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Cervical Ectopy and the Acquisition of Human Papillomavirus in Adolescents and Young Women

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Abstract

Objective—Higher rates of human papillomavirus (HPV) in adolescents and younger women have been attributed to their greater extent of “cervical ectopy,” defined as columnar and metaplastic epithelia on the ectocervix. Our objective was to estimate associations between ectopy and incident HPV in healthy adolescents and young women.

Methods—Enrolled between October 2000 and October 2002, this prospective cohort included women aged 13–21 years old; sexually active; without prior cervical intraepithelial neoplasia, cervical procedures, or immunosuppression; with menarche within 6 years before enrollment; and HPV DNA negative at baseline. Every 4 months, extent of ectopy was quantitatively measured using colposcopy and computerized planimetry. Cox proportional hazards models examined associations between ectopy and incident HPV, defined as the first positive HPV result during follow-up.

Results—The 138 women attended 509 total visits. At baseline, mean age was 16.7 years and mean extent of ectopy was 25% of the total cervical face. Incident HPV of any type was detected in 42 (30%) women and was not significantly associated with baseline ectopy (hazard ratio=1.09, 95% CI=0.96–1.25, $p=0.20$, ectopy in units of 10%), or with ectopy measured 4 months before HPV detection (HR=1.09, CI=0.94–1.26, $p=0.25$). Our sample size had 80% power to detect a hazard ratio of 1.9, with two-tailed $\alpha=0.05$. Results were similarly insignificant for HPV subgroupings of incident high-risk, low-risk, $\alpha 9$, and $\alpha 3/\alpha 15$ types, and when adjusted for new sexual partners.

Conclusions—Extent of cervical ectopy was not associated with HPV acquisition in healthy adolescents and young women. Biological vulnerabilities may lie in immune function or other characteristics of the cervical epithelium.

Introduction

Human papillomavirus (HPV) is the known cause of cervical cancer and the most common sexually transmitted infection. (1, 2) The highest prevalence and incidence rates of HPV infection are found in adolescents and young women. HPV genotypes that infect the genital

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mucosa are classified as high-risk or low-risk, based on their oncogenic potential in cervical cancer. (3) Most cervical cancers arise in the transformation zone, which is the juncture between the proximal single-layered columnar epithelium and the distal stratified squamous epithelium. Embryologically, this juncture is derived from the single layer of Mullerian columnar cells that are partially replaced by urogenital stratified squamous epithelium, creating a squamo-columnar junction that is relatively stable through childhood. (4) During puberty, the physiologic process termed squamous metaplasia gradually transforms columnar cells into squamous cells. (5) Cells representative of this transformation are referred to as metaplastic cells. The clinical term “ectopy” refers to the presence of columnar and metaplastic epithelia visible on the ectocervix. Over time, squamous metaplasia leads to the relocation of the squamo-columnar junction to a more proximal position. Thus, adolescents and younger women are unique in having a larger area of ectopy compared to older adults. However, the timeline of this relocation in position varies by individual such that at any given age, the distribution of epithelial cell types on the ectocervix is highly variable among adolescents and young women. (6)

The presence of ectopy has long been assumed to constitute a biological vulnerability to HPV infection, since HPV infection requires access to basal epithelial cells, and columnar and metaplastic epithelia are thin and fragile compared to the thicker stratified squamous epithelium. Furthermore, the epidemiologic evidence of higher HPV incidence in younger women (7) coincides with the age range for greater areas of ectopy. However, scientific evidence of any associations between ectopy and HPV infection is lacking. A prior cross-sectional study was limited to observations of prevalent infection in an older population. (8) Our study aim was to estimate the extent of ectopy as a risk factor for HPV acquisition in a prospective cohort of healthy adolescents and young women. We hypothesized that a larger extent of ectopy is associated with increased risk for incident HPV infection.

Materials and Methods

Participants and setting

This prospective study enrolled healthy adolescents and young women from an ongoing cohort participating in a study of the natural history of HPV infection that has been described elsewhere.(9) The original cohort was enrolled from two sites, a family planning clinic and a university student health center. Eligible women were those 13-21 years of age, sexually active for a maximum of 5 years, not pregnant, and without history of immunosuppression, cervical intraepithelial neoplasia (CIN-2 or CIN-3), or surgical treatment of the cervix. The Committees on Human Subject Research at the University of California, San Francisco, and at San Francisco State University approved the study. Voluntary informed consent was obtained from each participant.

Study design

Women were seen for a baseline visit and follow-up visits at 4-month intervals. At every visit, an individual interview was conducted by a research assistant to evaluate sociodemographic characteristics, sexual behaviors, and medical history; cervical and vaginal samples were collected to test for infection, pregnancy, and cervical cytology; and colposcopy was conducted to document the cervical epithelium. Each visit included testing for bacterial vaginosis, *Trichomonas vaginalis*, and yeast vaginitis by routine wet prep and KOH microscopy.(10) At annual visits and when symptomatic, *Chlamydia trachomatis* and *Neisseria gonorrhoeae* were tested by commercial assays. Genital infections were treated according to current clinical guidelines from the Centers for Disease Control and Prevention.

The current analyses examined a consecutive convenience sample of women who enrolled between October 2000–October 2002 and reported menarche having occurred within 6 years prior to study enrollment. The intent of the menarche criterion was to identify a sample of women who would have a relatively wide distribution of the extent of ectopy. Women were excluded who had any positive HPV result or pregnancy at baseline, did not attend any follow-up visits, or did not have adequate colposcopic photographs available for measurement. All data were collected before HPV vaccines were available to this population.

Quantitative measurement of colposcopic photographs

Colposcopy was performed as previously described.⁽¹¹⁾ In brief, 3% acetic acid was applied to the cervix, and color slides and photographs (35mm film) were taken at 10× and 16× colposcopic magnifications. The images were digitized at a minimum resolution of 1024 × 1536 pixels and viewed in Adobe Photoshop®. Cervical ectopy was defined as the area(s) of columnar epithelium and early- to mid-squamous metaplasia according to colposcopic tissue characteristics.⁽¹²⁾ The total cervical face was defined as the visible cervical portio. These areas were manually marked using a pencil-mouse and quantitatively measured as pixel counts. Ectopy was summed and expressed as a percentage of the total cervical face. All colposcopic photographs were measured in random order by one investigator (J.L.) who was blinded to all patient characteristics. The first 10% of random-order colposcopic photographs were also measured by a second investigator blinded to patient characteristics (A-B.M.). Any discordant measurements were re-evaluated and consensus was reached.

Detection of human papillomavirus infection

At each visit, HPV infection by 37 types was diagnosed by Roche Reverse Line Blot assay (Roche Molecular Diagnostics, Pleasanton, CA)⁽¹³⁾ applied to samples obtained by directed cervical lavage. The lavage was performed by using a plastic pipette to wash 10ml of sterile normal saline over the ectocervix, recollect the saline and repeat for a total of 3 lavages over the ectocervix before final collection.

Data analyses

The main independent variable was the extent of cervical ectopy. The primary dependent variables were the following: HPV incidence, defined as the first detection of a positive HPV DNA result during follow-up for any of the 37 detectable HPV types; the incidence of high-risk HPV, defined as the first positive detection for HPV types 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, or 82; and the incidence of low-risk HPV, defined as the first positive detection for HPV types 2, 6, 11, 40, 42, 54, 55, 57, 61, 62, 64, 67, 69, 70, 71, 72, 81, 83, 84, or 89. For the purpose of comparison to another study of ectopy and prevalent HPV infection,⁽⁸⁾ additional secondary outcomes were the incidence of α 9-HPV types (which are high-risk), defined as HPV types 16, 31, 33, 35, 52, 58, or 67; and the incidence of α 3/ α 15-HPV types (which are low-risk), defined as HPV types 61, 71, 72, 81, 83, 84, or 89.

Analytical statistics were conducted using t-tests, Chi-square tests, and Fisher's exact test as appropriate. Cox proportional hazards models were constructed, with each model including one HPV variable and one ectopy variable. Visits after an incident HPV infection were censored. Visits were also excluded at which the participant was pregnant because of the possibility of biased or imprecise measurement of cervical ectopy since increased stromal volume during pregnancy may cause cervical eversion and the appearance of ectopy on examination.⁽¹⁴⁾ We examined ectopy measured at the baseline visit, as well as ectopy measured at the nearest visit prior (typically 4 months prior) to HPV detection. Each ectopy variable was analyzed as a continuous variable or categorized into quartiles. Ectopy as a

continuous variable was expressed with a unit of measurement of 10% of the total cervical face, since our previous work indicated an error rate of 5-10% upon repeat measurement of a single photo due to the practical limitations of freehand outlining. (11, 15) According to our power calculations, our sample size of 138 women would be able to detect an effect size approximately equivalent to a hazard ratio of 1.9, with $\beta=0.80$ and $\alpha=0.05$ (two-tailed). Additional adjusted models included the number of new sexual partners during the 8 months prior to HPV detection, based on prior evidence that new partners during this time interval contributed significantly to the risk for incident HPV, (16) and study site, given possible differences between clinical sites. The time since menarche, oral contraceptive use, and progestin-only contraceptive use were also examined as covariates. Abnormal cytology and CIN-1 were rare in this sample of adolescents and young women (4 cases of LSIL, no known cases of CIN-1), were not the focus of the study, and thus were not analyzed.

For all statistical analyses, α was set at 0.05 (two-tailed), and we used SAS® version 9.2. (SAS Inc., Cary, NC). Missing data was addressed by excluding the datapoint; imputation was not performed.

Results

Enrollment to the original cohort during our study dates included 261 women from the family planning clinic site and 249 women from the university health center site. However, for the current analyses, many women were not eligible due to the requirement for menarche within 6 years before enrollment, especially at the university site. After applying the additional exclusion criteria as stated above, we reached a final dataset of 138 women who attended a total of 509 visits.

The 138 women were seen for a median of 4 (interquartile range=3-4, range=2-8) visits and followed for 12 (IQR=9-17; range=3-31) months. Women entered the study at a mean age of 16.7 (standard deviation, 1.5; range=13-21) years; and reported age of menarche of 12.8 (SD, 1.4; range=9.3-16.5) years; age at first sexual intercourse of 15.4 (SD, 1.6; range=11-18.8) years; and number of lifetime partners of 4 (SD, 4; range=1-30). Race/ethnicity was reported by 48 (36%) women as Latina/Hispanic, 40 (30%) Caucasian, 30 (22%) Asian-American, 14 (10%) African-American, and 3 (2%) Mixed/Other. Additional characteristics and behaviors are shown in Table 1.

Incident HPV of any type was detected in 42 (30%; confidence interval=23-39%) women; incident high-risk HPV in 35 (26%; CI=19-34%); incident low-risk HPV in 18 (13%; CI=8-20%); incident $\alpha 9$ -HPV type in 12 (9%; CI=5-15%); and incident $\alpha 3/\alpha 15$ -HPV type in 13 (9%; CI=6-15%). For the overall sample, the mean extent of ectopy at baseline was 25% of the total cervical face (SD, 23%; CI=22-29%), and ectopy at the end of the study was 20% (SD, 19%; CI=17-24%). Women who acquired HPV during follow-up had a mean baseline ectopy of 27% (SD, 23%; CI=20-34%) and study-end ectopy of 22% (SD, 22%; CI=15-29%). Women who remained HPV negative throughout follow-up had a mean baseline ectopy of 25% (SD, 23%; CI=20-29%), and study-end ectopy of 20% (SD, 18%; CI=16-23%). Figure 1 shows an example of a colposcopic photograph with the area of ectopy outlined manually.

Incident HPV of any type was not significantly associated with the extent of baseline ectopy, whether ectopy was measured as a continuous variable (hazard ratio (HR)=1.09, 95% CI=0.96-1.25, $p=0.20$), or categorized into quartiles (HR=1.23, CI=0.94-1.62, $p=0.14$). Similarly, incident HPV of any type was not significantly associated with the extent of ectopy measured 4 months prior to HPV detection (continuous variable, HR=1.09, CI=0.94-1.26, $p=0.25$; quartile variable, HR=1.17, CI=0.86-1.59, $p=0.33$). As shown in

Table 2, none of the ectopy variables were significantly associated with incident high-risk HPV or incident low-risk HPV. Results were unchanged when adjusted for the number of new sexual partners in the prior 8 months, which itself was significantly associated with incident HPV of any type, high-risk type, and low-risk type (HR, CI, and p for new partners ranging from 1.54-2.18, 1.06-3.65, and <0.01-0.02 respectively); and study site, which was not independently associated with the incident HPV outcomes. Results were also unchanged when adjusted for time since menarche, oral contraceptive use, and progestin-only contraceptive use (data not shown). Additional analyses similarly indicated no significant association between incident α 9-HPV and baseline ectopy (continuous variable, HR=0.90, CI=0.67-1.21, p=0.49) or ectopy at prior visit (continuous variable HR=0.92, CI=0.68-1.26, p=0.61); and no association between incident α 3/ α 15-HPV and baseline ectopy (continuous variable HR=1.17, CI=0.93-1.48, p=0.17) or ectopy at prior visit (continuous variable HR=1.20, CI=0.93-1.53, p=0.16).

Discussion

In this prospective study of the extent of cervical ectopy as a risk factor for HPV acquisition among young sexually active women, no significant associations were found, whether ectopy was measured at study baseline or closer in time to the HPV detection (4 months beforehand), whether ectopy was treated as a continuous or ordinal variable using broad categories of quartiles, or whether incident HPV was grouped as any of 37 detectable types, or as high-risk, low-risk, α 9, or α 3/ α 15 types. Further adjustment for the number of new sexual partners and study site did not alter results.

The main strengths of the study were the prospective study design, the multiple approaches in assessing the ectopy and HPV variables, and the quantitative measurement of cervical ectopy. The prospective design allowed for frequent HPV testing at 4-month intervals, focusing on the initial acquisition rather than prevalence of infection. Our assessment of ectopy at different time points preceding the HPV detection was a more comprehensive attempt to capture the potential effect of ectopy, since the incubation period for HPV may be several months before the infection is detectable by clinical assays. (17) Additionally, another prospective study of 600 young women identified new partners to be most strongly associated with incident HPV detection when the new partnership was reported at 5-8 months prior to HPV detection. (16) We also evaluated multiple subgroups of HPV (any type, high-risk, low-risk, α 9, α 3/ α 15) because it cannot be assumed that all genotypes of HPV demonstrate similar pathophysiology in the biological establishment of infection. The quantitative ectopy measurement by computerized planimetry was more precise than a simple qualitative assessment of presence or absence of ectopy by visual inspection without magnification. Although colpophotography is inherently limited by clinical variations in the photographic conditions at each visit, we applied a proportional measure of ectopy (percentage of the total cervical face) to mitigate these photographic issues.

Interestingly, the study findings were in contrast to our initial hypothesis that larger areas of ectopy would be associated with higher risk for HPV acquisition. Castle et. al. had conducted a large cross-sectional study of 945 women in Costa Rica who were found to have an α 9 and/or α 3/ α 15 HPV infection by HPV DNA testing of cervical swabs. Among these infected women, there were trends for increasing α 9 positivity with larger areas of ectopy, and increasing α 3/ α 15 positivity with smaller areas of ectopy. The authors suggested that these findings may be due to differences in tissue tropism (columnar and metaplastic versus squamous epithelia) between HPV genotype groups. Our findings are in contrast, likely because of differences in study design, study population, and sample size. As stated, our prospective design focuses on new acquisition of HPV infection, whereas a cross-sectional design would detect prevalent infections including those that were relatively

recently established and those that have been chronically persistent. Since Castle's study population was largely older adult age, these prevalent infections were more likely to be dominated by persistent rather than new infections, and the role of ectopy may differ in the settings of persistence versus acquisition. Furthermore, although Castle's study included an age-stratified analysis, the youngest age stratum was <35 years, which is a rather broad age range given that the widest distribution of ectopy is typically seen in adolescents and young adults in their earlier 20's. As far as our discordant findings specifically regarding the $\alpha 9$ and $\alpha 3/\alpha 15$ types, our small sample size for these subanalyses is an important and prominent limitation. In our study, only 9% of women acquired each of these HPV groups, which makes our findings difficult to interpret for these HPV subgroups.

Nevertheless, we were surprised by our non-significant findings, and we propose alternative explanations for the biological vulnerability of younger women to HPV acquisition. First and foremost, differences in immune protection may be a major factor. Younger women would be expected to be immunologically naïve in their genital exposure to HPV, whereas older women would be more likely to have experienced prior exposures, cleared infections in the past, and developed immune memory that would decrease their risk for new infection. The development of immune memory with age is suggested by international population-based studies in which HPV seroprevalence is typically low to negligible before middle adolescence; rises around the adolescent age of sexual debut; continues to rise during young-to-middle adulthood; and then commonly declines after 30 years of age. (18-20) In contrast, among women who are seropositive, quantitative antibody titers do not vary by age group. (18) Furthermore, mathematical modeling suggested that the seroprevalence decline at older ages is likely attributable to differences in risk status between birth cohorts rather than waning antibody titers, lending support for immunity that persists. Immune susceptibility at younger ages may be a more influential factor than cervical ectopy. Another possibility is that the extent of squamous metaplastic activity at the transformation zone contributes to risk rather than the extent of ectopy. In a previous study, baseline ectopy was not associated with incident low-grade squamous intraepithelial lesions (LSIL). (11) However, changes in the extent of ectopy over time, which may represent metaplastic activity, was associated with LSIL. The HPV viral life cycle is understood to require host cell replication and differentiation, (21) which is accelerated during squamous metaplasia.

The main limitations of our study were the small sample size, the inherently imprecise nature of colposcopy and computerized planimetry, and the inability to determine true incident new infection rather than reactivation of latent viral infection. The sample size was such that we could detect an effect size of a hazard ratio of 1.9 or more for the association between ectopy and HPV acquisition. Certainly we note that the hazard ratio estimates in our study were typically in the direction of risk for acquisition but not statistically significant. To address the clinical limitations of colposcopy in capturing a consistent view of the cervix among different women, we calculated a proportional measure of ectopy, but it is possible that the absolute size of the ectopy area could be more salient than the proportional ectopy. However, we felt that the advantages of a proportional measure were a priority in order to obtain a more precise measurement of ectopy. Lastly, it was impossible to distinguish true incident new infections from viral reactivation, as this would require study participation from the time of first sexual contact. However, a recent study of another prospective cohort of 2400 women in Brazil found that repeat detection of incident HPV, defined as having a repeat positive result following 3 consecutive negative results over a minimum of 1.5 years, was associated with new sexual partners and likely represents new infections and not reactivation of latent infections. (22) In addition, our participants were enrolled relatively soon after experience of first sexual intercourse, and the mean number of lifetime sexual partners reported at study entry was 4, which is relatively limiting for previous exposure.

In summary, cervical ectopy does not appear to increase risk for HPV acquisition among healthy sexually active adolescent females. Alternatively, the higher incidence and prevalence of HPV among younger women may be more attributable to immunological vulnerabilities or other characteristics of the cervical epithelium. Next steps could include larger prospective cohort studies that measure the influence of dynamic metaplastic activity and the immune function of ectopy tissues, to identify the biological vulnerabilities of younger women.

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Figure 1. Example of a colpophotograph. Area of cervical ectopy is outlined manually by a solid black line.

Table 1

Sociodemographic, Behavioral, and Biological Characteristics* for 138 Study Participants in 509 Visits

Characteristic or Behavior	Acquired HPV of Any Type During Follow-Up (n=42 Women, 181 Visits)	Remained HPV-Negative During Follow-Up (n=96 Women, 328 Visits)	P
Age at baseline (y)	16.7±1.2 (13–19)	16.8±1.6 (12–21)	.75 [†]
Age at menarche (y)	12.9±1.1 (10.1–15.7)	12.8±1.5 (9.3–16.5)	.56 [†]
Age at first sexual intercourse (y)	15.4±1.6 (12.9–18.5)	15.4±1.7 (11–18.8)	.92 [†]
No. of lifetime partners, reported at baseline	3.9±3.9 (1–17)	3.5±3.8 (1–30)	.63 [†]
No. of new partners in previous 8 mo, reported at follow-up visits	1.1±1.0 (0–4)	0.6±0.9 (0–5)	<.01 [†]
Ectopy (% of total cervical face) at baseline	27±23 (1–78)	25±23 (1–90)	.57 [†]
Ectopy (% of total cervical face) at last follow-up visit	22±22 (1–82)	20±18 (1–90)	.57 [†]
Ethnicity or race			
Latina	16 (38)	32 (34)	.91 [‡]
White	10 (24)	30 (32)	
Asian or Pacific Islander	10 (24)	20 (22)	
African American	5 (12)	9 (10)	
Mixed or other	1 (2)	2 (2)	
History of previous <i>Chlamydia trachomatis</i> infection, reported at baseline	3 (7)	5 (5)	.70 [‡]
History of previous <i>Neisseria gonorrhoeae</i> infection, reported at baseline	1 (2)	1 (1)	.52 [‡]
History of previous pregnancy, reported at baseline	21 (9)	13 (14)	.24 [‡]
Current oral contraceptive use	40 (22)	103 (31)	.03 [‡]
Progestin-only contraceptive use	24 (13)	19 (6)	<.01 [‡]
Always used condoms since last visit	56 (41)	120 (47)	.24 [‡]
Current smoking	75 (41)	120 (37)	.28 [‡]
<i>Chlamydia trachomatis</i> infection	15 (8)	2 (0.6)	<.01 [‡]
<i>Neisseria gonorrhoeae</i> infection	1 (0.5)	3 (0.9)	1.0 [‡]

HPV, human papillomavirus.

Data are mean±standard deviation (range) or n (%) unless otherwise specified.

* Denominators vary because of instances of missing data.

[†] Differences between groups examined by *t* test.[‡] Differences between groups examined by χ^2 or Fisher exact test, as appropriate.

Table 2
Associations Between Extent of Ectopy and Incident Human Papillomavirus Infection

	HPV Any Type			HPV High-Risk Type			HPV Low-Risk Type		
	Unadjusted		Adjusted*	Unadjusted		Adjusted*	Unadjusted		Adjusted*
	HR (95% CI)	P	HR (95% CI)	HR (95% CI)	P	HR (95% CI)	HR (95% CI)	P	HR (95% CI)
Ectopy at baseline									
Continuous	1.09 (0.96–1.25)	.20	1.07 (0.93–1.22)	.34	1.06 (0.91–1.22)	.46	1.04 (0.89–1.20)	.65	1.12 (0.92–1.37)
Quartiles	1.23 (0.94–1.62)	.14	1.19 (0.90–1.58)	.22	1.26 (0.93–1.70)	.15	1.20 (0.88–1.63)	.26	1.19 (0.78–1.82)
Ectopy at Previous Visit									
Continuous	1.09 (0.94–1.26)	.25	1.04 (0.89–1.21)	.63	1.05 (0.90–1.23)	.55	1.00 (0.84–1.19)	.99	1.10 (0.88–1.38)
Quartiles	1.17 (0.86–1.59)	.33	1.08 (0.78–1.48)	.66	1.21 (0.86–1.71)	.28	1.14 (0.80–1.62)	.47	0.83 (0.50–1.41)

HPV, human papillomavirus; HR, hazard ratio; CI, confidence interval.

Cox proportional hazards models were used for all statistical analyses.

* Adjusted for number of new sexual partners in the prior 8 months and study site.