Mediators of the Association Between Age of First Sexual Intercourse and Subsequent Human Papillomavirus Infection

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ABSTRACT. *Objective.* **Previous studies have demonstrated that early age of first sexual intercourse is associated with human papillomavirus (HPV) infection. The objective of this study was to identify a set of risk behaviors and partner characteristics that mediate the association between age of first sexual intercourse and subsequent HPV infection in adolescent and young adult women.**

Methods. **Female university students completed surveys and underwent HPV testing every 6 months for up to 3 years. HPV-positive participants were matched to HPV-negative participants (252 pairs, total $N = 504$). Associations were examined between risk behaviors/partner characteristics and both age of first sexual intercourse and HPV infection. Those variables associated with either age of first sexual intercourse or HPV infection were entered into a generalized estimating equation (to account for the matched study design) modeling the association between age of first sexual intercourse and HPV infection.**

Results. **Mean age of first sexual intercourse was 16.7 (±1.8) years, and early age of first sexual intercourse was associated significantly with HPV infection ($\beta = -0.20$; odds ratio: 0.82; 95% confidence interval: 0.74–0.90). The association was mediated by number of sexual partners in the past 6 months, history of sexually transmitted infection, alcohol and drug use related to sexual behaviors, and partner's number of sexual partners.**

Conclusion. **A set of behavioral risk factors and partner characteristics partially mediate the association between age of first sexual intercourse and subsequent HPV infection.** *Pediatrics* **2002;109(1). URL: http://www.pediatrics.org/cgi/content/full/109/1/e5;** ***human papillomavirus, sexual intercourse, adolescent, risk behaviors, mediator.***

ABBREVIATIONS. HPV, human papillomavirus; STI, sexually transmitted infection; GEE, generalized estimating equation.

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Genital human papillomavirus (HPV) infection is one of the most common sexually transmitted infections in the United States, with a prevalence of approximately 50% in sexually active adolescent and young adult women.[1,2] Infection with certain HPV types, particularly types 6 and 11, is associated with the development of anogenital warts, which has a prevalence of approximately 2% in sexually active men and women.[3] HPV infection with high-risk oncogenic types, such as 16, 18, 31, and 45, may progress from infection to cervical dysplasia, carcinoma in situ, and invasive cervical cancer.[4–8] Although HPV infection is frequently transient in adolescent and young adult women and the natural history of HPV infection and cytologic abnormalities is still being defined,[9] this population has a relatively high incidence of abnormal Papanicolaou (Pap) smears. Mount and Papillo[10] reported that the incidence of Pap smears with squamous intraepithelial lesion was higher in adolescents 10 to 19 years of age than in adult women, and other investigators[11,12] have proposed that the prevalence of abnormal Pap smears and cervical dysplasia is increasing worldwide in young women.

An understanding of the risks for HPV acquisition in adolescent and young adult women is critical for the design of programs to prevent primary infection and its sequelae, such as condylomata and cervical cancer. Recent studies have demonstrated that risk factors include number of sexual partners, partner's number of sexual partners, and early age of first sexual intercourse.[2,13–18] Although several investigators have reported a significant association between early age of first sexual intercourse and subsequent HPV infection, the mechanisms by which early age of first sexual intercourse leads to HPV infection; ie, the mediators of the association, are unknown.

Behavioral variables, biological variables, or both may play key roles in mediating the association between early age of first sexual intercourse and subsequent HPV infection. A behavioral or biological variable acts as a mediator of this association if early age of first sexual intercourse is causally associated with the mediating variable, which in turn is causally associated with HPV infection. For instance, number of sexual partners mediates the association between early age of first sexual intercourse and HPV infection if 1) early age of first sexual intercourse is a predictor of number of sexual partners, and 2) number of sexual partners is causally associated with

HPV infection.[19] There is evidence that behavioral variables, such as sexual and other risk behaviors and partner selection, are possible mediators of this association. Greenberg et al[20] reported that adolescents who reported early age of first sexual intercourse were more likely to practice sexual behaviors that would increase the risk of sexually transmitted infection (STI) and to choose partners who were more likely to transmit STI. Other risk behaviors such as alcohol and drug use are also associated with sexual practices that increase the risk of STI.[21,22] It remains unclear whether substance use is causally related to risky sexual behaviors, either through impaired judgment regarding contraceptive use or choice of a partner, or is a marker for the tendency to practice risky behaviors in general.[23] In addition to behavioral variables, biological variables such as cervical immaturity may play a role in mediating the association between early age of first sexual intercourse and subsequent or persistent HPV infection. Evidence suggests that the cervix may be particularly vulnerable to HPV infection early in puberty for a number of reasons, including cervical ectopy, which is characterized by rapid physiologic changes in the cervical epithelium, or immature immune response to HPV infection.[24–27]

A more detailed understanding of the behavioral and biological mechanisms that account for the association between early age of first sexual intercourse and subsequent HPV infection in adolescents has important implications for primary prevention of HPV infection, prevention of HPV-related disease, and future research initiatives. This study was designed to identify specific behavioral mediators of the association between age of first sexual intercourse and HPV infection, using data from a longitudinal cohort study of adolescent and young adult women. The first aim of the study was to identify a set of risk behaviors and partner characteristics that mediate the association between age of first sexual intercourse and subsequent HPV infection. The second aim was to define the extent to which this set of risk behaviors and partner characteristics mediates the association.

METHODS

Study Sample

The study population consisted of female students of a state university, who were invited to participate in a longitudinal study examining the natural history of cervicovaginal HPV infection between 1993 and 1994. Details of recruitment were described previously.[18] Eligibility criteria included first or second year in college and/or planning to stay in the area for at least 2½ years, not currently pregnant and not planning to become pregnant in the next 3 years, and no history of a cervical biopsy or ablative treatment for cervical intraepithelial lesions. Of the 1090 respondents to advertisements, 608 (56%) participated, 150 (14%) were ineligible, and 332 (30%) declined to participate (Fig 1).

Forty-eight women who had never been sexually active and did not become sexually active during the study period were excluded from analysis (Fig 1). Nine of the remaining 560 participants were excluded from further analysis because of missing data on covariates. Of the remaining 551 participants, HPV-positive participants were defined as those women who were positive for HPV infection at baseline or became positive for HPV during the study period. To minimize bias toward older and more sexually experienced young women using these longitudinal data, we used the following procedures. A participant was defined as HPV-positive if she tested positive for HPV at the first visit or any subsequent visit. Each HPV-positive participant was matched by age (within 1 year) and visit number to a participant who never became positive for HPV infection during the study period. The visit used for matching an HPV-positive to an HPV-negative participant was the first visit at which a participant presented with a positive HPV result. After a participant became HPV-positive once, she was excluded from further analysis. This led to 252 pairs (504 participants) of HPV-positive and HPV-negative women who could be matched by age and visit number.

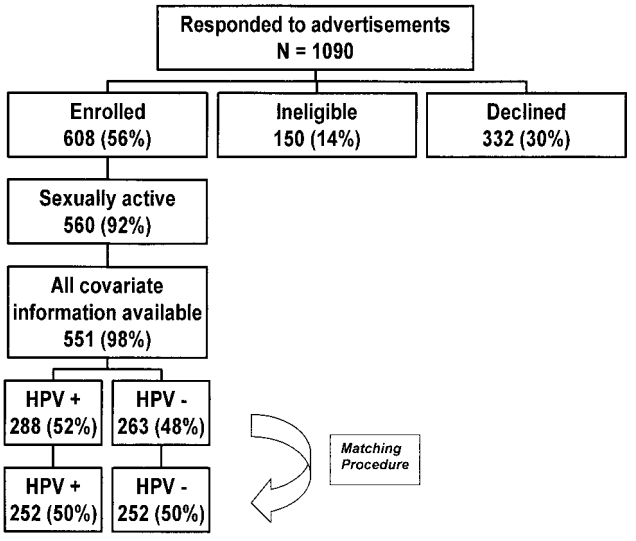

Fig 1. Study sample.

Data Collection

At the baseline and each subsequent visit, each participant completed a self-administered questionnaire assessing sociodemographic characteristics, sexual history, alcohol and drug use as it relates to sexual behaviors, cigarette smoking, sociodemographic and behavioral characteristics of sexual partners, and gynecologic history. Participants were asked to report lifetime sexual behaviors as well as sexual behaviors for the 6-month period before the baseline visit. Sexual behaviors with 2 types of sexual partners were assessed: regular partners (with whom participants had ongoing sexual contact for ≥1 month) and casual partners (with whom participants had sexual contact for <1 month). A pelvic examination was performed at the baseline and at each subsequent visit. A Pap smear was obtained using a cytobrush for endocervical samples and a spatula for ectocervical samples. After the Pap smear, exfoliated cervicovaginal cells were obtained by lavage for HPV determination.[28] Samples were tested by polymerase chain reaction for the following HPV types: 2, 6, 11, 13, 16, 18, 26, 31–35, 39, 40, 42, 45, 51–59, 61, 62, 64, 66–70, 72, 73 (PAP238A), 81 (AE7), 82 (W13B), 83 (PAP291), 85 (PAP155), AE2, AE6, and AE8. Samples were tested by Southern blot hybridization using ^{32}P-labeled HPV DNA types 11, 16, 18, 51, 52, and 53. HPV positivity was defined as detection of HPV DNA by either polymerase chain reaction or Southern blot hybridization. Self-administered surveys and HPV testing were conducted every 6 months for the study duration, up to 3 years.

Statistical Analysis

Both univariate statistics and multivariate models were used to determine whether risk behaviors and partner characteristics mediate the association between age of first sexual intercourse and subsequent HPV infection (Fig 2), and multivariate models also were used to examine possible moderators of the association. A variable that functions as a mediator accounts for the relation between the independent variable (age of first sexual intercourse) and the dependent variable (HPV infection).[29] For example, age of first intercourse is causally associated with number of lifetime sexual partners (a proposed mediator), which, in turn, is causally associated with HPV infection.[19] We assessed whether risk behav-

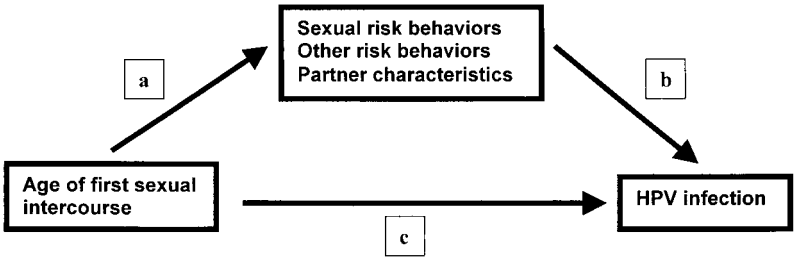

Fig 2. Model of the association between age of first sexual intercourse and HPV infection, as mediated by sexual and other risk behaviors and partner characteristics.

iors and partner characteristics functioned as mediators by testing whether the following 3 conditions were met.[19,29] First, we determined which risk behaviors and partner characteristics were significantly associated with age of first sexual intercourse (Fig 2, path a). Second, we determined which risk behaviors and partner characteristics were significantly associated with HPV infection (Fig 2, path b). Third, we assessed whether age of first sexual intercourse was associated significantly with HPV infection using generalized estimating equation (GEE) regression modeling (Fig 2, path c), as well as whether the effect size (β coefficient, representing the magnitude of the association) diminished when risk behaviors and partner characteristics were added into the model. The degree to which the effect size, or β coefficient, is reduced demonstrates the potency of a mediator.

To test for mediation, we first performed univariate analyses to determine the associations between risk behaviors and partner characteristics and both age of first sexual intercourse and HPV infection. The variables were chosen on the basis of findings of previous studies.[2,13–18,20,21] Sexual risk behaviors and associated outcomes included number of sexual partners during the past 6 months, frequency of vaginal intercourse during the past 6 months (per participant, averaged across all partners), condom use during the past 6 months, oral contraceptive use during the past 6 months, history of STI other than HPV, and history of pregnancy. Other risk behaviors assessed were current cigarette smoking, alcohol use as it relates to risky sexual behaviors, and drug use as it relates to risky sexual behaviors. Alcohol use as it relates to sexual behaviors was measured using a 4-item scale. Affirmative responses were scored as 1, and negative responses were scored as 0. Examples of items were, "When I'm drinking, I'm more likely to have sex with a person I don't know very well," and, "When I'm drinking, I'm less likely to use protection/contraception." Drug use as it relates to sexual behaviors was measured similarly, using a 5-item scale. The first 4 items were identical to those used in the alcohol use scale, except "when I'm doing drugs" was substituted for "when I'm drinking." The fifth item assessed use of sexual intercourse to obtain drugs. The responses to items about drug and alcohol use were summed for each participant to create a scale score measuring substance use as it relates to sexual behaviors. Partner characteristics included the main partner's age, race, and number of lifetime sexual partners as estimated by the respondent. Age of first sexual intercourse was analyzed as a continuous variable, and HPV infection was analyzed as a dichotomous variable. The risk behaviors and partner characteristics used for analysis were those measured at the same visit during which the participant tested positive for HPV. Variables were chosen to measure potential mediators, when possible, after age of first sexual intercourse and before HPV infection; for instance, the variable chosen to measure number of sexual partners was the number of sexual partners in the 6 months before the study visit. The statistical procedures used to evaluate whether univariate associations were statistically significant varied depending on whether the mediating variable was dichotomous, categorical, or continuous but included the following: χ^2, analysis of variance, *t* test, and Pearson correlation coefficient.

We then performed 2 GEE regression analyses to identify the set of risk behaviors and partner characteristics that mediated the association between first sexual intercourse and HPV infection.[30] GEE analyses were used to account for the matched study design, using the statistical package SAS PROC GENMOD (SAS Institute, Inc, Cary, NC). The first regression model included the age of first sexual intercourse entered alone as the independent variable and HPV infection as the dependent variable. The second, or combined, regression model included as independent variables those risk variables and partner characteristics that were associated at $P < .10$ with age of first sexual intercourse or HPV infection in univariate analyses, in addition to age of first sexual intercourse. This model also controlled for the participant's race. The set of variables that was associated at $P < .05$ with HPV infection in the combined regression model was considered to be the set of mediators of the association between age of first sexual intercourse and HPV infection and is the set of variables reported in the final model.

A moderator, in contrast to a mediator, is a variable that affects the direction and/or the strength of an association between the independent variable (age of first sexual intercourse) and the dependent variable (HPV infection); that is, the moderator interacts with age of first sexual intercourse so as to have an impact on HPV infection.[29] Those variables that were significant in the combined regression model but not associated with both age of first sexual intercourse and HPV infection in univariate analyses were considered to be possible moderators of the association between age of first sexual intercourse and HPV infection. To test for moderation, we estimated a third regression model. In this model, interaction terms (consisting of the potential moderators and age of first sexual intercourse) were added to the second, or combined, regression model and assessed for significance.[19]

RESULTS

Descriptive Characteristics of the Study Sample

The racial and ethnic distribution for this study sample was 59% white, 12% black, 13% Hispanic, 9% Asian, and 7% other. Mean participant age was 20.4 years (±2.1 years), mean age of menarche was 12.3 years (±1.2 years), and mean age of first sexual intercourse was 16.7 years (±1.8 years). Mean lifetime number of sexual partners was 4.2 (±3.9), mean number of sexual partners in the past 6 months was 1.3 (±0.9), and mean frequency of vaginal intercourse in the previous 6 months was 1.4 times per week. Condom use during the past 6 months was reported by 144 participants (28.8%) as never or rarely, by 80 participants (16.0%) as sometimes, and by 259 participants (51.8%) as most or all of the time. Forty-seven percent reported use of oral contraceptives in the previous 6 months, and 10% reported a history of an STI other than HPV. More than 25% of participants reported having smoked at least 100 cigarettes in the past, 152 (42.0%) drank alcohol at least once a week, and 30 (8.5%) used illicit drugs at least once a week. The mean score on the scale measuring alcohol and drug use related to sexual behaviors was 3.4 out of a possible 9. The mean age of the main sexual partner was 21.3 years (±2.8 years). The racial distribution of the main sexual partner was 47.8% white, 10.6% black, 11.0% Hispanic, 2.4% Asian, and 28.2% other. The mean number of partners' sexual partners was 2.6 (±2.5). The racial and ethnic distribution of the participants was representative of the ethnic distribution of the total female undergraduate population. Compared with nonparticipants, participants were slightly older and had

more lifetime male sexual partners. Therefore, the results may overestimate the HPV prevalence in the sexually active female college population.

Univariate Analyses

Risk variables and partner characteristics significantly associated with earlier age of first sexual intercourse included >1 sexual partner in the past 6 months, use of condoms "sometimes," history of pregnancy, current smoking, higher score on the scale assessing alcohol and drug use related to sexual behaviors, and partner's lifetime number of sexual partners. History of STI was associated with early age of first sexual intercourse at a marginally significant *P* value (Table 1). Risk variables and partner characteristics that were significantly associated with HPV infection included >1 sexual partner in the past 6 months, higher frequency of vaginal intercourse, history of STI, current smoking, higher score on the scale assessing alcohol and drug use related to sexual behaviors, higher partner age, partner's race (black), and higher number of partner's sexual partners (Table 2). Participant's race (black) was significantly associated with HPV infection but not with age of first sexual intercourse.

Multivariate Analyses

GEE models demonstrated that earlier age of first sexual intercourse was significantly associated with HPV infection (Table 3). When those risk variables and partner characteristics that were found to be significantly associated with age of first sexual intercourse or HPV infection were added to the model, the β coefficient (a measure of the strength of the association) decreased by 20% ($\beta = -0.20$ to -0.16), indicating that these variables partially mediate the association between age of first sexual intercourse and HPV infection. The standard error was essentially unchanged in the combined model, suggesting that the independent variables were not highly collinear. The *P* value remained significant in the combined model but was attenuated. The set of variables associated both with age of first sexual intercourse and HPV infection in univariate analysis and also independently associated with HPV infection in the combined GEE model was considered to be the set of mediators of the association between age of first sexual intercourse and HPV infection. They included number of sexual partners in the previous 6 months, history of STI, alcohol and drug use related to sexual behaviors, and partner's number of sexual partners.

TABLE 1. Associations Between Age of First Sexual Intercourse and Sexual Behaviors, Other Risk Behaviors, and Partner Characteristics

	Age of First Sexual Intercourse (Mean [SD])	Pearson Correlation Coefficient	*P* Value*
Sexual risk behaviors			
Sexual partners†			
1	17.00 (1.7)		<.0001
>1	16.02 (1.9)		
Frequency of vaginal intercourse†		−0.08	.061
Condom use†			
Never/rarely	16.66 (1.6)		.014
Sometimes	16.24 (2.1)		
Most/all of the time	16.90 (1.8)		
Oral contraceptive use†			
Yes	16.86 (1.8)		.73
No	16.78 (1.6)		
History of STI			
Yes	16.26 (1.7)		.059
No	16.77 (1.8)		
History of pregnancy			
Yes	16.11 (2.2)		.009
No	16.79 (1.7)		
Other risk behaviors			
Current cigarette smoking			
Yes	16.26 (1.7)		.002
No	16.86 (1.8)		
Drinking/drug use related to sexual behavior‡			
Scale score 0	16.91 (1.8)		.002
Scale score ≥1	16.40 (1.7)		
Partner characteristics			
Partner's age§		0.09	.079
Partner's race§			
White	16.70 (1.7)		.24
Black	16.40 (2.2)		
Hispanic	16.91 (1.5)		
Asian	17.08 (1.9)		
Partner's number of sexual partners§		−.092	.038

SD indicates standard deviation.
* The *P* value is derived from a Pearson correlation coefficient if the behavioral/partner characteristic variable is continuous and from a *t* test or analysis of variance procedure if the behavioral/partner characteristic variable is categorical.
† These variables were assessed during the 6 months before testing positive for HPV.
‡ Self-report of risky sexual behaviors while using alcohol or illicit drugs, measured using a 9-point scale.
§ Assessed for main sexual partner.

TABLE 2. Associations Between HPV Infection and Sexual Behaviors, Other Risk Behaviors, and Partner Characteristics*

	HPV-Positive (N [%])	Mean (SD), HPV-Positive	Mean (SD), HPV-Negative	*P* Value†
Sexual risk behaviors				
Number of sexual partners‡				
1	152 (42.2)			.001
>1	100 (69.4)			
Frequency of vaginal intercourse‡		38.5 (47.5)	27.3 (38.6)	.004
Condom use‡				
Never/rarely	67 (46.5)			.07
Sometimes	49 (61.3)			
Most/all of the time	132 (47.8)			
Oral contraceptive use‡				
Yes	64 (49.6)			.85
No	59 (50.9)			
History of STI				
Yes	37 (74.0)			.001
No	215 (47.5)			
History of pregnancy				
Yes	33 (61.1)			.08
No	219 (48.7)			
Other risk behaviors				
Current cigarette smoking				
Yes	72 (61.5)			.005
No	180 (46.6)			
Drinking/drug use related to sexual behavior§				
Scale score 0	140 (44.3)			.001
Scale score ≥1	112 (59.6)			
Partner characteristics				
Partner's age‖		21.9 (3.3)	20.7 (2.3)	.0001
Partner's race‖				
White	126 (42.4)			.001
Black	51 (87.9)			
Hispanic	39 (60.9)			
Asian	13 (28.3)			
Other	23 (59.0)			
Partner's number of sexual partners‖		7.8 (10.2)	3.3 (4.8)	.0001

SD indicates standard deviation.
* Several of these associations have been reported previously, using different sample selection and methods of analysis, in Ho et al[2] and Burk et al.[18]
† The *P* value is derived from a χ^2 statistic if the behavioral/partner characteristic variable is categorical and from a *t* test or analysis of variance procedure if the behavioral/partner characteristic variable is continuous.
‡ These variables were assessed during the 6 months before testing positive for HPV.
§ Self-report of risky sexual behaviors while using alcohol or illicit drugs, measured using a 9-point scale.
‖ Assessed for main sexual partner.

Participant's race (black) and older age of the main sexual partner were associated with HPV infection (but not age of first sexual intercourse) in univariate analyses and were also independently associated with HPV infection in the combined GEE model. To assess whether these variables were moderators of the association between age of first sexual intercourse and HPV infection, we added interaction terms to the combined model. These included the interaction of race and age of first sexual intercourse and the interaction of partner's age and age of first sexual intercourse. These interaction terms were not significantly associated with HPV infection. Therefore, although these variables may modify the association between age of first sexual intercourse and HPV infection to a small degree, they likely are not strong moderators of the association.

DISCUSSION

Our analyses confirmed the findings of previous studies that demonstrated that age of first sexual intercourse is significantly associated with subsequent HPV infection,[13–16] but extended previous findings in that we specifically examined which risk behaviors and partner characteristics mediate the association between age of first sexual intercourse and subsequent HPV infection. As previously discussed, a risk behavior or partner characteristic acts as a mediator of the association between age of first sexual intercourse and HPV infection if age of first sexual intercourse is causally associated with the potential mediator and the potential mediator is causally associated with HPV infection.[19,29] Previous studies have explored these associations separately. Greenberg et al[20] demonstrated that early age of first sexual intercourse in a female population was associated with sexual risk behaviors such as multiple sexual partners and higher likelihood of having had sexual intercourse with risky partners, including bisexual, intravenous drug-using, or HIV-infected men. Coker et al[31] reported that early sexual initiation was associated not only with sexual risk behaviors (number of sexual partners and inconsistent condom use) but also with other risk behaviors such as alcohol and cigarette use. A number of studies have demonstrated that sexual risk behaviors are associated with HPV infection, particularly with high oncogenic risk types. These behaviors include multiple

TABLE 3. GEE Models Examining the Association Between Age of First Sexual Intercourse and HPV Infection

HPV infection regressed on age of first sexual intercourse						
Variable	β Estimate	Standard Error	Odds Ratio	95% Confidence Interval		*P* Value
Age of first sexual intercourse*	−0.20	0.05	0.82	0.74	0.90	.0001
HPV infection regressed on age of first sexual intercourse controlling for risk variables, partner characteristics, and participant race						
Variable	β Estimate	Standard Error	Odds Ratio	95% Confidence Interval		*P* Value
Age of first sexual intercourse*	−0.16	0.06	0.85	0.76	0.97	.013
Number of sexual partners†	0.50	0.14	1.65	1.26	2.16	.0003
History of STI	0.80	0.34	2.23	1.14	4.35	.019
Drinking/drug use related to sexual behavior‡	2.95	0.80	19.1	4.01	91.8	.0002
Partner's lifetime number of sexual partners§	0.06	0.03	1.06	1.01	1.12	.014
Partner's age§	0.14	0.05	1.15	1.04	1.27	.006
Participant's race‖						
White	−1.00	0.37	0.37	0.18	0.76	.007
Black	1.58	0.55	4.85	1.63	14.3	.004
Hispanic	0.0008	0.45	1.0	0.42	2.41	1.00
Asian	−1.36	0.48	0.26	0.10	0.65	.004

* Age assessed as a continuous variable; odds are per year of age.
† This variable was assessed during the 6 months before testing positive for HPV.
‡ Self-report of risky sexual behaviors while using alcohol or illicit drugs, measured using a 9-point scale: scale dichotomized into ever versus never practiced risky behaviors while using alcohol or illicit drugs.
§ Assessed for main sexual partner.
‖ "Other" race served as the reference group.

sexual partners and frequency of vaginal intercourse.[14,15,32–35] Other risk behaviors that have been associated with HPV infection include smoking and alcohol use.[14,15] Black race has also been associated with HPV infection.[16,36] Our analyses support these findings by demonstrating that age of first sexual intercourse was associated with sexual and other risk behaviors and partner characteristics and that similar sexual and other risk behaviors and partner characteristics were in turn associated with HPV infection. The finding that the magnitude of the association between age of first sexual intercourse and HPV infection diminished when specific risk behaviors and partner characteristics were added into the model indicates that these characteristics are among the mechanisms by which early age of first sexual intercourse leads to HPV infection.

The finding that risky behaviors and partner characteristics partially mediate the association between age of first sexual intercourse and HPV infection has implications both for clinicians who provide health care to adolescents and for the development of adolescent-specific cervical cancer prevention programs. To prevent HPV infection and development of cervical dysplasia, providers should encourage adolescents who have not yet had sexual intercourse to postpone sexual initiation. Providers should be aware that those who have a history of early sexual initiation are a group especially vulnerable to HPV infection and need in-depth counseling about their risks and the importance of modifying sexual behaviors. Key messages to these adolescents should include the importance of limiting the number of sexual partners and choosing sexual partners who have not themselves had multiple partners. Providers should incorporate discussion of whether patients practice risky sexual behaviors under the influence of alcohol or illicit drugs. Future research should focus on the establishment of effective ways to communicate this information to providers and patients and whether interventions to decrease risk actually prevent HPV infection.

These findings indicate that young women who initiate sexual intercourse at a young age are more vulnerable to HPV infection in part because of behaviors and partner characteristics that place them at risk for infection. However, the modest reduction in the magnitude of the association between age of first sexual intercourse and HPV infection when these mediators are included in the model suggests that other factors are likely to play a major role in mediating the association. These data do not permit direct measurement of biological variables, but biological factors such as cervical immaturity may play a role in mediating the association between age of first sexual intercourse and either HPV acquisition or persistence. Investigators have postulated that the adolescent cervix is particularly vulnerable to STI for reasons such as inadequate production of cervical mucus, which acts as a protective barrier against infectious agents,[37] and cervical ectopy, which is characterized by immature columnar and metaplastic cells that may be susceptible to infection with STI including HPV.[24,27,38–41] The significance of establishing cervical immaturity as a risk factor for HPV infection may lie in interventions using either hormonal manipulation or other methods to accelerate the process of squamous cell metaplasia or alter local immune responses, decreasing the risk of HPV infection or persistence. If cervical immaturity proves to be a risk factor for HPV infection or persistence, then an additional implication is that young women who initiated sexual intercourse at a young age (including those who were sexually abused) may benefit from

regular Pap smear screening beginning early in adolescence.

There are several limitations to these analyses. The participants were university students, who may differ from other populations of young women in several ways, including mean age of first sexual intercourse. The findings of this study may not be generalizable to other populations of young women. That all participants were university students may also have an impact on the interpretation of tests for moderation. Significant moderator effects may be difficult to identify statistically if samples are relatively homogeneous, because all of the values of the moderator and the independent variable may not be represented.[42] These data were obtained by self-report. Although self-reported data on sexual behaviors and sexually transmitted infections have been shown to have adequate validity and reliability,[43–47] there are few data on the validity of reported partner characteristics, such as number of sexual partners.[48] Finally, although we attempted to measure potential mediators that occurred after the age of first sexual intercourse and before HPV infection and that were plausible mediators of the association, mediation is difficult to distinguish from confounding. For example, these analyses suggest that history of other STI acts as a mediator of the association between early first sexual intercourse and HPV infection. This is plausible if adolescents who initiate sexual intercourse at a young age are more likely to acquire other STI and if previous acquisition of other STI (eg, herpes simplex virus or other genital ulcer disease) increases the risk of HPV acquisition. However, an alternative explanation for the findings is that history of other STI confounds the association between age of first sexual intercourse and HPV infection.

CONCLUSION

These findings indicate that specific behavioral factors partially mediate the association between age of first sexual intercourse and HPV infection, with implications for clinical practice and for the design of adolescent-specific cervical cancer prevention programs. Future investigations that clarify the roles of biology and behavior in HPV infection and determine which aspects of biology and behavior predict persistence of high-risk HPV infection and development of cervical dysplasia will be critical to the design of effective cervical cancer prevention programs for adolescents.

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