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## Genital Herpes in a Primary Care Clinic: Demographic and Sexual Correlates of Herpes Simplex Type 2 Infections

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### Abstract

**Background and Objectives:** Genital herpes remains one of the most prevalent sexually transmitted diseases (STDs). The sexual behavioral correlates of herpes simplex virus type 2 (HSV-2) infection in the general population have not been well characterized.

**Goals:** To assess demographic and sexual behavioral correlates of symptomatic and subclinical HSV-2 infection.

**Study Design:** Cross-sectional survey of 922 randomly chosen patients and 78 of their partners (1,000 total) in a family practice. Sexual behavior information was collected in 492 people.

**Results:** Two hundred twenty-five (23%) heterosexual people had HSV-2 infection, but only 59 (26%) reported a history of genital herpes. HSV-2 seroprevalence was 63% in African-American women, 27% in white women, 40% in African-American men, and 12% in white men. In multivariate analyses of risk factors for HSV-2 infection among men, 10 or more sexual partners and a prior STD were statistically significantly associated with HSV-2 infection. Among white women, number of sexual partners, a prior STD, marriage or cohabitation, and less than a college education were predictive of HSV-2 infection. A history of oral sex was the only statistically significant predictor of HSV-2 infection in African-American women.

Conclusions: Risk factors for HSV-2 infection differ by gender and ethnic group. Traditionally recognized behavioral correlates of STD acquisition may not identify people in communities with high prevalence of HSV-2 infection.

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RECENT STUDIES INDICATE that infection with herpes simplex virus type 2 (HSV-2) is epidemic in the United States. Between 1978 and 1990, the prevalence of HSV-2 infection increased 32%, and currently more than one fifth of adults have antibody to HSV-2.<sup>1,2</sup> Genital herpes is the most common cause of genital ulcer disease in the developed world. The morbidity associated with genital herpes infections is varied. The most serious, albeit infrequent, outcome of genital herpes infections is neonatal herpes.<sup>3,4</sup> Among immunosuppressed people, HSV infections may result in severe, extensive, and persistent lesions that resist standard therapy.<sup>5,6</sup> The morbidity of recurrent genital herpes includes considerable psychosocial impairment in people with symptomatic genital herpes.<sup>7</sup> Finally, studies have shown an association between genital ulcer disease and transmission of human immunodeficiency virus infection.<sup>8-10</sup>

Most studies of HSV-2 prevalence have been limited to female populations attending specialized clinics, such as family planning, student health, or sexually transmitted disease (STD) clinics.<sup>11-14</sup> Few studies included men and assessed sexual behavior.<sup>15,16</sup> To investigate the demographic and sexual behavioral correlates of symptomatic and subclinical HSV-2 infections, we interviewed and screened for HSV-2 antibody adult patients presenting for primary care at a family medicine clinic.

## Methods

### Study Setting, Subjects, and Procedures

The study was conducted at the University of Washington Family Medical Center in Seattle between November, 1991 and December, 1993. Patients were randomly chosen for participation if they were between the ages of 18 and 45 years, spoke English, and were not pregnant. Of an initial 500 people approached, 62% agreed to participate.<sup>17</sup> Participants were asked to provide demographic information and whether they had had, or had been told that they had, oral or genital herpes. A blood sample was obtained for serologic testing from all subjects, and their partners were invited to participate in the study. The study included 922 randomly recruited patients and 78 partners who volunteered for the study. Because HSV-2 seroprevalence was the same among the randomly chosen subjects as among the partners, the groups were combined for analyses. All HSV-2-seropositive patients were asked to return to clinic for counseling. A sexual history questionnaire was administered to participants during the counseling visit and, beginning with patient 578, all subjects were asked sexual history during the initial interview. Thus, sexual behavior was ascertained in 492 sexual patients. The study was approved by the University of Washington Human Subjects Research Committee, and subjects signed a written consent form.

### Laboratory Methods

The serum was tested for the presence of HSV-1 and HSV-2 antibodies using Western blot.<sup>18</sup> This technique has been shown to be the most accurate assay for distinguishing antibodies to HSV-1 and HSV-2.<sup>19,20</sup>

### Statistical Analysis

The analysis of demographic and serologic data on the initial 500 subjects tested has been published.<sup>17</sup> This project extends the findings to 961 heterosexual subjects and includes detailed sexual history information that was obtained on a subset of patients.

Associations between HSV-2 seropositivity and demographic and sexual variables were characterized by chisquare tests, Fisher's exact test, Mann-Whitney U test for comparison of medians, or logistic regression. Initially, we performed separate analyses for men and women and white and African-American subjects. If associations between covariates and HSV-2 seropositivity were similar for each subgroup, the groups were combined in further analyses. The relationship between the number of lifetime sexual partners and HSV-2 seropositivity was examined using both the number of partners as a continuous variable and as a categorical variable (1 to 3, 4 to 9, and 10 or more). Distributions of number of sexual partners between men and women were compared using the Kolmogorov-Smirnov test, and the chi-square test was used to compare the proportion of men and women with multiple sexual partners. Correlations between covariates were examined with the Spearman correlation coefficient. Analysis was limited to sexually active heterosexual people; people known to be homosexual or bisexual were excluded. All *P* values were two-sided, [ $\alpha$ ] = 0.05.

Subjects with HSV-2 antibody who denied a history of genital herpes were defined as having subclinical HSV-2 infection. Demographic characteristics of patients with symptomatic HSV-2 infection were compared with patients with subclinical HSV-2 infection using logistic regression. The influence of prior HSV-1 infection on symptomatic versus subclinical HSV-2 infection was assessed with the chi-square test.

In multivariate analysis, subjects other than white or African American were excluded because their number was small and they were an ethnically heterogeneous group. Separate models were constructed for African-American and white men and women. The analysis was carried out by forward stepwise entry of covariates using a likelihood ratio statistic to decide whether a given variable should remain in the model. A variable was entered into the model if the probability of its score statistic ( $P$ -value) was less than 0.05 and removed if the probability was greater than or equal to 0.10. The estimates of relative risks were adjusted for age. Computations were done with SPSS-PC for Windows (SPSS Inc., Chicago, IL) and Epi-Info (Centers for Disease Control and Prevention, Atlanta, GA).

## Results

### Study Population

Of the 1,000 subjects, 8 people who were sexually inexperienced and 31 people who were homosexual or bisexual were excluded from the analyses. Among the remaining 961 subjects, 610 (63%) were women and 351 (36%) were men. Eighty percent were white, 9% were African American, and 11% were of other racial backgrounds. The mean age was 33 years; most patients (82%) had private health insurance. Overall, the subjects were well educated; 57% had completed college. The demographic characteristics of the 492 patients from whom the sexual history was obtained were similar to those of patients on whom sexual history was not obtained.

### Frequency of HSV-1 and HSV-2 Infection

Two hundred twenty-five (23%) subjects tested positive for HSV-2 antibodies. Of these, 102 (11%) had HSV-2 antibodies only and 123 (13%) had both HSV-1 and HSV-2 antibodies. An additional 398 (41%) patients had HSV-1 antibodies only; 7 (1%) patients had antibody profiles that could not be classified, and the remaining 331 (34%) patients were HSV seronegative (Table 1).

Graphic

TABLE 1. Prevalence of HSV-2 Infection According to Gender and Race

Among the 225 patients with HSV-2 infection, only 59 (26%) patients reported a history of genital herpes. Conversely, among the 70 patients with a history of genital herpes, 2 were seronegative and 9 were seropositive for HSV-1 only. The proportion of subjects with symptomatic HSV-2 infection compared to subclinical infection did not vary significantly with gender or race. However, 32% of patients with HSV-2 antibodies only had a history of genital herpes, compared with 21% of patients with HSV-1 and 2 infection (odds ratio [OR] = 1.8; 95% confidence interval [CI] 0.9, 3.4). Thus, prior HSV-1 infection appeared to reduce the frequency of clinically recognized genital herpes.

### Univariate Demographic Correlates of HSV-2 Seropositivity

We examined the demographic correlates of HSV-2 seropositivity separately for women and for men. In a univariate analysis, age was significantly associated with HSV-2 seropositivity among both women and men (OR = 1.1 per year; 95% CI 1.0, 1.1). Fewer years of education was a marker for HSV-2 infection. People who did not finish college were more likely to be HSV-2 seropositive than those who finished college (OR = 2.3; 95% CI 1.6, 3.3 for women and OR = 2.3; 95% CI 1.2, 4.4 for men). Receiving public health insurance, or having no insurance, was associated with an elevated risk for HSV-2 infection among women and men (OR = 2.4; 95% CI 1.6, 3.6 and OR = 3.1; 95% CI 1.5, 6.3, respectively). Marital status was associated with HSV-2 infection among women, but not among men. Women who had ever been married were more likely to be HSV-2 seropositive compared with never-married women (OR = 1.5; 95% CI 1.0, 2.2). African-American background was also a strong predictor of HSV-2 infection: 63% of African-American women were HSV-2 infected compared with 27% of white women (OR = 4.6; 95% CI 2.6, 8.3), and 40% of African-American men were HSV-2 infected compared with 12% of white men (OR = 5.1; 95% CI 2.3, 11.6). The HSV-2 seroprevalence was 13.2% in people of other ethnic background; however, this group was heterogeneous and may not accurately reflect the risk of genital herpes for people of other descents.

### Sexual Behavior Correlates of HSV-2 Seropositivity

Information regarding sexual activity was provided by 492 subjects. Subjects answered between 98% and 100% of questions about sexual behavior. Thirty-eight subjects did not know whether they had had an STD in the past. In both women and men, initiation of sexual activity at age 18 years or younger was associated with increased risk for HSV-2 infection (Table 2). Forty-eight percent of women and 21% of men who initiated sexual activity at 18 years of age or younger were HSV-2 seropositive, compared with 25% of women and 4.3% of men who delayed sexual activity until at least age 19 years. Lifetime number of sexual partners was also an important determinant of HSV-2 infection. Of interest, none of the women with only 1 lifetime sexual partner and none of the men with 1 to 3 partners had HSV-2 infection, whereas 64% of women and 28% of men with 10 or more lifetime partners had HSV-2

infection (Figure 1). Among both men and women, the risk of HSV-2 increased with increasing number of lifetime partners. In contrast, the number of partners in the last 12 months was not significantly associated with HSV-2 seropositivity among men or women. A history of an STD other than genital herpes was a risk factor for HSV-2 infection because 19% of those without such history were HSV-2 seropositive compared with 49% of those with history of an STD. Among women only, having ever had oral sex or having ever had rectal sex was associated with HSV-2 infection. However, history of these sexual practices was higher among women with multiple sexual partners.

Graphic

TABLE 2. Univariate Analysis of Sexual Behavior Risk Factors for HSV-2 Seropositivity

Graphic

Fig. 1. Prevalence of HSV-2 antibodies stratified by race, gender, and number of sexual partners.

Condom use appeared protective against HSV-2 infection for women, but not for men. We defined condom use as never or rare (0% to 10%), occasional (11% to 50%), frequent (51% to 90%), and usual or always (91% to 100%). We asked separately about the percentage of partners with whom condoms were used and the percentage of sexual encounters in which condoms were used. The percentage of partners but not percentage of encounters was associated with decreased risk of HSV-2 infection. However, for both men and women the use of condoms was correlated inversely with the number of partners, so that subjects with greatest number of partners were least likely to report frequent condom use ( $r = 0.3, P < 0.001$ ). Among people with HSV-2 antibodies, the proportion of subjects who used condoms did not differ significantly between those people who had symptomatic herpes and those who had subclinical herpes. For example, only 15% of people with history of genital herpes and 21% of people without history of genital herpes used condoms with more than 50% of partners. Thus, it does not appear that prior diagnosis of genital herpes influenced condom use. Whether condom use was considered unnecessary (e.g., in a monogamous couple in which both partners have genital herpes) was not assessed.

#### Multivariate Analysis of Correlates of HSV-2 Seropositivity

In a multivariate analysis of demographic and sexual determinants of HSV-2 infection among women, strong racial differences persisted. Thus, we constructed separate models for white and for African-American women. Among white women, the lifetime number of sexual partners, history of STD, years of education, and marital status remained statistically significant determinants of HSV-2 (Table 3). Among African-American women, history of oral sex was the only statistically significant determinant of HSV-2 infection. Among African-American women who had ever had oral sex, 83% were HSV-2 seropositive, compared with 22% of women who had never had oral sex ( $P = 0.002$ ). In addition, women who reported oral sex were more likely to have had more sexual partners: all women with 10 or more sexual partners and 93% of women with 4 to 9 partners reported oral sex, compared with 38% of women with 1 to 3 partners ( $P = 0.003$ ). Thus, oral sex among African-American women was a marker for having had a greater number of sexual partners. The association was weaker for white women because overall 94% have engaged in oral sex.

Graphic

TABLE 3. Multivariate Analysis of Correlates of HSV-2 Infection Among Women and Men, Adjusted for Age

Among men, only the number of sexual partners and history of prior STD remained statistically significant in the multivariate analyses. Race was not associated with HSV-2 seropositivity in men after adjustment for the number of sexual partners.

#### HSV-2 Infections and Number of Sexual Partners in Subgroups of Patients

Because the number of lifetime sexual partners appeared to be the strongest predictor of HSV-2 infection among men and white women, but was not a predictor for black women, we analyzed this risk factor and its relationship with race and gender in greater detail. As the number of prior partners increased from 1 to 3, 4 to 9, and 10 or greater, the percentage of people with HSV-2

antibodies rose from 0% to 3.2% to 26% for white men, from 0% to 33% to 39% for black men, and from 7.8% to 31% to 58% for white women (Figure 1). In contrast, the percentage of HSV-2 seropositive black women was 50%, 81%, and 86%, as the number of sexual partners increased from 1 to 3, 4 to 9, and 10 or more, respectively. Overall, the median number of sexual partners was 10 for white men and 7 for white women. Among African Americans, the median number of sexual partners was 16 among men and 6 among women. In addition, among African Americans, the proportion of men with 10 or more sexual partners was significantly higher than the proportion of women with at least that many partners, 72% compared with 23% ( $P = 0.003$ ). In contrast, the proportion of white men versus white women with 10 or more sexual partners did not differ significantly, 52% versus 42% ( $P = 0.15$ ). The distributions of numbers of sexual partners differed significantly for African-American men and women ( $P = 0.007$ ), but not for white men and women ( $P = 0.41$ ), as illustrated in Figure 2.

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**Graphic**

Fig. 2. Number of lifetime sexual partners by race and gender.

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## Discussion

We examined the demographic and sexual behavioral determinants of genital herpes in a primary care population. The overall HSV-2 seroprevalence was 23%, similar to what has been reported from a recent nationwide serosurvey.<sup>2</sup> Because herpesvirus infections persist for life, the prevalence increases with age through the sexually active years.<sup>1, 11, 21, 22</sup> Also, seroprevalence is higher for women than men.<sup>1, 13, 15, 23, 24</sup> This disparity in infection rates between genders may reflect anatomic differences in susceptibility to infection and greater efficiency of transmission from men to women than from women to men.<sup>25</sup> This is supported by the observation that none of the men with one to three lifetime sexual partners had HSV-2 infection. History of STD was also associated with HSV-2 infection,<sup>11, 13, 16</sup> perhaps reflecting the risk of acquiring multiple STDs during high-risk exposures. Although condoms may protect from acquisition of HSV-2,<sup>24, 25</sup> those people with the greatest number of sexual partners were least likely to use them.

The number of prior sexual partners remained the strongest determinant for HSV-2 infection for men and for white women, a finding reported in other studies.<sup>11, 21, 23, 24</sup> Among African-American women, the number of sexual partners was not predictive of HSV-2 infection, which may reflect the high rate of acquisition earlier after sexual debut in this patient population. This was illustrated by the 50% prevalence rate of HSV-2 among African-American women with only one to three lifetime partners. One interesting relationship was the association between reported oral–genital sexual activity and HSV-2 seroprevalence in African-American women. Further analyses suggested that oral–genital sex was a marker for high number of sexual partners. Oral sex may also have been a marker for sexual relations with high-risk partners. In communities with a very high prevalence of infection, “traditional” risk factors for STDs, such as the number of sexual partners, may lose predictive value, because sexual activity with even a few partners may pose significant risk of infection.

High prevalence of HSV-2 infection in the African-American community has been noted previously.<sup>1, 11, 15, 16</sup> In our study, the high HSV-2 prevalence among African-American men may be explained by high numbers of reported sexual partners.<sup>26–28</sup> In contrast, African-American women tended to have a lower median number of sexual partners, and fewer had had 10 or more partners compared with white women. The pattern of sexual activity differed markedly for black men and women, but was quite similar for white men and women. In models based on empiric data for human immunodeficiency virus and bacterial STDs, high variation in the rate of sexual partner change in a population contributes to a rapid spread of sexually transmitted pathogens.<sup>29</sup> Whether similar dynamics in sexual activity account for a differential rate of spread of HSV infection has not been assessed.

Only a quarter of people with HSV-2 infection reported genital herpes; this finding is consistent with previous studies.<sup>3, 11–13, 15, 30</sup> Prior HSV-1 infection was associated with marginal protection against symptomatic HSV-2 disease, and neither gender nor race were associated with greater likelihood of symptomatic disease. Similarly, among women attending STD clinics, a lower incidence of HSV-2–related symptoms in women with prior HSV-1 infections has been noted: 31% of women with HSV-2 antibodies only, compared with 16% of women with HSV-1 and 2 antibodies had a clinical history of genital herpes.<sup>12</sup>

Our sample included a relatively small proportion of subjects from communities of color, reflecting the ethnic mix of the population in Seattle. The findings of high HSV-2 seroprevalence among African Americans suggest that risk factors for acquisition of STD may vary with the prevalence of the infection and should be investigated with a larger sample. Our study is limited by incomplete participation of invited subjects.<sup>19</sup> The demographic profile of those who agreed to participate did not differ from those who

refused, but the two groups may have differed by important characteristics that we were unable to measure. However, among those who agreed to participate, we achieved excellent cooperation, as demonstrated by high response rates to intimate questions.

We conclude that HSV-2 infection is common but largely unrecognized among people seen for primary care. Risk factors for HSV-2 differed by gender and by ethnicity. In communities with a high prevalence of STDs, traditionally recognized risk factors, such as a high number of sexual partners, may not predict risk of HSV-2 infection.

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