JOURNAL OF WOMEN'S HEALTH
Volume 12, Number 10, 2003

Candida Transmission and Sexual Behaviors as Risks for a Repeat Episode of *Candida* Vulvovaginitis

BARBARA D. REED, M.D., M.S.P.H.,[1] PHILIP ZAZOVE, M.D.,[1] CARL L. PIERSON, Ph.D.,[2] DANIEL W. GORENFLO, Ph.D.,[1] and JULIE HORROCKS, Ph.D.[3]

ABSTRACT

Objective: **To assess associations between female and male factors and the risk of recurring *Candida* vulvovaginitis.**

Methods: **A prospective cohort study of 148 women with *Candida* vulvovaginitis and 78 of their male sexual partners was conducted at two primary care practices in the Ann Arbor, Michigan, area.**

Results: **Thirty-three of 148 women developed at least one further episode of *Candida albicans* vulvovaginitis within 1 year of follow-up. Cultures of *Candida* species from various sites of the woman (tongue, feces, vulva, and vagina) and from her partner (tongue, feces, urine, and semen) did not predict recurrences. Female factors associated with recurrence included recent masturbating with saliva (hazard ratio 2.66 [95% CI 1.17–6.06]) or cunnilingus (hazard ratio 2.94 [95% CI 1.12–7.68]) and ingestion of two or more servings of bread per day ($p \leq 0.05$). Male factors associated with recurrences in the woman included history of the male masturbating with saliva in the previous month (hazard ratio 3.68 [95% CI 1.24–10.87]) and lower age at first intercourse (hazard ratio 0.83 [95% CI 0.71–0.96]).**

Conclusions: **Sexual behaviors, rather than the presence of *Candida* species at various body locations of the male partner, are associated with recurrences of *C. albicans* vulvovaginitis.**

INTRODUCTION

CANDIDA VULVOVAGINITIS IS ONE OF THE most common diagnoses made by physicians caring for women in the United States. It occurs in approximately 75% of women in their lifetimes[1] and recurs in approximately 40%.[2] Although it is rarely life threatening, the costs of the disease to patients and society are great, including medical evaluation costs ($700 million to $1.2 billion per year),[3] physical disability,[4] psychological stress, and concern about the possibility of a more serious diagnosis.[5]

The theory that recurrences are caused by reinfection of the woman by her male sexual partner has been suggested repeatedly, with some data suggesting sexual transmission does occur.[6–9] *Candida* species may be harbored in the male gastrointestinal tract, semen, oral cavity, and urine.[3,10] Male colonization is associated with vaginal colonization, often with the same strain.[6,7] Studies suggest oral sex performed by the male partner (cunnilingus) is associated with both incident and recurrent *Candida* infections.[8,9] Whether this is due to transmission of the organism is unknown.

[1]Department of Family Medicine and [2]Department of Pathology, University of Michigan, Ann Arbor, Michigan.
[3]Department of Mathematics and Statistics, University of Guelph, Guelph, Ontario, Canada.
This project was funded by a grant from the National Institute of Allergy and Infectious Diseases, National Institutes of Health, AI29648.

Risk factors for an episode of *Candida* vulvovaginitis have been published elsewhere.[11] This report describes a prospective, multivariate analysis of the risk of a repeat episode of *Candida* vulvovaginitis based on historical and microbiological characteristics of the woman, her male sexual partner, and their sexual relationship.

MATERIALS AND METHODS

The data for this study were collected as part of the University of Michigan Vaginitis Study, a combination case-control and prospective study of *Candida* vulvovaginitis conducted between 1990 and 1994. Findings from the case-control comparison at enrollment have been published elsewhere.[8] Here we report on the prospective study of women with confirmed *Candida* vulvovaginitis at enrollment (defined as women with vaginal symptoms of discharge, itching, or odor and a positive *Candida* culture), who were evaluated for recurrences of *Candida* vulvovaginitis over the following year. The project was approved by the University of Michigan Investigational Review Board. The women were enrolled at two University of Michigan Family Practice offices in the Ann Arbor, Michigan, area. Women were eligible for the study if they were between 18 and 60 years of age, were currently sexually active, had a male sexual partner who would potentially participate in the study, and agreed to participate in four additional follow-up visits over the next year. Because of the small number of women with female sexual partners ($n = 2$), these are not included in this report.

At the initial visit, informed consent was obtained, and each participant completed a comprehensive, self-administered questionnaire. The questionnaire included items on potential risk factors for *Candida* vulvovaginitis, including questions on demographic variables, symptoms, past medical history, past vulvovaginitis history, medication usage, current and past birth control methods, sexual history and practices, clothing history, and dietary history.

The participating physician performed a pelvic examination and recorded examination data. Specimens of vaginal and cervical discharge and vaginal washings were collected for the following tests: in-office testing for KOH and normal saline preparations, pH of vaginal secretions, and whiff test for aromatic amines; bacterial culture of vaginal and cervical specimens; fungal culture of vaginal, vulvar, tongue, and rectal specimens; and cell culture of endocervical scrapings for *Chlamydia trachomatis*. In addition, blood was drawn for glycosylated hemoglobin determination.

The participant was then asked to take to her current partner(s) an informed consent document, a detailed questionnaire, and materials for urine, fecal, and semen collection, as well as a tongue swabbing specimen for fungal culture. The urine, feces, and semen samples were to be directly deposited in the sterile specimen cups supplied. The tongue swabbing consisted of rubbing the culture collection swab down the center of the tongue and then three swipes from side to side of the tongue. The partners' specimens were returned to the office within 12 hours of collection. If collection occurred more than 4 hours prior to their return, the specimens were refrigerated by the participant.

Follow-up studies

Patients were asked to return at 2 weeks, 1 month, 6 months, and 12 months after treatment. At these visits, a short questionnaire asking about symptoms, sexual activity, and change in risk factors was administered to each participant, and the pelvic examination, in-office laboratory testing, and specimen collection procedures (with the exception of blood collection) were repeated. Each woman was given an abbreviated questionnaire for her partner if that partner had been enrolled at the initial visit. Cultures for *Candida* species were collected by the partners from four sites (urine, feces, semen, and tongue) as before. In addition, the women were told to return to be evaluated for possible recurrent *Candida* vulvovaginitis any time they had symptoms of vaginitis. At these symptomatic visits, the women completed a specific questionnaire designed for symptomatic visits, were examined, and had the in-office laboratory testing and vaginal cultures repeated. Male specimens and questionnaire data also were obtained in conjunction with symptomatic episodes. Data from the routinely scheduled follow-up visits were used to assess colonization rates and changes in risk factors, and data from the symptomatic visits were used to assess recurrences.

Laboratory testing

Microbiological testing for *Candida* species, *Gardnerella vaginalis*, group B beta-hemolytic *Streptococcus*, *Staphylococcus aureus*, *Mycoplasma hominis*, *Ureaplasma urealyticum*, and *Neisseria gonorrhoeae* was performed at the University of Michigan Clinical Laboratory using conventional isolation and culture techniques. Isolation and identification of *Candida* species were performed using Mycosel-Sabouraud's dextrose agar with chloramphenicol and cycloheximide, and all yeasts were evaluated for germ tube production, with germ tube-negative yeasts being further identified using the API yeast identification test. *Trichomonas vaginalis* was cultured in modified Diamond's medium (Remel, Lenexa, KS) at the individual clinical offices, and *C. trachomatis* was cultured at the clinical laboratories of the McAuley Health Center (Ann Arbor, MI), as previously described.[8]

Data analysis

We used Cox (proportional hazards) regression to assess factors associated with number of days to first recurrence of symptomatic *Candida* vulvovaginitis in both univariate and multivariate models. For each woman who did not experience a recurrence, censoring time was calculated as the time from enrollment to her final follow-up visit (maximum 365 days). Candidate variables considered for entry into the multivariate models included demographic variables, factors associated with *Candida* vulvovaginitis occurrence or recurrences in the literature, and factors associated with recurrences in the univariate analysis ($p < 0.10$) and their interactions ($p < 0.20$). Stepwise regression was used to assist in the selection of multivariate models. The functional form of covariates and the proportional hazards assumption were assessed graphically. Hazard ratios representing the relative risk or hazard of *Candida* vulvovaginitis recurrence were calculated, along with their 95% confidence intervals (95% CI). Data analyses were conducted using SPSS software (Chicago, IL). In the text, summary statistics are presented as mean ± standard deviation (SD).

RESULTS

Between January 11, 1990, and July 29, 1993, 336 women with vaginal symptoms suggestive of vaginitis were enrolled in the University of Michigan Vaginitis Study. Of these, 156 (46.4%) were confirmed to have *Candida* vulvovaginitis (92.3% *Candida albicans*, 3.2% *Candida parapsilosis*, 1.9% *Torulopsis glabrata*, and lesser numbers of others), as defined in Materials and Methods. These women were treated with a 7-day course of terconazole and were followed for subsequent recurrences during the next year. All responded clinically to the treatment by the 2-week follow-up visit.

Of these 156 women, 148 (94.9%) with *Candida* vulvovaginitis returned for follow-up at least once during the subsequent year. The mean number of visits per participant, including both symptomatic and routine follow-up visits, was 4.2 ± 1.7 visits, with 83% following up at least twice and 39% returning four or more times. Fifty-four of the 148 women (36.5%) returned for one or more symptomatic follow-up visits (98 visits), and 35 were found to be culture positive for *Candida* species, of which 33 were *C. albicans*, during the year of follow-up. Days of follow-up (from enrollment to recurrent *Candida* vulvovaginitis or, if none, to the final visit or 365 days, whichever was less) averaged 223.4 ± 135.1 days, with 106, 83, and 64 women returning for follow-up after 100, 200, and 300 days, respectively.

The participants with at least one follow-up visit averaged 31.8 ± 7.4 years of age, had 14.8 ± 2.5 years of formal education, were primarily Caucasian (83.0%), and were predominantly married or living as married (59.2%). Male partners of 78 of these women (52.7%) provided historical information and specimens for yeast culture from various sites. These men averaged 34.9 ± 8.0 years of age and had 15.3 ± 2.7 years of formal education, and 76.9% stated they were married or living as married.

The women varied in their history of *Candida* vulvovaginitis. Twenty-three percent reported no history of *Candida* vulvovaginitis in the year prior to enrollment with documented *Candida* vulvovaginitis. Similarly, 23.0% met criteria for recurrent *Candida* vulvovaginitis by reporting at least four episodes of *Candida* vulvovaginitis in the past year.

Microbiological findings from the women

Of the 148 participants, only 10 (6.8%) had a fungal organism other than *C. albicans* at enrollment. Besides the 33 women who had a docu-

mented recurrence with *C. albicans*, 2 additional women grew a non-*albicans* species—1 who had grown *C. albicans* at the initial visit and 1 who recurred with *T. glabrata*—and these were not included in further analyses. Of the 54 women with recurrent symptoms of vaginitis, 33 women (61.1%) were confirmed to have recurrent *C. albicans* vulvovaginitis, with those recurrences occurring an average of 148.7 ± 90.5 days after enrollment. Therefore, 22.3% of the 148 participants during the year had recurrent *C. albicans* vulvovaginitis. Recurrences were not associated with whether the woman was originally infected with a non-*albicans* organism (10% recurred) or with *C. albicans* (23.4% recurred, hazard ratio 0.35 [95% CI 0.05–2.58], $p = 0.30$). Throughout the rest of this report, recurrent *Candida* vulvovaginitis refers to the 33 women who were culture positive for *C. albicans*.

At the 2-week and the 1-month follow-up visits, all women were clinically asymptomatic. Vaginal colonization with *Candida* species was noted in 20.2% of those evaluated at 2 weeks (23 of 114 women) and in 29.2% (33 of 113) of those evaluated at 1 month. Of these, 60.9% and 70.6% were *C. albicans*, respectively. *T. glabrata* was the second most common organism found on vaginal culture at the 2-week and 1-month visits, comprising 21.7% and 17.6% of the positive cultures at those visits, respectively. The presence of *Candida* colonization in the vagina at 2 weeks and at 1 month was not associated with symptomatic recurrences ($p = 0.58$ and 0.62, respectively) (Fig. 1). This was found when considering only those with recurrences of *C. albicans* and when considering those with recurrences of any *Candida* species.

At enrollment, a large proportion of women with *Candida* vulvovaginitis had positive cultures for *Candida* species from the rectum and the tongue (73% and 48%, respectively). Of these, 92.4% and 95.8% were *C. albicans*. Using Cox regression analysis, there was no significant association between recurrences and the presence or absence of *Candida* on the tongue (hazard ratio) [HR] = 1.55 (0.78–3.11)) or in the rectum (HR = 0.80 (0.38–1.67)) at enrollment. *Candida* species were isolated from the rectum and the tongue in 27.4% and 34.2%, respectively, of women at the 2-week follow-up visits and in 23.9% and 42.1%, respectively, of the women at the 1-month follow-up visit. The proportion of positive cultures that were *C. albicans* were 58.1% and 67.9% *C. albicans* in the rectum at 2 weeks and 1 month, respectively, and 92.1% and 98.0% in the tongue cultures. Symptomatic recurrences (*C. albicans* only or any *Candida* species) were not associated with *Candida* on the tongue or in the rectum at the 2-week or 1-month follow-up visits.

In addition to having *Candida* vulvovaginitis at enrollment, a subset of these patients also were culture positive for group B beta-hemolytic *Streptococcus* (19.0%), *S. aureus* (4.8%), *N. gonorrhea*

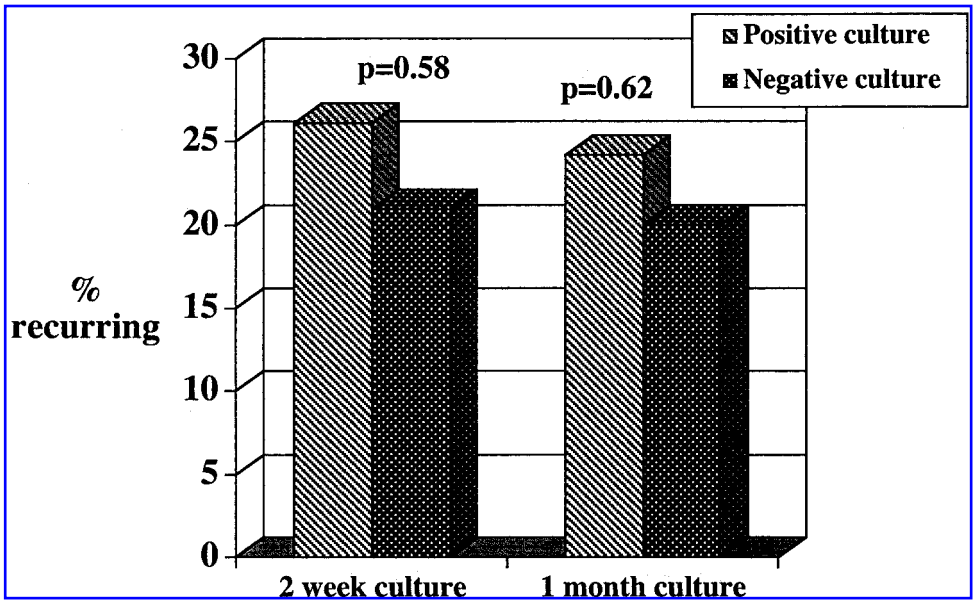

FIG. 1. Percentage of women with a recurrent case of *Candida* vulvovaginitis, following a positive or negative vaginal culture at 2 weeks or at 1 month after previous infection.

(0.7%), *M. hominis* (15.0%), *U. urealyticum* (44.3%), *C. trachomatis* (2.8%), or bacterial vaginosis (11.4%, by Amsel criteria). None of these concomitant infections were associated with increased recurrences of *Candida* vulvovaginitis.

Microbiological findings from male partners

After the first visit, 78 partners of the 156 original women with *Candida* vulvovaginitis (50%) returned specimens from the tongue, urine, feces, and semen, of which 46.8%, 3.9%, 45.9%, and 6.9%, respectively, were culture-positive for *Candida* species. Of these positive cultures, 88.2% of the rectal samples, 91.4% of the tongue samples, 60.0% of the semen samples, and 100% of the urine samples were *C. albicans*. Of the 78 partners, all returned the tongue sample, and 1, 4, and 6 men failed to return the urine, fecal, and semen samples, respectively. The presence of *Candida* species in any of these specimens was not associated with *Candida* at the vulva, rectum, or tongue of the female at enrollment. The recurrence of *Candida* vulvovaginitis was similar in those with and without positive *Candida* cultures at each site at enrollment (Table 1) and at the 1-month follow-up visit (data not shown). When only those male cultures positive for *C. albicans* were considered, again, no associations between positive cultures of the males in any of the four sites and recurrences of *Candida* vulvovaginitis of the female were found. Controlling the analysis for previously reported risk factors (such as oral contraceptive use or recent antibiotic use) or for female or male risk factors later identified in this report did not alter these results.

Female factors

Using Cox regression analysis of *C. albicans* vulvovaginitis, we investigated univariate associations between recurrences during the year of follow-up and characteristics of the women. These factors included demographic characteristics; exposures such as smoking, oral contraceptives, or antibiotic use; diet; gynecological history; sexual behavior history; and current genital symptoms. More than 12 years of education was the only demographic variable significantly associated with a recurrent episode of *Candida* vulvovaginitis, with no association seen with age, ethnic group, income, or marital status (Table 2). Consumption of two or more servings of bread was also associated with recurrent *Candida* vulvovaginitis, whereas use of oral contraceptives or antibiotics in the past month, smoking or allergy history, and increased milk intake were not. Women with a history of more than one yeast infection in the past year were more likely to have recurrences, but a past history of bacterial vaginosis was not associated with recurrences.

Sexual risk factors associated with recurrences included having received cunnilingus or having masturbated with saliva in the past month, whereas age at first intercourse, lifetime number of partners, duration of current relationship, and frequency of intercourse or anal intercourse in the past month were not associated.

TABLE 1. ASSOCIATION BETWEEN RECURRENT *CANDIDA* VULVOVAGINITIS AND MICROBIOLOGICAL FINDINGS OF MALE SEXUAL PARTNER AT ENROLLMENT

Findings	*Recurred (%)*[a]	*Hazard ratio (95% CI)*[b]	p *value*[b]
Candida species[c] on tongue		0.74 (0.32, 1.74)	0.50
Yes (n = 36)	25.0		
No (n = 41)	31.7		
Candida species[c] in rectum		1.12 (0.48, 2.65)	0.79
Yes (n = 34)	32.4		
No (n = 40)	25.0		
Candida species[c] in urine		Not calculable	0.55
Yes (n = 3)	0.0		
No (n = 74)	29.7		
Candida species[c] in semen		0.71 (0.10, 5.34)	0.74
Yes (n = 6)	33.3		
No (n = 70)	31.4		

[a]Percent with recurrences within 1 year, regardless of time from enrollment to recurrence.
[b]From univariate Cox regression.
[c]Results were similar when limited to *Candida albicans* species at each site.

Table 2. Association of Recurrent *Candida* Vulvovaginitis with Female Characteristics (Univariate Analysis)

Characteristic	*Recurred (%)*[a]	*Hazard ratio (95% CI)*[b]	p *value*[b]
Education > 12 years		6.06 (1.45–25.31)	0.01
Yes (n = 110)	28.2		
No (n = 36)	5.6		
Oral contraceptive use (past month)		1.52 (0.76–3.01)	0.23
Yes (n = 51)	29.4		
No (n = 97)	18.6		
Antibiotics (past month)		0.98 (0.45–2.12)	0.96
Yes (n = 35)	25.7		
No (n = 108)	21.3		
Bread servings (more than 2 per day)		2.32 (1.15–4.66)	0.02
Yes (n = 59)	30.5		
No (n = 86)	16.3		
Candida vulvovaginitis more than once in past year		2.51 (1.19–5.30)	0.02
Yes (n = 66)	33.3		
No (n = 72)	13.9		
Candida vulvovaginitis four or more times in the past year (RCVV)		2.19 (1.07–4.49)	0.03
Yes (n = 32)	37.5		
No (n = 107)	18.7		
Cunnilingus during past month		2.90 (1.11–7.54)	0.03
Yes (n = 97)	27.8		
No (n = 43)	11.6		
Masturbation with saliva during past month		2.83 (1.29–6.23)	0.01
Yes (n = 20)	45.0		
No (n = 118)	16.9		

[a]Percent with recurrences within 1 year, regardless of time from enrollment to recurrence.
[b]From univariate Cox regression.

The associations between the risk factors identified in Table 2 with recurrent *Candida* vulvovaginitis were not significantly altered when adjusted for age, education, oral contraceptive use, or antibiotic use.

Multivariate analysis of female factors

Candidate variables considered for inclusion in the multivariate analysis of female factors included those found to be significant in the univariate analysis and those previously suggested as risks in the literature. These included age, education, ethnic group, parity, use of oral contraceptives or antibiotics in the month prior to enrollment, history of allergies, milk and bread intake, duration of the relationship, history of cunnilingus or fellatio in the previous month, or history of masturbation with saliva in the previous month.

This analysis resulted in three models that indicated similar associations with recurrent *Candida* vulvovaginitis (Table 3). Factors associated with an increased risk of recurrence were the dietary intake of two or more servings of bread per day plus either recent masturbation with saliva (Model 1) or cunnilingus (Model 2). No other variables were significant in the presence of the strong effects of these factors. Adjusting for bread consumption, cunnilingus increased the risk of recurrence by a factor of 2.94, and masturbation with saliva increased the risk by a factor of 2.66. If masturbation with saliva and cunnilingus were both included in the multivariate model, cunnilingus was no longer statistically associated with recurrent *Candida* vulvovaginitis because of the strong association between these two sexual activities (chi-square = 4.46, $p = 0.03$). However, masturbation with saliva was a relatively uncommon behavior, being reported by 14.5% of the women studied, whereas cunnilingus in the previous month was reported by 69.3%. Therefore, the absolute number of women impacted by the risk factor is greater with cunnilingus than with masturbation with saliva. Finally, in Model 3, the practice of either cunnilingus or masturbation with saliva (or both) was considered a dichotomous variable. This variable was also statistically significant and increased the risk of recurrent *Candida* vulvovaginitis by a factor of 3.43.

TABLE 3. ASSOCIATION OF RECURRENT *CANDIDA* VULVOVAGINITIS WITH FEMALE CHARACTERISTICS (MULTIVARIATE ANALYSIS)

	Adjusted hazard ratio[a] *(95% CI)*	p *value*[a]
Model 1 (n = 123)		
Recent masturbation with saliva	2.66 (1.17, 6.06)	0.02
Two or more bread servings per day	2.11 (1.00, 4.46)	0.05
Model 2 (n = 125)		
Recent cunnilingus	2.94 (1.12, 7.68)	0.03
Two or more bread servings per day	2.40 (1.18, 4.96)	0.02
Model 3 (n = 123)		
Either masturbation with saliva or recent cunnilingus	3.43 (1.20, 9.82)	0.02
Two or more bread servings per day	2.41 (1.18, 4.93)	0.02

[a]From multivariate Cox regression.

Although masturbation with saliva was found to be associated with recurrences, our previous study of factors associated with the occurrence of *Candida* vulvovaginitis at enrollment suggested that masturbating with saliva was protective.[8] In our previous report, masturbation with saliva was more prevalent among controls than among cases, indicating a protective association among these control women. However, only the cases from that cross-sectional report were evaluated for recurrences in the prospective analysis reported here. Therefore, using our previous data at enrollment, we duplicated the assessment of the risk of recurrent *Candida* vulvovaginitis, among cases only, by using the history of *Candida* vulvovaginitis in the previous year as a surrogate for recurrent *Candida* vulvovaginitis. Masturbation with saliva was found to be associated with having had *Candida* vulvovaginitis in the previous year among those with this infection at enrollment, similar to that seen in the prospective recurrence analysis reported here.

Male factors

Cox regression was used to assess the univariate associations between recurrent *Candida* vulvovaginitis during the 1-year follow-up and characteristics of the male partner. A younger age at first intercourse for the male partner was associated with recurrences (HR = 7.30 (0.98–54.39), $p = 0.05$), and the male reporting masturbation with saliva in the past month was associated with recurrence at marginal significance (HR = 2.38 (0.87–6.53), $p = 0.09$). No association was noted between recurrences and the partner's age, education, marital status, history of allergies or smoking, recent use of antibiotics, number of lifetime partners, previous partners with *Candida* vulvovaginitis, personal history of yeast infections, or reported fellatio or cunnilingus in the previous month.

Multivariate analysis of male factors

Factors assessed in the multivariate analysis of male factors included demographic variables, factors suggested as risk factors for the female, and sexual variables. These included male age, marital status, antibiotics in the previous month, history of allergies, history of yeast infections or partners with yeast infections, age at first intercourse, length of current relationship, and frequencies of recent sexual activities (intercourse, cunnilingus, fellatio, masturbation with saliva). Two male risk factors identified in the univariate analysis (younger age at first intercourse and recent masturbation with saliva) continued to be associated with recurrences in the multivariate analysis (Table 4).

Multivariate assessment of combined female and male factors

The combination of the female risk factors plus the male risk factors was assessed using Cox regression. When male factors were combined with the first model of the female risk factors identified in Table 3, histories of masturbation with saliva in the past month by either the female or the male were associated with recurrences, as was a lower age of first intercourse for the male partner (Table 5). Bread intake was no longer significantly associated. Conversely, when combined with the second model including cunnilingus instead of female masturbation with saliva in the

Table 4. Association of Recurrent *Candida* Vulvovaginitis with Partner Characteristics (Multivariate Analysis) (n = 72)

Characteristic	*Adjusted hazard ratio (95% CI)*[a]	p *value*[a]
Masturbation with saliva by the male partner	3.68 (1.24, 10.87)	0.02
Male age at first intercourse	0.83 (0.71, 0.96)	0.01

[a]From multivariate Cox regression.

model, the male factors persisted (history of masturbation with saliva and lower age at first intercourse), as did increased bread intake, but cunnilingus was no longer associated with risk ($p = 0.44$). The variable combining the history of either masturbation with saliva or recent cunnilingus (Model 3) did not add to the combined model. Hence, when this was used, the final model included only the two male factors (masturbation with saliva and age at first intercourse) and the bread intake variable of the woman (not shown).

We did not include the number of past episodes of *Candida* vulvovaginitis in the multivariate analysis until after all models were evaluated because we postulated that the factors identified in the analysis would be contributing to the history of recurrences and, hence, would not be independent. After the analysis was completed, we entered the variable denoting whether the patient had had four or more episodes of *Candida* vulvovaginitis in the past year into each of the models in Table 5. In each case, the model remained very similar to that seen without the recurrent *Candida* vulvovaginitis factor, and in neither case was the recurrent *Candida* vulvovaginitis variable statistically associated with a recurrent infection, suggesting the risk seen with previous infections may be, in part, explained by the variables in Table 5. Similarly, we evaluated the final models assessing factors associated with a recurrence within 4 months after the enrollment episode (rather than the full 1 year). The models in Table 5 remained unchanged, with all factors except the bread intake variable remaining statistically associated with the recurrence at $p \leq 0.01$.

DISCUSSION

The role of the male partner in conferring risk of recurrent *Candida* vulvovaginitis to his female companion has been of great interest to researchers, clinicians, and patients.[12,13] Women[14,15] and their partners[13] often carry yeast in the genital area, the rectum, and the oral cavity and are likely to share the same strain of *Candida* species at these sites.[6,7] It has been suggested that the presence of *Candida* in the male oral cavity causes reinfection of the female partner during oral sex, but treating the male partner with antimycotics has given inconsistent results.[16,17] Hence, whether transfer of the organism from the male or female oral cavity (or other sites) to the vaginal area predisposes the woman to symptomatic recurrences remains unclear.

The results reported here confirm that *Candida*

Table 5. Association of Recurrent *Candida* Vulvovaginitis with Female and Male Partner Characteristics (Multivariate Analysis) (n = 68)

Characteristic	*Adjusted hazard ratio*[a] *(95% CI)*	p *value*[a]
Using Model 1 of female factors		
Masturbation with saliva by woman	6.08 (2.10–17.65)	0.001
Masturbation with saliva by male partner	5.64 (1.72–18.50)	0.02
Male age at first intercourse	0.83 (0.71–0.96)	0.01
Using Model 2 of female factors		
Masturbation with saliva by male partner	3.40 (1.15–10.01)	0.03
Two or more bread servings per day	2.82 (1.08–7.41)	0.03
Male age at first intercourse	0.82 (0.70, 0.96)	0.01

[a]From multivariate Cox regression.

species are often carried by the woman and by her male sexual partner in the rectum or oral cavity or both, and, occasionally, in the male urine and semen, but this carriage is not associated with recurrences. The HR of recurrence when *Candida* was cultured on the tongue of the male was estimated to be 0.74 (95% CI 0.32–1.74) times the hazard when no *Candida* was present. Even an HR of 1.74 (the upper limit of the CI) would be considered a relatively low risk and would explain only a small proportion of the recurrences seen.

In addition, the presence of *Candida* species in the vagina of a woman with a history of *Candida* vulvovaginitis, as seen in roughly one quarter of participants at the 2-week and 1-month follow-up visits, was not associated with symptomatic recurrences. This lack of association remained when controlled for sexual activities that might be associated with organism transmission, such as masturbation with saliva (of the male or female), anal intercourse, and oral sex (cunnilingus or fellatio).

Self-collection of specimens by the male partner was used to maximize partner participation by decreasing the time demands, discomfort, and embarrassment that might occur if an office visit were required for participation. The techniques for collection were straightforward, and participants knew to refrigerate the specimens if a delay of greater than 4 hours for delivery to us was anticipated. Previous studies, primarily conducted in women, indicate that self-collection is well accepted by patients (compared with physician collection)[18–21] and that results from self-collected genitourinary samples have been comparable to those from physician-collected samples.[21,22]

Strong associations between recurrent *Candida* vulvovaginitis and sexual behaviors of both the woman and her partner were identified, including masturbation with saliva by either partner, cunnilingus, and early age of first intercourse by the male partner. Previous studies have demonstrated an association between cunnilingus and both *Candida* vulvovaginitis[8] and recurrent *Candida* vulvovaginitis.[9] The mechanism by which this might occur, however, has not been addressed. These data confirm the association between oral sex and recurrences but clarify that *Candida* in the male oral cavity does not explain the association.

If the association between orogenital contact and recurrent *Candida* vulvovaginitis is not mediated by transmission of the organism, how might increased risk be conferred? Previous study of the immunopathogenesis of recurrent *Candida* vulvovaginitis suggests that a delicate equilibrium exists among *C. albicans*, vaginal bacterial flora, and vaginal defense mechanisms, and that changes in the host environment promote the transformation of *C. albicans* from a saprophytic to a pathogenic existence.[23] We suggest that the effects of genital washing with saliva—from either the male or the female—might upset this balance, either by upsetting the normal surface environment by saliva or by microtrauma mechanisms or by the introduction of immunological elements, stimulants, or modifiers that cause an altered environment that promotes the development of symptomatic recurrent *Candida* vulvovaginitis. Such physical and immunological effects of genital grooming have been noted in animals.[24]

Similarly, the mechanism by which a younger age at first intercourse for the male partner is associated with risk of recurrent *Candida* vulvovaginitis for the woman is not clear. Previous studies, however, have suggested that for a given patient, age at first intercourse is associated with risk of recurrent *Candida* vulvovaginitis[9] and with risk of STDs.[25–27] One might speculate that early exposure to foreign antigens (pathological and nonpathological) may have a long-term effect on the immune system, which might in turn affect immune components in saliva. Further study is needed to clarify this association.

Masturbation with saliva was found to be a risk for recurrences in this study, even after controlling for previous episodes of *Candida* vulvovaginitis. This finding differs from our previous case-control study on the occurrence (not recurrence) of *Candida* vulvovaginitis, in which this activity was found to be protective.[8] Our analysis suggests that women not at high risk for *Candida* vulvovaginitis, such as the controls who had not had *Candida* vulvovaginitis in the past year, are able to masturbate with saliva without increasing their risk of *Candida* vulvovaginitis, whereas those with a recent history of *Candida* vulvovaginitis increase the probability of recurrence with this activity.

The role of diet in recurrent *Candida* vulvovaginitis remains controversial. In this study, the history of increased bread ingestion was statistically associated with recurrences in the multivariate assessment of female risk factors and in two of the combined male/female multivariate

models. Our previous research on these women indicated that less milk ingestion was associated with the occurrence of *Candida* vulvovaginitis, with bread ingestion not being significantly associated.[8] Other studies on the association between diet and *Candida* vulvovaginitis or recurrent *Candida* vulvovaginitis have been inconsistent. Some suggested a greater risk associated with increased dairy products, artificial sweeteners, and sucrose ingestion,[4] whereas others suggested high carbohydrate intake alone as a risk[28] or that high fiber, carbohydrates, and increased total calories might increase the risk.[29] This study implicates increased bread ingestion as a risk for recurrent *Candida* vulvovaginitis but clarifies that this does not act via an increased probability of yeast being carried in other body sites prior to the recurrence.

Limitations of this study exist. We were able to assess only those women who returned for evaluation during the year of follow-up. Furthermore, only 39% of the women returned for at least four follow-up visits as planned. In addition, only a subset (50%) of the male partners submitted their questionnaires and specimens, thereby limiting the power to assess factors in the combined male/female analysis that may have a smaller association with recurrences. Male specimens were self-collected, and, hence, handling of the samples may have varied, despite simple collection requirements. Furthermore, the patient recall of sexual activities practiced in the previous month may be inaccurate, as evidenced by the disparity in the reported frequency of activities between the women and their partners. However, there is no reason to expect this inaccuracy was more likely in those with recurrences than in those without. Thus, any bias would be expected to be nondifferential.

CONCLUSIONS

In summary, recurrent *Candida* vulvovaginitis caused by *C. albicans* was found to be unrelated to the presence of *Candida* in various body sites of the female or her male partner prior to the recurrence. Even *Candida* carriage in the vagina failed to predict subsequent symptomatic *Candida* vulvovaginitis. Sexual risk factors for recurrent *Candida* vulvovaginitis were, however, identified: the female masturbating with saliva or cunnilingus from her partner and the male masturbating with saliva or having had a younger age at first intercourse. Similar risks were found when recurrences within 4 months were used as the outcome variable and when the models were controlled for whether the women had had four or more episodes of *Candida* vulvovaginitis in the year prior to enrollment. The risks identified may be related to immune characteristics of the women and their partners. Further evaluation of the association among recurrent *Candida* vulvovaginitis, sexual activities, and immune characteristics of women and their partners is warranted.

ACKNOWLEDGMENTS

We greatly appreciate the contributions of Susan Countryman for project management and of Robin Williams, Beth Duncan, and Jill Bowdler for manuscript preparation.

REFERENCES

1. Berg AO, Heidrich FE, Fihn SD, et al. Establishing the cause of genitourinary symptoms in women in a family practice. Comparison of clinical examination and comprehensive microbiology. JAMA 1984;251:620.
2. Hurley R. Inveterate vaginal thrush. Practitioner 1975; 215:753.
3. Reed BD. Risk factors for *Candida* vulvovaginitis. Obstet Gynecol Surv 1992;47:551.
4. Horowitz BJ, Edelstein SW, Lippman L. Sugar chromatography studies in recurrent *Candida* vulvovaginitis. J Reprod Med 1984;29:441.
5. Ryan CA, Courtois BN, Hawes SE, Stevens CE, Eschenbach DA, Holmes KK. Risk assessment, symptoms, and signs as predictors of vulvovaginal and cervical infections in an urban US STD clinic: Implications for use of STD algorithms. Sex Transm Infect 1998;74(Suppl 1):S59.
6. Schmid J, Rotman M, Reed B, Pierson CL, Soll DR. Genetic similarity of *Candida albicans* strains from vaginitis patients and their partners. J Clin Microbiol 1993;31:39.
7. Lockhart SR, Reed BD, Pierson CL, Soll DR. Most frequent scenario for recurrent *Candida* vaginitis is strain maintenance with "substrain shuffling": Demonstration by sequential DNA fingerprinting with probes Ca3, C1, and CARE2. J Clin Microbiol 1996;34:767.
8. Reed BD, Gorenflo DW, Gillespie BW, Pierson CL, Zazove P. Sexual behaviors as risk factors for *Candida* vulvovaginitis. J Wom Health Gender-Based Med 2000;9:645.

9. Hellberg D, Zdolsek B, Nilsson S, Mardh PA. Sexual behavior of women with repeated episodes of vulvovaginal candidiasis. Eur J Epidemiol 1995;11:575.
10. Horowitz BJ, Edelstein SW, Lippman L. Sexual transmission of *Candida*. Obstet Gynecol 1987;69:883.
11. Foxman B. The epidemiology of vulvovaginal candidiasis: Risk factors. Am J Public Health 1990;80:329.
12. Witkin SS. Immunology of recurrent vaginitis. Am J Reprod Immunol Microbiol 1987;15:34.
13. Spinillo A, Carratta L, Pizzoli G, et al. Recurrent vaginal candidiasis. Results of a cohort study of sexual transmission and intestinal reservoir. J Reprod Med 1992;37:343.
14. Hilton AL, Warnock DW. Vaginal candidiasis and the role of the digestive tract as a source of infection. Br J Obstet Gynaecol 1975;82:922.
15. Sobel JD. Pathogenesis and epidemiology of vulvovaginal candidiasis. Ann NY Acad Sci 1988;544:547.
16. Buch A, Christensen ES. Treatment of vaginal candidosis with natamycin and effect of treating the partner at the same time. Acta Obstet Gynecol Scand 1982;61:393.
17. Bisschop MP, Merkus JM, Scheygrond H, van Cutsem J. Co-treatment of the male partner in vaginal candidosis: A double-blind randomized control study. Br J Obstet Gynaecol 1986;93:79.
18. Holland-Hall CM, Wiesenfeld HC, Murray PJ. Self-collected vaginal swabs for the detection of multiple sexually transmitted infections in adolescent girls. J Pediatr Adolesc Gynecol 2002;15:307.
19. Verhoeven V, Avonts D, Van Royen P, Denekens J. Self-collection of vaginal swab specimens: The patient's perception. Sex Transm Dis 2002;29:426.
20. Wiesenfeld HC, Lowry DL, Heine RP, et al. Self-collection of vaginal swabs for the detection of *Chlamydia*, gonorrhea, and trichomoniasis: Opportunity to encourage sexually transmitted disease testing among adolescents. Sex Transm Dis 2001;28:321.
21. Torok PG, Dunn JR. Self-collection of antepartum anogenital group B streptococcus cultures. J Am Board Fam Pract 2000;13:107.
22. Polaneczky M, Quigley C, Pollock L, Dulko D, Witkin SS. Use of self-collected vaginal specimens for detection of *Chlamydia trachomatis* infection. Obstet Gynecol 1998;91:375.
23. Fidel PL Jr, Sobel JD. Immunopathogenesis of recurrent vulvovaginal candidiasis. Clin Microbiol Rev 1996;9:335.
24. Hart BL, Korinek E, Brennan P. Postcopulatory genital grooming in male rats: Prevention of sexually transmitted infections. Physiol Behav 1987;41:321.
25. Ford K, Norris AE. Sexually transmitted diseases: Experience and risk factors among urban, low income, African American and Hispanic youth. Ethnicity Health 1996;1:175.
26. Miller HG, Cain VS, Rogers SM, Gribble JN, Turner CF. Correlates of sexually transmitted bacterial infections among U.S. women in 1995. Fam Plann Perspect 1999;31:4, 23.
27. Greenberg J, Magder L, Aral S. Age at first coitus. A marker for risky sexual behavior in women. Sex Transm Dis 1992;19:331.
28. Samaranayake LP, MacFarlane TW. The effect of dietary carbohydrates on the *in vitro* adhesion of *Candida albicans* to epithelial cells. J Med Microbiol 1982; 15:511.
29. Reed BD, Slattery ML, French TK. The association between dietary intake and reported history of *Candida* vulvovaginitis. J Fam Pract 1989;29:509.

Address reprint requests to:
Barbara D. Reed, M.D., M.S.P.H.
University of Michigan
1018 Fuller Street
Ann Arbor, MI 48109-0708

E-mail: barbr@umich.edu