

# Anal Dysplasia: A Growing Problem

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**Women's health clinicians who screen and diagnose cervical dysplasia have the potential to contribute to the prevention of anal cancer.**

**T**he incidence of anal carcinoma and intra-anal neoplasia has been increasing in both women and men. Squamous cell carcinoma of the anus has been growing at a rate of 2.6% per year.<sup>1</sup> Traditionally, women have been more likely to have anal carcinoma, but with the spread of HIV, greater numbers of men have developed this problem. Although anal intercourse is not a requisite for anal disease, men who have sex with men (MSM) are at greater risk for developing the disease than those who do not. HIV infection adds to that risk.<sup>2</sup> The incidence of anal dysplasia and carcinoma also varies among ethnic groups (higher in white and black women than in black men and Hispanics) and within those groups, by gender and age (growing most consistently in young and middle-aged women).<sup>1</sup>

The similarities between cervical dysplasia/carcinoma and its anal counterparts are strong. The association with high-risk human papillomavirus (HPV), the risk factors, and the screening diagnostic tests for each condition are almost identical. High-risk HPV types have been found in 56% of low-grade anal lesions and 88% of high-grade anal lesions.<sup>3</sup> Up to 93% of anal cancers are associated with HPV, most often with HPV 16.<sup>1,3-5</sup> The risk factors for precancerous lesions and carcinoma in 2 areas

overlap considerably, including external genital warts, multiple sexual partners, smoking, and immunosuppression.<sup>3</sup>

HIV-infected individuals have a prevalence of anal intraepithelial neoplasia (AIN) of 36% to 52%.<sup>6</sup> For HIV-infected women, that translates to a 7-fold higher risk for anal cancer than the general population.<sup>7,8</sup> Current use of highly active antiretroviral therapy (HAART) does not decrease the risk of anal cancer but may actually increase its prevalence by prolonging the time HPV infections have to transform infected cells into malignancy.<sup>9</sup> Similarly, organ transplant recipients have a 10-fold increased risk.<sup>10</sup> Women with cervical carcinoma who were followed for 12 years had a 2.2-fold increased risk for rectal cancer.<sup>11</sup> To put this risk into context, women who have had cervical intraepithelial neoplasia (CIN) or cervical carcinoma are more likely to develop anal cancer (HPV-related) than colon cancer (not HPV-related) (odds ratio [OR], 5.2; 95% CI, 3.3-8.3).<sup>3-5,12</sup>

There are considerable similarities between cervical and anal testing protocols. The screening tests (cytology) and the Bethesda criteria for reporting those test results are the same for both cervical and anal disease. Diagnosis is best made by high magnification-directed biopsies. AIN 2 and 3 are precursors to invasive anal cancer, just as CIN 2 and 3 are recognized as precursors to cervical carcinoma.<sup>13</sup> Treatment of each dysplasia involves destruction of the affected cells. Invasive disease requires the expertise of colorectal surgeons and oncology specialists. However, preinvasive lesions, AIN 2 and 3, can often be successfully diagnosed and treated in the outpatient setting.

Women's care clinicians are well trained in all aspects of cervical disease. They are an appropriate group to acquire the skills to help implement the emerging guidelines for

## FOCUSPOINT

**Women who have had CIN or cervical carcinoma are more likely to develop anal cancer (HPV-related) than colon cancer (not HPV-related).**

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early detection and treatment of precursors. Thus, they can help prevent anal carcinoma in women (and perhaps in men). Some clinicians may just collect anal Pap smears in those at risk, while others will extend their colposcopic skills and learn high-resolution anoscopy (HRA). The treatment of anal lesions requires experience with different instruments than those used to treat cervical dysplasia.

Although many similarities exist between anal and cervical dysplasia, there are also important differences. It is recognized that most HPV infections will clear from the cervix over time.<sup>14</sup> Persistence of HPV infection has been found to be the important feature for the development of cervical dysplasia. This observation is the basis for clinical recommendations to avoid cervical cytologic testing in young women, as well as for the suggestion to use dual testing (with both cytology and high-risk HPV screening) for women older than 30.

By contrast, the prevalence of anal HPV infection is not affected by age; in a study of HIV-negative MSM, the prevalence of HPV was high (50%-60%) and was the same among 25-year-olds as among 55-year-olds.<sup>15</sup> Non-16/18 HPV subtypes are more frequently encountered in low-grade lesions of the anus and in high-grade anal lesions in immunosuppressed individuals.<sup>3</sup>

HPV infection is a regional infection, so anal receptive intercourse is not a necessary condition for development of anal disease. Only half of women who have anal and cervical screening are found to have the same type of HPV in each site. In a recent analysis of women, anal receptive intercourse was found to be a risk factor for low-grade AIN but not for high-grade lesions.

**CANDIDATES FOR SCREENING**

Anal carcinoma is increasing in younger women. Thus, recommendations for screening continue to evolve. At present, most experts agree that women and men with HIV infection and all MSM require screening (Table). As noted, HIV status is important. A recent study found that 16% of HIV-infected women had AIN.<sup>6</sup> The incidence of anal cancer is also higher—7 to 28 times higher—among HIV-infected women compared to the general population.<sup>6</sup>

**TABLE. Candidates for Screening for Anal Dysplasia/Carcinoma**

**Currently Recognized Candidates**

- Men and women with HIV infection
- All men who have sex with men

**Other Possible High-Risk Candidates**

- Immunocompromised patients
  - Organ transplant recipient
  - Chronic corticosteroid users
  - Chemotherapy recipients
  - Connective tissue disease
- Women with other lower genital tract disease
  - HPV-related disease, especially high-grade vulvar intraepithelial neoplasia
- Men and women with perianal external genital warts

However, there is more controversy about screening recommendations for the other possible high-risk groups listed in the Table. Perhaps the most controversial are the recommendations to evaluate people with anal condyloma and women who have vulvar dysplasia.<sup>16-18</sup> Some have even suggested that cytologic screening may not be adequate to screen high-risk populations (the sensitivity for high-grade lesions was only 16%) and that other modalities should be added to the initial test.<sup>19</sup>

**SAMPLE COLLECTION**

Most experts recommend using moistened Dacron swabs to collect the specimen.<sup>20</sup> Cytobrushes may create unnecessary discomfort. The patient may be sampled when she is in the traditional dorsal lithotomy position or she may be positioned in a left lateral position with her knees flexed and pulled up to her trunk. Obese women may help expose the sampling area in the lateral position by elevating the superior buttock.

The swab should be introduced through the anal verge (the opening) and gently advanced in a posterior direction until it reaches the rectal vault. Only slight resistance should be felt as the swab passes through the sphincters, and all that resistance is lost as the rectal vault is entered. The distance the swab is introduced is generally less than 5 to 6 cm, but it varies de-

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pending upon the soft tissue dystocia and the relative exposure of the anal opening.

The swab should be rotated to contact the walls circumferentially in a motion that slowly spirals outward toward the opening. Just as with endometrial sampling, the objective is to collect cells from all surface areas—in this case, from the distal rectal vault to the anal verge. The sample should be suspended in a liquid preservative for later cytologic study. Liquid-based cytology has the advantage over traditional slide preparation of filtering out inevitable contaminants and more accurately detecting abnormalities.<sup>21</sup>

The cytology results are reported using the 2006 Bethesda system, which parallels the cervical cytology terminology for atypical squamous cells of undetermined significance (ASC-US), atypical squamous cells high-grade cannot be ruled out (ASC-H), low-grade intraepithelial neoplasia (LSIL), and high-grade intraepithelial neoplasia (HSIL). The adequacy of the specimen is reflected in the presence of cells from the transformation zone (rectal cells, squamous metaplasia, and anucleated cells from the distal anal canal) and by the presence of a total of at least 3,000 nucleated squamous cells.

## DIAGNOSTIC TESTING

If the screening test is negative, the schedule of routine testing depends on the patient's risk factors. If the test detects epithelial abnormalities, follow-up testing is needed. There is some controversy about the appropriateness of viral testing as part of that follow-up evaluation. On the one hand, the prevalence of HPV is relatively high in the anus, so not much benefit can be achieved by testing for its presence. On the other hand, a negative high-risk HPV result may rule out the need for future evaluation of low-grade lesions detected on cytology.<sup>22</sup> The use of adjunctive molecular techniques has been recommended to improve the identification of lesions most likely to progress to carcinoma.<sup>23</sup>

The anal counterpart to cervical colposcopy is HRA. The most comfortable position for women undergoing HRA has been found to be the left lateral position. A digital exam is done first with the tip of the examining finger lubricated with a mixture of a water



**FIGURE 1.** Intra-anal squamocolumnar junction (boundary between the colonic columnar epithelium and the squamous epithelium of the anus). All figures are courtesy of Mary Rubin, PhD, NP.



**FIGURE 2.** Intra-anal squamocolumnar junction (high-powered view).

soluble lubricant and lidocaine ointment (2%-5% concentration). A lubricated anoscope is introduced and opened. A cotton-tipped swab with gauze soaked in 3% to 5% solution of acetic acid wrapped around its tip is introduced through the anoscope and left behind to prepare the tissue as the anoscope is removed for 1 to 2 minutes.

The gauze and swabs are removed, and the anoscope is reintroduced. A “colposcopic” examination of the tissue under high magnification is made as the anoscope is withdrawn. Areas of greatest abnormalities are identified. Skip lesions are not uncommon. Most high-grade AIN can be found within or near the transformation zone. However, identifying the transformation zone is more technically difficult in the anus than on the cervix, which is usually stabilized by the speculum.

Examining this area is similar to examining the vaginal walls during removal of the



**FIGURE 3.** Low-grade intra-anal warty lesions.



**FIGURE 5.** Intra-anal lesions with atypical vessels consistent with early squamous cell cancer.



**FIGURE 4.** High-grade intra-anal lesion with aceto-white epithelium and punctation.

speculum. Special techniques utilized when withdrawing the anoscope can help visualize all of the areas that need to be assessed. The squamocolumnar junction is seen in Figures 1 and 2.

Vascular and epithelial patterns indicating dysplastic changes are similar to those found on the cervix, but subtle differences exist. Figures 3, 4, and 5 demonstrate examples of both low- and high-grade lesions, as well as an early invasion. Biopsies of suspicious areas are done using small (2-3 mm) forceps (eg, Baby Tischler) to avoid blood loss. Monsel's solution (ferric subsulfate) is used to control bleeding.

### TREATMENTS

Treatment and follow-up recommendations are based not only on the pathology found on biopsy but also on the severity of the initial cytology, the results of the digital exam, and the findings of the HRA exam. Straight-forward office-based treatments of anal dysplasia, such as bichloroacetic acid, trichloroacetic acid, infrared coagulation, and laser, can be offered by trained clinicians.

The use of infrared coagulation in the office has dramatically reduced the need for operative procedures. This therapeutic device delivers short pulses of visible and infrared light, which cause thermal coagulation resulting in controlled tissue necrosis. Referral to colorectal surgeons and radiation and medical oncologists is mandatory for a patient diagnosed with anal carcinoma, since radiation and chemotherapy are often the treatments of choice.

### AVAILABLE RESOURCES

Several resources exist to help clinicians master these techniques. Formal training in HRA is frequently offered at colposcopy courses. In particular, courses by the American Society for Colposcopy and Cervical Pathology provide detailed instruction on state-of-the-art techniques for diagnosing and treating anal dysplasia. Excellent descriptions of all aspects of anal disease can be found in modern textbooks.<sup>24</sup>

### CONCLUSION

Anal carcinoma is a growing problem affecting both women and men. Diagnostic testing is needed for individuals with palpable anal lesions. Routine screening should be done for women with HIV and may be appropriate for women who are immunocompromised and those who have high-grade high-risk HPV-related dysplasia elsewhere in the lower genital tract, especially on the vulva. Given that much of the technology and most of the techniques needed to evaluate women (and maybe men?) are extensions of those used in screening and evaluating women for cervical dysplasia/carcinoma, experienced women's health clinicians may well be able

to play a significant role in reducing the incidence of anal carcinoma in the future.

*Dr Nelson has been on the speakers bureau for Merck & Co and an advisory board for Graceway Pharmaceuticals. Dr Rubin is on an advisory board for GlaxoSmithKline and an advisory committee for Graceway.*

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