

Risk Factors for Abnormal Anal Cytology in Young Heterosexual Women¹

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Abstract

Although anal cancers are up to four times more common in women than men, little is known about the natural history of anal human papillomavirus (HPV) infections and HPV-related anal lesions in women. This study reports on the prevalence of and risks for anal cytological abnormalities over a 1-year period in a cohort of young women participating in a study of the natural history of cervical HPV infection. In addition to their regularly scheduled sexual behavior interviews and cervical testing, consenting women received anal HPV DNA and cytological testing. Anal cytology smears were obtained from 410 women whose mean age was 22.5 ± 2.5 years at the onset of the study. Sixteen women (3.9%) were found to have abnormal anal cytology: 4 women had low-grade squamous intraepithelial lesions (SILs) or condyloma; and 12 women had atypical cells of undetermined significance. Factors found to be significantly associated with abnormal anal cytology were a history of anal sex [odds ratio (OR), 6.90; 95% confidence interval (CI), 1.7–47.2], a history of cervical SILs (OR, 4.13; 95% CI, 1.3–14.9), and a current anal HPV infection (OR, 12.28; 95% CI, 3.9–43.5). The strong association between anal intercourse and the development of HPV-induced SILs supports the role of sexual transmission of HPV in anal SILs. Young women who had engaged in anal intercourse or had a history of cervical SILs were found to be at highest risk.

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Introduction

Although HPV³ infections have been associated with anal cancers, little is known about the natural history of anal HPV infections. Because transitional epithelium lining the anus is similar to that found in the cervix, the natural history of anal cancer has often been compared to that of cervical cancer. In addition, precancerous lesions have been found adjacent to invasive cancers in the anus (1–3), a pattern that has also been observed in the cervix. These data suggest that if precancerous SILs of the anus do exist, they may have the same potential to progress to invasive cancer as cervical precancerous lesions.

Although there are no published studies in the general female population, several studies have verified the existence of anal SILs in specific groups, including immunosuppressed females and known i.v. drug users (4, 5). It has also been observed that women with other anogenital cancers such as vulvar or cervical cancer are more likely to have anal SILs and cancer (6, 7). Given that women with other HPV-related cancers are at risk for the development of anal cancer, we examined the prevalence of and risks for anal cytological abnormalities over a 1-year period in a group of young women participating in a longitudinal study of cervical HPV infections.

Materials and Methods

Subject Population. Starting in March 1994, women participating in an ongoing natural history study of HPV were recruited into this study according to the guidelines set forth by the Committee for Research on Human Subjects, University of California, San Francisco. This cohort has been described in detail elsewhere (8). Briefly, women ages 13–20 years who were attending one of two family planning clinics were screened for cervical HPV DNA detection using a commercially available test, HPV Profile (Digene Diagnostics, Silver Spring, MD). Women who tested positive for cervical HPV DNA were asked to participate, and those who consented were seen at a baseline visit and at 4-month intervals. Women found to be negative for cervical HPV DNA were randomly recruited as controls and seen at baseline and at 6-month intervals, unless they became HPV DNA positive during follow-up, at which time they were asked to return every 4 months. At the time the study was initiated, 532 women were actively participating, and their average time in study to date was 29 ± 18.4 months.

Physical Examination. Women who consented to participate had samples obtained for anal HPV DNA at all subsequent routine visits and for anal cytology at each annual visit. A moistened Dacron swab or Cytobrush was inserted into the anal canal up to 2 cm and turned twice in 360-degree rotations. The

³ The abbreviations used are: HPV, human papillomavirus; SIL, squamous intraepithelial lesion; ASCUS, atypical cells of undetermined significance; LSIL, low-grade SIL; HSIL, high-grade SIL; OR, odds ratio; CI, confidence interval; SEER, surveillance, epidemiology and end results.

collected material was then inserted into transport media (Digene Diagnostics). During the first visit and each annual visit, an additional sample was collected, smeared onto a glass slide, and immediately fixed in ethanol for cytological evaluation. At visits in which testing for both HPV DNA and cytological abnormalities was done, the sample for cytology preceded the sample for HPV testing. All visits also included cervical testing for HPV DNA, cervical cytology, and face-to-face interviews to obtain information on sexual behaviors, anal intercourse practices, contraceptive use, and cigarette and substance use. Colposcopic examination of the vulva, vagina, cervix, and perianal areas was performed with the aid of 3% acetic acid at each visit. Cervical testing for *Chlamydia trachomatis* and *Neisseria gonorrhoea* was performed during the baseline and annual examinations and on women who were symptomatic for lower genital tract infections at the interval visits (8).

Definition of Anal Cytological Abnormalities. Anal cytological abnormalities were identified using the Bethesda criteria (9). Women diagnosed with LSILs or HSILs were asked to return for anoscopic examination, during which time areas thought to be HPV related (*i.e.*, leukoplakia, aceto-whitening, vascular punctation, and papillary topography) were biopsied with the aid of a colposcope and 3% acetic acid (10). Women with ASCUS were given an option of following with cytology only or returning for an anoscopic examination with biopsy. Women found to have HSILs on histology were referred for treatment, whereas those with LSILs of the anus were left untreated and are currently being observed.

HPV DNA Testing. Samples for HPV were detected using the PCR technique. Methods of amplification have been described previously (11). The presence of amplified HPV product was sought separately in a dot blot format using an enhanced chemiluminescence method. A generic probe mix that determined the presence of 1 or more of 25 different HPV types nonspecifically was used. Samples were also probed for HPV-6, -11, -16, -18, -31, -33, -35, -42, -43, -45, -51, -52, -56, and -58.

Data Analysis. This study determined prevalence over a 1-year period, which included each subject's first two anal cytology visits or the first visit for subjects tested only once. A positive outcome was determined as a positive cytology result during the first year in the anal study. A negative outcome was defined as a negative cytology result on both of the first two visits or on the first visit when only one had taken place. Covariates included in the analysis corresponded to the second of two negative visits for women with two visits, the first negative visit for women with only one visit, and the visit at which positive cytology was diagnosed.

Preliminary analyses investigated the risk of development of abnormal anal cytology for a range of risk factors using the OR as a measure of association and the associated 95% CIs as a basis for inference. Because anoscopic examination and biopsies were performed at a later date than cytology and some women refused biopsy, we used cytology only rather than biopsy as the outcome measurement, recognizing that this may overestimate disease states (see below). Potential effects of underestimation are discussed later in this section. Logistic regression was used to examine univariate associations for abnormal anal cytology, as well as associations in the presence of additional (and possibly confounding) variables, and investigate possible interactions between variables. Risk factors measured on continuous scales (or ordinal scales with large numbers of levels) were analyzed as continuous variables in regression models.

To investigate possible nonlinearities and examine the

potential undue influence of extreme observations on our conclusions, we fit additional models including quadratic terms using categorized (based on the quartiles of empirical distributions for all nonmissing observations of the variables concerned for the 410 women in the study) and log-transformed versions of the variables. Two-way interactions were investigated for all multivariate models; however, the small sample size precluded an investigation of higher order interactions. To investigate the impact of misclassification of the outcome on estimated regression coefficients, additional models were fit incorporating a range of probabilities of false negative outcomes using methods reported in Magder and Hughes (12).

Although data on follow-up after the first two visits were limited, we conducted additional confirmatory analyses to examine the importance of controlling for length of follow-up on our conclusions about selected risk factors. These were based on a nested case-control approach using the first abnormal cytological result as the outcome. Each case was matched to 10 concurrent negative controls, and the data were analyzed using conditional logistic regression. The results from these analyses were virtually identical to those presented and will not be discussed further.

Finally, Fisher's exact test and Wilcoxon's rank-sum test were used to examine possible differences between women who refused anal cytology and those who participated and between those included in the study and those excluded because of insufficient anal smears.

Results

Of 532 women who were currently actively participating in the larger cohort, 90 refused to participate in the anal study; therefore, no anal smears were available for these women. Of the 442 women enrolled, 32 women had anal smears containing insufficient cellular material and were excluded from the analysis. The resulting study group consisted of 410 women. The racial/ethnic distribution for this group was 51% non-Hispanic white, 8% African-American, 16% Hispanic, 12% Asian, and the remainder of other or mixed origin. The average age of the group on entry into the anal study was 22.5 ± 2.5 years, and 58.3% had mothers with at least some college education. These women had a median of nine sex partners during their lifetime, and a 5.0% rate of chlamydia and gonorrhea; 49.3% reported ever having engaged in anal intercourse. Thirty-one percent of the anal cohort entered the larger cohort study as HPV-negative controls (using HPV Profile as described above).

An analysis was conducted to compare women enrolled in the study with those who refused to participate. Refusers were younger (mean age = 21 ± 2.3 years; $P < 0.0001$), were less likely to have reported engaging in anal intercourse (32%; $P = 0.004$), and were three times more likely to have a history of *C. trachomatis* or *N. gonorrhoea* (16%; $P = 0.001$) than the participating women. They also had fewer lifetime sexual partners (median = 6; $P = 0.001$). No differences were found between the two groups for race/ethnicity or the other characteristics listed in Table 1. Using mother's level of education, the group that refused anal testing was of slightly lower socioeconomic status than the participating group (38% with some college or higher; $P = 0.0008$).

Women excluded from the analysis because of insufficient smears were also compared to those who participated. The only significant difference between these two groups was that the insufficient group was older (23.7 years as compared to 22.5 years for those in the study; $P = 0.02$).

Table 1 Univariate analysis of risk for abnormal anal cytology

Risk factor		n	% Abnormal cytology	OR (95% CI)
Anal sex variables				
Age at entry into anal study (yr)	<22.9	209	3.35	
	≥22.9	201	4.48	1.05 (0.9–1.3) ^a
Having ever engaged in anal intercourse	No	208	1.44	1.0
	Yes	202	6.44	4.70 (1.5–20.7)
Anal HPV infection ^b	No	314	1.59	1.0
	Yes	55	18.18	13.73 (4.7–45.8)
Anal sex reported in last two visits	No	343	4.08	1.0
	Yes	67	2.99	0.72 (0.1–2.7)
History of perianal warts	No	372	3.76	1.0
	Yes	38	5.26	1.42 (0.2–5.4)
Age at first anal sex ^c (yr)	<20	106	5.66	0
	≥20	109	6.42	0.99 (0.8–1.2) ^a
Years of anal sexual activity ^c	<3.8	98	8.16	0
	≥3.8	98	5.10	0.96 (0.75–1.2) ^a
Always used condoms during anal sex ^c	No	167	5.39	1.0
	Yes	35	8.57	1.65 (0.35–5.87)
Other risk variables				
Age at entry (yr) into cohort	<20	204	4.41	
	≥20	206	3.40	1.00 (0.8–1.3) ^a
HPV positive at the cervix at baseline visit ^d	No	128	3.91	1.0
	Yes	282	3.90	0.99 (0.36–3.23)
Ever HPV positive at the cervix	No	49	2.04	1.0
	Yes	360	4.17	2.08 (0.41–38.14)
Age of sexual debut (yr)	<16	207	3.86	
	≥16	202	3.96	1.02 (0.8–1.3) ^a
Years of sexual activity	<6	201	4.98	
	≥6	208	2.88	0.99 (0.8–1.2) ^a
History of vulvar warts	No	279	2.51	1.0
	Yes	131	6.87	2.80 (1.0–8.1)
History of cervical SILs	No	299	2.01	1.0
	Yes	111	9.01	4.90 (1.7–14.9)
History of cervical STD ^e	No	384	3.91	1.0
	Yes	20	5.00	1.29 (0.1–7.0)
No. of different sex partners since last visit	1	276	4.71	
	≥1	101	1.98	0.60 (0.2–1.3) ^a
Monogamy over the last two visits	No	206	3.88	1.0
	Yes	183	4.37	1.13 (0.4–3.1)
Abstinence over the last two visits	No	389	4.11	1.0
	Yes	21	0.00	— ^f
No. of sex partners during lifetime	<9	200	4.00	0
	≥9	209	3.83	1.01 (0.95–1.1) ^a
Months on hormonal contraception	<35.5	178	5.62	0
	≥35.5	182	2.75	0.99 (0.98–1.01) ^a
Always used condoms during vaginal sex	No	391	4.09	1.0
	Yes	10	0.00	— ^g
Smoking (pack-years) ^h	<0.0876	120	4.17	0
	≥0.0876	121	6.61	1.21 (0.9–1.6) ^a

^a OR was obtained by modeling as a continuous or discrete variable in logistic regression.

^b Positive HPV test during the 1-year observation period.

^c Women reporting no anal sex are excluded from analysis.

^d Baseline visit for cohort, not anal study.

^e Laboratory-confirmed chlamydia or gonorrhea. STD, sexually transmitted disease.

^f No recently abstinent women developed abnormal cytology.

^g No women who reported always using condoms developed abnormal cytology.

^h Nonsmokers were excluded from analysis.

Abnormal Cytology. Sixteen women (3.9% prevalence) were found to have abnormal smears; of these, four were diagnosed with LSILs, and 12 were diagnosed with ASCUS. Of the four women with LSILs, one had LSILs on biopsy, two had chronic inflammation, and one refused examination. Of the 12 women with ASCUS, 2 had HSILs on biopsy, 2 had LSILs, 1 had chronic inflammation, 1 was benign, and 6 deferred anoscopy and/or biopsy.

Anal HPV Testing. A total of 369 samples had adequate β -globin for analysis of HPV DNA status. Of those women

with abnormal anal cytology, 66.67% were positive for HPV within a year prior to the visit at which they were diagnosed. Of these, 20% were positive for both HPV-16 or HPV-18 and HPV-6/11, 30% were positive for the HPV-6/11/42/44 mix only, 10% were positive for the HPV-39/51/52 mix, and 40% were not typeable.

Risk for Abnormal Anal Cytology. Several covariates were found to be significant risk factors for abnormal anal cytology in univariate analysis: (a) a positive anal HPV test at or prior to the time of cytology; (b) a history of anal intercourse; (c) a

Table 2 Multivariate analysis of risks for abnormal anal cytology

Risk factor	Adjusted OR (95% CI)	P
Anal HPV infection	12.28 (3.91–43.53)	<0.001
History of vulvar warts	2.41 (0.75–8.23)	0.14
History of cervical SILs	4.13 (1.29–4.85)	0.02
Having ever engaged in anal intercourse	6.90 (1.71–47.15)	0.02

history of cervical SILs; and (d) a history of vulvar warts. Table 1 summarizes the univariate analyses examining risks for abnormal anal cytology. To illustrate their distribution, in this table, continuous variables were divided at the median to yield the percentage of outcome in each group; however, these variables were entered into the analysis as continuous variables. Univariate models in which continuous variables were entered as categorized variables based on the quartiles of these variables for the 410 women in the study were also analyzed and yielded similar results. The inclusion of log-transformed versions of continuous variables, such as lifetime sex partners, provided no evidence of a need to control for outlying values in these variables.

Table 2 presents adjusted ORs for a multivariate model including the variables that tested significant in univariate analysis. In multivariate analysis, anal HPV status remained highly significant. A history of anal intercourse was also significant, as was a history of cervical SILs. A history of vulvar warts lost significance in the model containing four variables; however, a goodness-of-fit test (13) applied to this model was not significant, indicating that the model including four covariates was adequate ($P = 0.1015$). A model excluding history of vulvar warts did not yield an acceptable fit ($P = 0.0472$). Although history of vulvar warts did not have a confounding effect on the other variables in the model, its presence in the analysis significantly improved the fit of the model; therefore, the final model retained all four variables. Additional models including quadratic terms did not detect any nonlinearity in the model, and results from these models are not presented.

To test for possible interactions, two-way interaction terms were included in the model (higher order interactions were difficult to assess due to the small sample size). None of the two-way interactions between pairs of the four variables in the analysis were significant. There was evidence of a weak interaction between cervical SILs and anal HPV ($P = 0.2$); however, due to the limited sample size, there was not sufficient power to investigate this relationship further.

An analysis was conducted to test the effects of potential cytological misclassification of the outcome on the estimates of effect. Additional regression models for selected covariates were fit incorporating different levels of sensitivity (90, 85, and 80%) of the anal cytology outcomes based on estimates from another published study (14). Because statistical significance of key results was unchanged, the results are not given. The small proportion of cases in our study precluded use of the techniques reported by Magder and Hughes (12) to examine the effects of varying levels of specificity on the analysis.

Discussion

Anal cytological abnormalities were found in approximately 4% of the young women in our cohort study, and strong risks for these abnormalities included anal HPV infection and anal intercourse. In comparison to rates of cervical SILs found in the general population of young women (0.12–7%), 4% would be considered relatively common (15–17). Unfortunately, no gen-

eral population studies of the anus are available for comparison. Few isolated studies have examined the rate of anal disease in selected nonimmunosuppressed populations. In a case-control study of immunosuppressed renal transplant patients, Ogunbiyi *et al.* (18) found that less than 1% of their nonimmunosuppressed control group showed evidence of anal disease by cytology. Reporting results more similar to our group, Williams *et al.* (4) found that approximately 7% of their HIV-negative group, who were at high risk for HIV (i.v. substance users or sex workers), had abnormal anal cytology. Although our population was representative of a general family planning population, most (70%) of the women participating in the cohort were selected because of their initial HPV DNA test from the cervix. This selection criterion most likely increased the risk of abnormal anal cytology in our cohort as compared to the Ogunbiyi group. It may have also been related to the level and type of sexual activity in our cohort as compared to the Ogunbiyi *et al.* cohort; however, sexual practices were not described in the latter.

In contrast to the low rates of abnormal cytology reported in nonimmunosuppressed groups, several studies have now shown a high rate of abnormal anal cytology among immunosuppressed individuals, whether male or female (5, 19–22). Rates as high as 60 and 12% have been reported in HIV-positive men and women, respectively (5, 19). We are currently testing all women in our study for HIV, and none have been found to be seropositive. In addition, women with abnormal anal cytology were advised to undergo HIV screening, and no case has been reported to date. Anonymous HIV screening at the clinic recruitment sites has revealed extremely low rates (less than 1%) for HIV infection (data not shown).

The risk associated with HPV DNA detection was not unexpected because several studies have linked HPV with anal SILs as well as invasive cancers (1, 3–5, 20–22). Somewhat alarmingly, two recent studies have shown that HPV-related anal cancers are associated with a younger age than non-HPV-related anal cancers (18, 23). This suggests that the natural history of HPV-associated anal cancers differs from that of anal cancers that are not associated with HPV.

Because of the multicentric nature of HPV-induced disease (24), the associations found with cervical SILs and vulvar warts merit discussion. Most of the multicentric disease reported has been in the cervix, vagina, and vulvar and perianal areas. A recent study has shown a similar association between cervical and anal SILs. Scholefield *et al.* (25) found that 19% of women with cervical HSILs had evidence of anal SILs, of which two women had invasive anal squamous cell carcinomas. Our data, as well as the data of Scholefield *et al.*, suggest that cervical SILs are an important risk for anal SILs.

Scholefield *et al.* (25) also reported that the risk for anal disease was strongest for women in the study who were found to have multifocal disease. Seven percent of the women with HSILs of the cervix alone had anal SILs compared to 57% of the women who had more than one focus of SILs. The loss of significance for vulvar warts in the multivariate analysis as well as the lack of association of abnormal cytology with multisite disease (i.e., cervix and vulva) using the two-way interaction models may have been due to the benign nature of vulvar disease (i.e., condyloma) found in our cohort compared to the more advanced disease (i.e., vulvar SILs) found in the study of Scholefield *et al.* On the other hand, the small number of women with abnormal cytology in our study may have contributed to these findings, because including vulvar warts in the model appeared to be important.

The risk associated with anal intercourse in our study was

specifically interesting to us because several studies in the United States have reported that neither anal cancer nor SIL is associated with anal sexual behavior (1, 4). The association with "any" history of anal intercourse and the lack of association with recent anal intercourse suggest that distant anal exposure may be a more significant risk factor than recent exposure and that latent HPV infections are common in the anus. The lack of association in other studies may be due to the sensitivity of the question and the difficulty of obtaining accurate information, as well as the fact that many studies inquire about recent intercourse only. Although studies have shown that anal intercourse is a common sexual experience among heterosexual women (26, 27), the willingness to report such behaviors may be hindered by social acceptability. A recent study in Denmark and Sweden found that anal intercourse, particularly at a young age, was a significant risk for anal cancer (28). Women who had anal intercourse before the age of 30 were at a 4-fold risk of anal cancer (OR, 4.4), a risk almost identical to our risk reported for abnormal anal cytology for those with a history of anal intercourse.

Because our conclusions are based on a very small number of cases, we have been particularly conscientious in addressing potential limitations and biases in our analyses and exploring alternative explanations for our findings. Therefore, we feel our significant findings are more likely to represent a real association rather than to result from chance or bias. The imprecision of our estimates, nonetheless, reflects our lack of knowledge about the actual magnitude of association.

Another limitation of our study was the inability to verify all of the abnormal cytology by histology. As described for the cervix, it is expected that only 40–50% of the women with cytology interpreted as ASCUS had HPV-associated SILs. The strong association between abnormal cytology and HPV in our study suggests that many of the women with ASCUS did have SILs. In addition, four of the six women with ASCUS who agreed to anoscopy had SILs verified by biopsy. It is also expected that a certain number of benign cytology smears were, in fact, falsely negative. However, when we investigated the impact of possible misclassification for anal cytology, the statistical significance of key results was unchanged. Because a common effect of nondifferential misclassification is to attenuate measured associations, the actual degree of association based on correctly classified anal SIL outcomes could be stronger than that reported here.

Although we have likened the natural history of anal SILs to that of cervical SILs, the significance of these anal SILs is unknown, primarily because no longitudinal studies have been performed. Circumstantial evidence suggests that anal SILs should be equated with cervical SILs because of their etiological and histological similarities (1, 5). The examination of recent data among immunocompromised individuals suggests that individuals with anal SILs may be at high risk for the development of anal cancer (29, 30). On the other hand, current estimates for the incidence of anal and cervical cancers using the SEER database show that anal cancer in women peaks several decades later than cervical cancer and occurs less frequently.⁴ As noted earlier, HPV-associated anal cancers seem

to be associated with younger age. If national data were corrected for this assumption, the age at which anal cancers peak may occur much closer to that of cervical cancer. For comparison, the rate of abnormal cervical SILs was approximately 10% or 2.5 times the rate of abnormal anal cytology during the same period we performed the anal testing (data not shown). In contrast, the rates of cervical cancer are approximately 8-fold higher than those of anal cancer in women in the United States.⁵

If the natural history of anal HPV infections were similar to those in the cervix, then it would seem apparent that screening practices for anal cancers and precancers should be based on models similar to those practiced for cervical screening (*i.e.*, cytology screening for precancerous lesions). From 1973 to 1989, the incidence of anal cancer in the United States increased over 35% in women and is currently rising at a rate of nearly 2% per year (31), supporting a need for some type of surveillance practice.

We conclude that HPV-induced SILs of the anus do occur in young women. One of the greatest risks for these lesions was a history of anal intercourse, which supports the role of sexual transmission of HPV in anal SILs. In addition, the association with cervical disease lends support to the notion that HPV frequently causes multisite infections and that women with a history of anal intercourse and cervical disease may be reasonable populations to target for screening. Future studies are needed to elucidate these findings and determine appropriate screening practices because the natural history of these lesions has yet to be determined. However, the occurrence of HPV-related anal cancers in young women and the greater risk of anal cancers among women with cervical and vulvar HPV disease suggest that these cytological abnormalities may indeed be precancerous lesions. Finally, our study suggests that referral to anal colposcopy for women diagnosed with ASCUS is critical in future studies because the sensitivity of the smear to detect HSILs was relatively low.

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