	Biopsy Results				
		Normal	KC	CIN I, II, or III	KC and CIN	RA
KC	99	22	51	8	8	10
CIN I, II, or III	6	1	3	1	1	—
KC and CIN	15	—	6	2	6	1
RA	4	1	1	1	1	—
KC and RA	7	3	3	1	—	—
RA and CIN	1	—	—	1	—	—

KC denotes koilocytotic atypia; CIN, cervical intraepithelial neoplasia; RA, reactive atypia.

When we looked at patients younger than 30 years of age (n = 89), we did not find a difference in the percentage of KC atypia on Papanicolaou and CIN on biopsy compared with the total population (14% and 16%, respectively). In 3 of the 10 women over 30 years of age, however, dysplasia was found on biopsy and only KC on cytology (16% total vs 30% over 30 years of age).

Interestingly, if the patients had two or more Papanicolaou smears before undergoing biopsy, then the cytology had better agreement with the histology, with fewer underlying dysplasias found. Dysplasia was found in 7 of the 28 (25%) women who had one Papanicolaou smear, whereas only 9 of the 71 (12.7%) women having two Papanicolaou smears had dysplasia. The negative predictive value increased after more than one Papanicolaou smear (NPV = .87) compared with a single Papanicolaou smear (NPV = .75); however, this was not statistically significant ($P > .10$).

A comparison of the biopsy results returned by the university's laboratory vs those reported by the other laboratories as a group revealed some differences in the likelihood of detecting dysplasia. Sixty-three of the 99 Papanicolaou smears that showed only KC atypia went to other laboratories. Of these, 14 (22%) showed CIN on biopsy, while only 2 of the 36 (5%) sent to the university laboratory revealed more advanced disease. The negative predictive value was considerably higher for the university laboratory (.94) than for the other laboratories (.78) ($P < .06$). Variation also appeared when we examined the results after one vs two Papanicolaou smears. The negative predictive value increased from .63 to .84 after the second Papanicolaou smear at other laboratories. At University Hospital, the NPV was 1.0 after one Papanicolaou smear and remained high at .93 after more than one Papanicolaou smear. None of these differences were statistically significant.

Discussion

The accuracy of the screening Papanicolaou smear has undergone years of debate, and its sensitivity and specificity still remain in doubt.[12] Estimates of the false-negative rate for patients with dysplasia have ranged widely depending on the study.[13,14] Possible reasons for this range include sampling variation, population differences, and lesion size. Because the criteria for the cytological diagnosis of KC atypia continue to change and the percentage of KC atypia nationwide increases, the primary care physician will have to deal with this diagnosis more often. The validity of the Papanicolaou smear becomes more important as we attempt to discern the true relationship between HPV and cervical cancer.

Our findings differed from those of Bolger and Lewis, and Morrison et al.[1,2] Most prominently, we found that only 16% of the Papanicolaou smears failed to reveal underlying dysplasia compared with the 62% reported by Bolger and Lewis and the 23% found by Morrison et al. Overall, 84% of our atypical cytologies proved adequate in that they did not fail to detect more severe disease. Also, only one of our biopsies returned as CIN III. Therefore, with regard to severity of disease, our results agree with those found by Morrison and colleagues, who discovered no biopsies beyond the CIN II category.

Although the skill of the colposcopist in directing the cervical biopsies could explain some variation, population differences may explain much of the disparity. Generally younger, nonparous, and predominantly white, the patients in the study came from a high socioeconomic class. They may also have smoked less than the other women studied. Thirty percent of the women older than 30 years (n = 10) in our study had underlying dysplasia after a Papanicolaou smear showing only KC atypia, compared with 14% of the women younger than 30 years old. This would suggest that KC atypia found on Papanicolaou smears in younger women may have different implications.

Morrison's study looked at the effect of obtaining two smears on the accuracy of Papanicolaou results.[2] His study found underlying CIN 43% of the time if the women had two or more Papanicolaou smears (n = 21) showing KC atypia compared with 23% who had only

one smear. By contrast, we discovered undetected disease in only 13% of women who had at least two Papanicolaou smears showing KC atypia, compared with 25% in women who had only one Papanicolaou smear with that finding. The spontaneous resolution of HPV and mild and moderate dysplasia (CIN I and II) could explain this result.

Lastly, we noted a significant difference in the results of the biopsies evaluated at the different laboratories. Our university laboratory missed only 5% of the underlying dysplasias, compared with the 22% rate of underlying dysplasia from the other laboratories. The fact that the university laboratory always had the cytological slides available when evaluating the biopsy tissue may explain this disparity. Alternatively, the laboratories may have used different criteria to diagnose dysplasia on the biopsies. We could also speculate that the differences in rates between the laboratories represent true differences in the specimens. Even with this variation, overall a smaller percentage of unnoted dysplasia was found when the Papanicolaou smear showed only KC atypia. Both laboratory groups showed no decrease in agreement between cytology and histology after two Papanicolaou smears.

Although our study does not address the popular issue of the relationship between HPV and cervical cancer, it does indicate that cytology can be utilized to predict histology if it is recognized that cytology is a screening tool, the validity of which depends on the adequacy of the sampling, the prevalence of the disease in the population screened, and the skills of the cytologist. In a population similar to ours, physicians may choose to wait for two Papanicolaou smears read as KC atypia before performing colposcopy and biopsy. Given the recent evidence that atypia and mild to moderate dysplasia regress at least 50% of the time after 3 to 6 months, patients may be saved unnecessary invasive procedures and the concomitant risks and costs.[15,16] The lack of satisfactory treatment for KC atypia also would support this approach. In the population studied, advanced disease (ie, invasive carcinoma) probably would not have gone undetected on Papanicolaou smear. The only medical risk of a "wait and see" approach involves low-grade (CIN I to II) lesions that quickly progress to invasive disease. Only limited evidence exists to suggest that such rapid malignant transformation occurs.[17,18]

The differences between this study and previous work accentuates the need for further investigation to clarify the significance of koilocytotic atypia. The inherent problems with retrospective studies suggest that well-designed, prospective clinical trials may provide more conclusive information.

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