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Colposcopy at a crossroads

Jose Jeronimo, MD, Mark Schiffman, MD, MPH

Hormonal and Reproductive Epidemiology Branch, Division of Cancer Epidemiology and Genetics (DCEG), National Cancer Institute, National Institutes of Health, Department of Health and Human Resources, Bethesda, MD

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New cervical cancer prevention strategies are arising from rapidly improving insight into human papillomavirus (HPV) natural history and cervical carcinogenesis, challenging the coventional roles of cytology and colposcopically directed biopsy as the reference standards of screening and diagnosis, respectively. HPV testing has high sensitivity but mediocre specificity and positive predictive value, making the role of colposcopy for the accurate identification of patients requiring treatment even more important. We believe that deficiencies of the colposcopically guided biopsy must be addressed, in particular, the inaccuracy of biopsy placement leading to low sensitivity for detection of CIN3. This opinion outlines our concerns and summarizes new data, suggesting posssible steps that may lead to improvement in colposcopic accuracy.
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New cervical cancer prevention strategies are arising from rapidly improving insight into human papillomavirus (HPV) natural history and cervical carcinogenesis. As a result, new technologies are challenging the conventional roles of cytology and colposcopically directed biopsy.

This commentary is directed to clinicians and will describe challenges now facing the role colposcopy currently fills as a tool to diagnose cervical neoplasia. Particularly, it will summarize recently completed research indicating that colposcopic impression, the determination of biopsy site, and histology are less reliable and accurate than previously presumed. We personally believe that to retain its place in cervical cancer prevention as the reference standard of disease diagnosis certain deficiencies of the colposcopically guided biopsy must be widely recognized and corrected. Fortunately, the new data suggest possible steps that may lead to immediate improvement in colposcopic accuracy. We offer these observations as the starting point for what we hope will be useful discussion and debate.

The changing context of cervical cancer screening programs

Focus on the present

As a starting point, we are encouraged that vaccination against HPV infection will eventually reduce the rates of cervical cancer and its precursors.[1] Eventually, screening programs will need to be reworked to account for decreased yield of abnormalities at each screening round. However, the impact of vaccination on screening programs will be felt over decades. In addition, computer-assisted imaging systems might someday replace colposcopy.[2] To our knowledge, no such system is yet validated. Therefore, we would like to focus on the present. Already, cervical cancer prevention programs, in which

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colposcopists play a critical role, are undergoing profound change because of the advent of HPV testing.[3,4]

Parts of a cervical cancer screening program

To discuss colposcopy in its changing context, the discrete parts of conventional cervical cancer screening programs must be distinguished. In the United States we currently rely on cytology with (for women aged 30 years and older) or without HPV tests for screening; repeat cytology, immediate colposcopy, or (increasingly) HPV testing for the triage of equivocal cytologic interpretations; colposcopy with guided biopsy for diagnosis of abnormalities; LEEP, cryotherapy, or cold-knife conization for treatment; and cytology, HPV-DNA testing or repeat colposcopy to confirm cure after treatment.

Major role of colposcopy

The major role of colposcopy is in guiding the diagnostic biopsy. Fundamentally, the clinicians in the United States follow a histologic standard of disease, in which the histologic diagnosis of the colposcopically directed biopsy is considered the true underlying disease severity. This severity dictates management.[5] The historical success of the conventional approach, based on cytology, colposcopy, and histology in reducing cervical cancer incidence, is undeniable.[6]

Changes in colposcopic practice brought by HPV testing

As contrasted with the conventional histologic model, there is also a strengthening virologic understanding of cervical carcinogenesis. HPV infection is the cause of virtually every case of cervical cancer and precancer.[7] HPV screening and triage will increasingly change the patient population referred to colposcopy. Fifteen years ago, most anxiety over cervical cancer prevention centered on inadequately sensitive cytology screening.[8] In comparison with cytology, HPV testing is highly sensitive and much more reliable.[9] As a corollary of high sensitivity, there is practically no immediate risk of cancer or precancer in the absence of ongoing HPV infection as measured by a DNA test.[10] Absolute safety cannot be provided by any test, but the absence of HPV comes closer than anything else we have (including colposcopy as discussed later). Therefore, HPV testing is gaining an increasingly important role at each step in cervical cancer prevention where the safety conferred by a negative test is paramount. Screening for HPV as an adjunct to cytology among women 30 years and older has already been approved by the Food and Drug Administration (FDA) and has been accepted in a few important settings.[3,4] Triage of atypical squamous cells of undetermined significance (ASC-US) was the first use to be accepted as more cost-effective than either colposcopy or repeated cytology.[11] HPV testing to confirm cure after treatment has substantial evidence supporting clinical adoption.[12] The focus for improving prevention has been on screening, particularly the adjunctive use of HPV testing. There has been very little attention paid to the practice pattern of the colposcopist in the ultimate detection and eradication of cervical cancer precursors and early cancers. The sensitivity of screening is now potentially excellent, cost-effective triage of equivocal cytology is available, outpatient treatment modalities for women needing treatment are well-established (albeit with occasional morbidity that must not be forgotten), and posttreatment surveillance techniques are improving. With the rapidly changing clinical situation, the role of colposcopy for the accurate identification of patients requiring treatment is becoming even more important.

Nonspecificity of HPV testing leaves a major role for colposcopy

The downside of HPV testing is its mediocre specificity and positive predictive value.[13] HPV infection is extremely common and usually transient, especially among young women[14]; thus, the risk associated with a single positive HPV test is low.[15] Where nonspecific referral to colposcopy used to be due mainly to ASC cytology and atypical metaplasia, now a roughly equal number of women are being referred with HPV infections that are destined to clear without the development of cervical intraepithelial neoplasia, grade 3 (CIN3) or cancer (As a possible exception, when the most carcinogenic genotypes of HPV [particularly HPV16 and HPV18] are present and persistent for more than 1 to 2 years, the level of risk might rise to a potentially important, even treatable, clinical diagnosis among women past the peak of HPV prevalence [ie, ≥ 30]).

Colposcopic evaluation and guided biopsy remain the critical tools in distinguishing which women require destruction of the cervical transformation zone where persistent HPV infections can lead to cancer. In fact, optimizing the accuracy of colposcopy and biopsy specimens is now one of the leading concerns in the entire cervical cancer screening process. The remainder of the commentary will focus on the state of the colposcopic examination and how performance can be improved for this critical function.

Challenges facing colposcopy today

Large numbers of colposcopic procedures required

Annually, approximately 50 million American women undergo cervical cancer screening and close to 3 million of them obtain a positive result[16] that refers them to colposcopy according to current guidelines.[5,17] Thus, many clinicians perform colposcopy, and expertise might be expected to vary depending on experience and practice.

Range of abnormalities

In the United States where screening colposcopy is not common, the purpose of colposcopy is to diagnose lesions in a cervix already suspected of abnormality. As part of diagnosis, the colposcopist performs triage. The cervical epithelium is directly evaluated through the colposcope, with the main goal to detect abnormal epithelium, to identify the area of epithelium with the highest degree of disease, and to direct biopsies to that area or areas as needed. Unfortunately, there is an imperfect correlation between the visual changes of the cervical epithelium and the severity of the preneoplastic and neoplastic changes, as pointed out by Reid and Scalzi[18] who created a colposcopic index widely used in the United States. These authors commented that "the most benign condyloma and the most worrisome intraepithelial neoplasia are linked by a spectrum of continuous morphologic changes." This strategy gained popularity because it was less invasive and less morbid than the previous diagnostic approach, diagnostic conization. Colposcopy continues to be the standard for cervical diagnosis, despite some studies suggesting that its accuracy is imperfect.[19-21] In part, this has been because of a paucity of alternatives, and in part because isolated reports of inaccuracy could be dismissed as due to poor technique by reporting clinicians.

Lack of sensitivity and colposcopic appearance

Of course, it is vital that colposcopists promptly recognize invasive cancers but, more often, they are called on to identify precancerous lesions. We consider CIN3 to be the best disease endpoint to study as precancer, because CIN2 is poorly reproducible and often regresses. Suboptimal sensitivity of colposcopy for finding CIN3 was evident during the ASCUS/LSIL Triage Study (ALTS),[22,23] a multicenter randomized trial involving more than 40 colposcopists. The large size and the multicentric, prospective nature of this trial that included nationally recognized expert colposcopists allowed direct testing of the accuracy of colposcopy. In ALTS, there were 3 management arms. In the immediate colposcopy arm in which all the women had colposcopy at enrollment, only 54.8% of women with a final histologic diagnosis of CIN3 at enrollment or during the 2-year follow-up had a positive colposcopic biopsy ($\geq$CIN2) at enrollment. Assuming that most of the CIN3 patients detected at the follow-up already had incipient CIN3 at the time of enrollment, we would expect that colposcopy could find a very high proportion of abnormalities during the first evaluation. In fact, more than 90% of the women found within 2 years to have CIN3 (as diagnosed by an independent Pathology Quality Control Group) were already HPV-DNA positive (with cytology of ASCUS or LSIL) at enrollment. HPV testing provided better discrimination of risk than cytology or colposcopy.[10]

In an attempt to understand insensitive colposcopic performance, ALTS clinician-investigators have performed many ancillary analyses concentrating on the enrollment colposcopic examination of women with eventual diagnosis of CIN3. They have observed poor sensitivity of enrollment colposcopic impression[24] and equally poor sensitivity of a modified Reid Index with its component scores of color, margin, and vessels.[25] Among women with an enrollment colposcopic examination that did not detect CIN2 or worse, ALTS investigators found an unexpected result: the risk of subsequent diagnosis of CIN3 was equivalent during the 2-year follow-up of women regardless of whether the initial colposcopy results were CIN1, negative colposcopically directed biopsies, or normal colposcopic impressions leading to no biopsies.[26] As a result, we believe that when CIN2 or worse is not found, subtler distinctions, including CIN1, are not very reliable or predictive, partly because of histologic variability[27] or difficulties in placing biopsies accurately (discussed later), and partly because many cases of CIN1 are just manifestation of recently acquired HPV infections that tend to be transient.

Colposcopic appearance and choice of biopsy site

The choice of whether and where to biopsy is more important than assigning a colposcopic impression. The reproducibility and accuracy of these judgments are difficult to study in real time. On the basis of static images, ALTS quality-control colposcopists demonstrated only mediocre agreement among themselves and compared with clinical center colposcopists.[28] To compare the location of biopsy with the underlying location of CIN, Guido et al[24] studied the location of biopsies taken around the portio of the cervix. They observed that the tendency of ALTS colposcopists to take more biopsy specimens from the anterior (12 o'clock) and posterior (6 o'clock) position was due to more than accessibility, because it related to significantly more severe colposcopic appearance regardless of final diagnosis at these locations (as assessed post hoc by digitized cervigrams). At each location, the more colposcopists biopsied, the more CIN they found, suggesting a possible value of taking additional biopsy specimens.

Indeed, the sensitivity of enrollment colposcopy was shown to increase steadily with additional biopsy specimens in another recent ALTS analysis (Gage et al for the ALTS Group, submitted), regardless of any other variable, including clinician type (nurse practitioner, gynecologist, gynecologic oncology fellow, or gynecologic oncologist). Gynecologic oncologists in ALTS tended to take only 1 biopsy from the perceived worst lesion site. The data strongly suggested that they, along with other clinicians, could have improved the sensitivity of their

examination for finding CIN2 and CIN3 by taking a second biopsy specimen.

The ALTS reports confirm other recently reported evidence of inadequate colposcopic sensitivity. Pretorius et al[29] published results from a large screening study in China in which gynecologist oncologists performed colposcopic evaluations of each quadrant of the cervix separately. A directed biopsy specimen was taken from any abnormality; but if there was no abnormal epithelium in a quadrant, a random biopsy specimen was taken from the squamocolumnar junction in that quadrant. Interestingly, 37.1% of CIN2 or worse lesions were diagnosed by random biopsy specimens taken from quadrants without colposcopic abnormality. Similar results were presented by Sellors et al[30] showing that in 19% of patients with CIN2 or worse, the disease was detected by random biopsy specimens from quadrants without visual abnormalities. We consider these articles interesting but emphasize that we are not recommending random biopsy specimens.

Size of CIN2 and CIN3 lesions and colposcopic sensitivity

Pretorius et al[29] additionally found that CIN2 and CIN3 lesions detected by random biopsy specimens were significantly smaller, involving fewer quadrants of the cervix than lesions detected by colposcopically directed biopsy specimens. Similarly, Sherman et al[31] observed that the cases of CIN3 missed by enrollment colposcopy in ALTS (but detected by HPV testing) were very small. Although there was no evidence of short-term regression, probably some of these lesions would have eventually regressed. It is logically more likely to find small lesions in populations with more sensitive cervical cancer screening that reduces the numbers of large prevalent lesions. Therefore, colposcopy might become more challenging when HPV testing becomes more common in the United States, as the high sensitivity of HPV testing leads to the detection of earlier and smaller CIN3 lesions.

Conclusion

In summary, there are new data showing that colposcopy and guided biopsies as typically practiced are missing a fair percentage of (mostly small) CIN2 and CIN3 lesions. There is no doubt that research on computer-assisted aids for colposcopy will continue. In the meantime, our data suggest 2 additional directions for immediate improvement.

First, colposcopists need to determine precisely which colposcopic features and abnormalities can and cannot be reliably distinguished, in relationship to HPV status and disease outcome. The National Cancer Institute (NCI), National Library of Medicine, and the American Society of Colposcopy and Cervical Pathology are currently collaborating on this issue, based on very large-scale review of digitized visual images, histology, cytology, and HPV typing from 2 NCI-sponsored studies, the ASCUS/LSIL Triage Study for cervical cancer (ALTS) and the Guanacaste study in Costa Rica.

Second, the accumulated data suggest very strongly that the heart of colposcopic practice is the identification of the most abnormal area for biopsy. Because colposcopic appearance is often complex, and the most abnormal area may be small, the sensitivity of the procedure will depend on taking more than a single biopsy in many cases. Our findings suggest that this is true for both novice and experienced colposcopists. We believe that it is worth considering a randomized trial of different approaches to diagnosis of patients presenting with HPV-DNA positivity and abnormal cytology. Issues of accuracy, cost, and comfort must be considered. As mentioned in a recent paper (Gage et al, submitted), it is worth comparing at least these options: additional biopsy specimen from another part of the worst-looking lesion, additional biopsy specimen of another abnormal area or areas, and random biopsy specimens of quadrants that have no evident abnormalities. However, in the absence of new data, we personally do not recommend random biopsy specimens of normal appearing cervices in a heavily screened population such as that seen in most United States practices.

By subjecting colposcopy to rigorous, formal study in collaboration with many colposcopists, we hope to help make the evaluation more robust, reliable, and sensitive within a few years.

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Condensation: This opinion addresses the limitations of the colposcopically-guided biopsy and suggests possible steps to improve colposcopic accuracy.