Colposcopy for Cervical Squamous Intraepithelial Lesions Found on Papanicolaou Smear

THE ARTICLE ON cost-benefit analysis of colposcopy for cervical squamous intraepithelial lesions found on Papanicolaou smear discusses an important topic in the field of women's health—the cost-benefit of follow-up and treatment of cervical precancerous lesions suggested by an abnormal cytologic smear. This issue has reached worldwide prominence during the past 20 years for several reasons: (1) The identification of squamous intraepithelial lesions on cytologic smears of the cervix and of human papillomavirus (HPV) infection of the cervix has increased dramatically in the past 20 years. (2) There has been a concomitant accumulation of evidence leading to the understanding of the role of this virus in causing cervical cancer. (3) It is now well recognized that only a minority of precancerous cervical lesions progress to high-grade lesions or cancer—even among those associated with high-risk types of HPV, such as type 16. (4) The substantial false-negative rate for cytologic testing of the cervix has been clarified. Together, this wealth of new knowledge puts those of us in the medical profession in the uneasy position of identifying a larger group of women at potential risk for cancer, but knowing little about how to identify those at greatest risk for progression, morbidity, and mortality. Hence, it is unclear whether all women with HPV infection or women with low-grade lesions of the cervix should be examined by colposcopy and biopsy vs repeated cytologic examination, and whether such lesions should be removed, followed up with colposcopy, followed up with more frequent cytologic examinations, tested for HPV, or merely smeared yearly.

The authors in this study present the management and treatment strategy that they use for women referred to them for evaluation after 1 or 2 abnormal cytologic screening tests. They then assess the costs per year of life saved by the treatment of high-grade lesions in their setting and find the costs to be comparable with those quoted elsewhere for other life-extending strategies.

The exact cost per case of cervical cancer prevented or year of life saved depends on a number of variables. The prevalences of precancerous lesions and of risk factors in the population are critical to any benefit analysis. Other variables affecting the cost include the evaluation and treatment protocol adopted, the level of uncertainty accepted, the risk and rate of progression of mild, moderate, and severe dysplastic lesions, the adherence of the patients to the protocol suggested, and the costs incurred in the evaluation or treatment setting. With the use of the protocol described in this article, as the proportion of women referred who have high-grade lesions requiring treatment increases, the cost per year of life saved decreases. Increasing the number of women with low-grade lesions adds only to the costs but not to the benefit of years of life saved. A significant flaw in the analysis is the failure to include the probability of progression of low-grade lesions to cervical cancer. Since this probability is small (compared with that of women with high-grade lesions), some increased cost per case detected would still be expected as the frequency of low-grade lesions identified increases.

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In the protocol described, there are several reasons the cost estimates per year of life saved may be low. The protocol used by the state health department to refer women for colposcopy required 2 consecutive abnormal cytologic smears rather than just 1 before referral for colposcopy. Hence, these women had already demonstrated persistence of lesions as opposed to early regression. This may lead to an elevated prevalence of higher-grade lesions requiring treatment in the management protocol provided. In addition, the women with low-grade lesions or less severe changes documented by cervical biopsy specimens were referred back to their original caregiver and were not followed up further in this study. The costs of follow-up of this large group are therefore not included in the costs per year of life saved. The choice to follow up these women with cytologic examination alone is also a lower-cost (and lower-accuracy) method than if repeat colposcopic evaluation had been recommended for patients with HPV-related lesions (such as mild dysplasia, cervical intraepithelial neoplasia, type 1). Thus, the benefit will not be the same for groups with the use of a different treatment protocol.

In fact, the calculations used by Chesebro and Everett determined only the number of cancers expected to develop in those patients with high-grade squamous intraepithelial lesions (48% by their estimate from the literature) and the number of years of life potentially added by treatment of these lesions before progression. Not included were the cases of cervical cancer that could be predicted among those patients with low-grade lesions (who in this protocol were followed up with cytologic screening). Although the prevalence of progression is lower in this subgroup, the majority of women with an abnormal cytologic smear will subsequently fall into this category, and hence the absolute numbers of missed cancers may approach the number identified among those found to have more advanced disease at the first colposcopic evaluation. However, the costs of colposcopic follow-up for

this large number of women will also be large. Similarly, the number of cases of cervical cancer that may have occurred in those with moderate dysplasia (who were treated with cryotherapy) was not included in the calculations.

The authors indicate that patients with only atypical squamous cells of uncertain significance on cytologic examination were not included in the study, in part because of the high prevalence of this finding (4%-30% of all cervical cytologic smears) and in part because of their experience (and support from the literature) that most (81%) have a low-grade lesion or less on biopsy specimens. However, 19% of their cases referred because of atypical squamous cells of uncertain significance did have a high-grade lesion present; this was similar to the percentage of women referred with a low-grade lesion on cytologic examination who were found to have moderate dysplasia on biopsy specimens. If 4% to 30% of cytologic smears have atypical squamous cells of uncertain significance, this implies that 1% to 8% may have a high-grade lesion and a greater risk of progression to cervical cancer than those with only a low-grade lesion detected. Whether these women should be denied colposcopic diagnosis with this level of risk remains controversial.

The authors indicate that the specific costs of evaluation and therapy that they used in the analysis may not be transferable to other settings, but they suggest that the relative cost comparisons will be transferable. This would be the case only if the relationship between the components of evaluation and treatment are constant. For example, if the costs of the procedures done on most patients, such as the colposcopy with biopsies, increases in price disproportionately to the costs of cryotherapy or large loop excision of the transformation zone, the costs per life saved will increase disproportionately as well. The costs used for the analysis are low compared with estimated national averages—for example, the physician charges per procedure, calculated for a yearly charge if performed 9 half-days per week, for 48 weeks per year, with a 60% collection rate and 30% benefits, results in a salary of $38 800 per year (lower than the national average for family physicians or gynecologists). Similarly, charges for the cryotherapy and large loop excision of the transformation zone are low estimates of routine charges. Deviations from the assumed costs will significantly increase the cost per year of life saved.

This study points out the high inherent costs of screening and subsequent evaluation of large numbers of women to identify the much smaller subset of women who are at substantially increased risk for development of cervical cancer. Cervical cytologic examination is a screening test rather than a diagnostic method. Relying on cytologic examination for follow-up, with the inherent inaccuracies of such a screening test, helps manage costs, but with a substantial risk of missed cases of dysplasia and a smaller risk of missed cases of cervical cancer. Whether women with an abnormal cytologic smear, followed by a biopsy confirming the presence of an HPV-related lesion (such as mild dysplasia), can be followed up with repeated cytologic screening only without incurring unacceptable risk of unrecognized progression of cervical disease is unclear. For example, the authors recommended cytologic testing every 1 to 3 years if the biopsy specimen disclosed only inflammation, atypia, cervicitis, or benign changes. However, these recommendations were not formulated to apply to a population with a recent cytologic smear suggesting low-grade squamous intraepithelial lesions—a population suspected to be at higher risk for cervical changes than the general population. Similarly, those with low-grade changes on biopsy (mild dysplasia, or cervical intraepithelial neoplasia, type 1) were to have repeated cytologic examinations until the result was negative, and presumably then return to the 1- to 3-year frequency of cytologic examination. My own experience with obtaining frequent negative cytologic studies concomitant with abnormal biopsy specimens in women who had had recent cytologic abnormalities is consistent with the literature, which suggests that a single negative cytologic examination is not conclusive evidence of regression. Additional analysis of alternative methods for follow-up of women at identified risk (including those with an abnormal cytologic smear, HPV infection of the cervix, etc) may result in more cost-beneficial strategies. Such methods might include the use of acetic acid and/or Lugol staining at the follow-up visit for cytologic examination, with possible cervical biopsies at that visit if indicated, improved cost accounting for the colposcopy procedure, assessing the accuracy of colposcopies performed by nurses or nurse practitioners with physician backup, and assessing new technologies for cytologic interpretation (such as HPV labeling), which might alter the screening accuracy.

The emotional impact for women of having an abnormal cervical cytologic smear, of becoming aware of having a viral sexually transmitted and transferable infection, of subsequent evaluation, and then of either treatment (in the case of high-grade lesions on biopsy) or reassurance and referral back to cytologic monitoring (in the case of low-grade lesions or less) was not addressed. The impact of this diagnosis and treatment on the women involved and on their sexual relationships may be substantial, may vary with the counseling given and the manner in which it is given, and clearly requires further study.

In light of these limitations, continued research is needed on risk factors associated with progression of low-grade lesions along with outcome studies on various protocols that evaluate in different risk subgroups the adherence to protocol, the psychological and physical effects on the women studied, and the risk of cervical lesion progression. Since the follow-up evaluation costs compose a substantial proportion of the total costs incurred, searching for an inexpensive method for accurately identifying cervical abnormalities in women with abnormal cytologic screens needs to be a high priority.

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