Published in final edited form as:
J Urol. 2010 August ; 184(2): 564–569. doi:10.1016/j.juro.2010.03.139.

Family History and Risk of Recurrent Cystitis and Pyelonephritis in Women

Delia Scholes[*], **Thomas R. Hawn**, **Pacita L. Roberts**, **Sue S. Li**, **Ann E. Stapleton**, **Lue-Ping Zhao**, **Walter E. Stamm**[†], and **Thomas M. Hooton**
Group Health Research Institute, Group Health Cooperative (DS), Department of Medicine, University of Washington (TRH, PLR, AES, WES), Division of Public Health Sciences, Fred Hutchinson Cancer Research Center (SSL, LZ), Seattle, Washington, and Miller School of Medicine, University of Miami, Miami, Florida (TMH)

Abstract

Purpose—Recurrent urinary tract infections and pyelonephritis have risk factors suggesting genetic sources. Family history variables indicative of genetic risk merit further investigation. We evaluated the risk of recurrent cystitis and pyelonephritis in women with and those without a family history of urinary tract infection.

Materials and Methods—We conducted a population based case-control study of 1,261 women 18 to 49 years old enrolled in a Northwest health plan. Participants were cases identified from plan databases with documented recurrent cystitis (431) or pyelonephritis (400). Shared controls (430) were similar age women with no urinary tract infection history. We evaluated the history of urinary tract infection and pyelonephritis in first-degree female relatives (mother, sister[s], daughter[s]) and other covariates, ascertained through questionnaires and computerized databases.

Results—Of the cases 70.9% with recurrent cystitis and 75.2% with pyelonephritis, and of the controls 42.4% reported a urinary tract infection history in 1 or more female relative ($p < 0.001$ for each case group vs controls). In both case groups odds ratios were significantly increased for women reporting a urinary tract infection history in their mother, sister(s) or daughter(s). Risk increased with a greater number of affected relatives. In women with 1 vs 2 or more relatives the ORs for recurrent cystitis were 3.1 (95% CI 2.1, 4.7) and 5.0 (3.1, 8.1), and the ORs for pyelonephritis were 3.3 (2.2, 5.0) and 5.5 (3.4, 9.0), respectively.

Conclusions—In these community dwelling women a urinary tract infection history in female relatives was strongly and consistently associated with urinary tract infection recurrence and pyelonephritis. Risk estimates increased with stronger family history indices, suggesting a genetic component for increased susceptibility to these infections.

Keywords

urinary tract infections; epidemiology; pyelonephritis; female; case-control studies

[†]Supported by Grant 2 P01 DK053369-11 from the National Institute of Diabetes and Digestive and Kidney Diseases, and Specialized Centers of Research Grant 5 P50 DK064540-08 from the National Institute of Diabetes and Digestive and Kidney Diseases and the Office of Research on Women's Health, National Institutes of Health.

[*]Correspondence and requests for reprints: Group Health Research Institute, Group Health Cooperative, 1730 Minor Ave., Suite 1600, Seattle, Washington 98101 (telephone: 206-287-2888; FAX: 206-287-2871; scholes.d@ghc.org).

Study received Group Health Human Subjects Committee approval.

Nothing to disclose.

Acute uncomplicated UTIs are a major source of morbidity and medical costs for premenopausal women. Young adult women experience approximately 0.5 to 0.7 episodes per woman per year1 and an estimated 60% of women experience a UTI at some point.2 A subset of these women have frequent recurrent infections.3,4 Pyelonephritis, the less common but more severe upper urinary tract infection, accounts for nearly 200,000 hospitalizations annually.5,6 In otherwise healthy premenopausal women behavioral host factors such as sexual and contraceptive practices are strongly associated with recurrent cystitis and pyelonephritis.1,2,7–9 However, substantial proportions of these women do not have strong behavioral risk factors.

Numerous studies now provide evidence that host genetics also influence susceptibility to infection. 10–12 For UTIs a few studies report that women with recurrent UTIs or pyelonephritis have stronger family histories of UTI compared to other women.7,8,13 However, more detailed evaluation is needed of family history patterns such as number and type of UTIs as well as risk of infection with increasing numbers of affected family members, particularly with the benefit of a control group. This study was performed to more fully characterize and to quantify the role of family history as a risk factor for the occurrence of UTIs. Specifically we evaluated UTI histories in first-degree female relatives as risk factors for recurrent cystitis and pyelonephritis in a population based case-control study of 1,261 adult women.

MATERIALS AND METHODS

Study Setting and Participants

This study was conducted at Group Health Cooperative, a mixed model health care organization headquartered in Seattle, Washington. During study enrollment (March 2004 to December 2007) approximately 135,000 women enrollees were 18 to 49 years old, the target age group. The Group Health Human Subjects Committee approved all study protocols. Participants provided written informed consent.

To select potential recurrent cystitis and pyelonephritis case subjects we used the health plan computerized databases. Using the enrollment, inpatient, ambulatory care, laboratory and pharmacy databases we created a UTI registry for the most recent 5-year period, identifying all age eligible women with at least 12-month enrollment who lived within the Group Health research clinic catchment area. Potential rUTI case subjects were identified based on 3 or more diagnosed cystitis episodes (ICD-9 codes 595.0, 595.9, 597.81, 599.0 with episodes separated by 30 days or more) within a 12-month period or 2 episodes within 6 months.7 Culture confirmation (10^3 cfu/ml or more of a urinary pathogen) or UTI guideline related treatment was required for all UTI episodes in the cluster.14 Potential pyelonephritis subjects were identified through having received a diagnosis of acute pyelonephritis (ICD-9 codes 590.1, 590.10, 590.3, 590.8, 590.80, 590.81). If they received only outpatient treatment an accompanying culture result of 10^3 cfu/ml or more of a uropathogen or antibiotic therapy appropriate for pyelonephritis was required. Uropathogens were the same as for earlier studies.8,15 During the sampling the case participants were assigned a reference date (first rUTI or pyelonephritis episode in the registry) subject to change based on participant study interview information.

The remainder of the women in the 5-year registry constituted the potential controls. Control women were selected randomly, frequency matching by case age group (age 18 to 29, 30 to 39, 40 to 49 years). Potential control participants also had some type of health care use during the registry interval. Control women were randomly assigned a reference date based on the reference dates from the completed cases in their age group. We updated the registry

at approximately 6-month intervals, adding new cases and new enrollees, and removing women already sampled. At each update the registry contained data for the most recent 5 years.

Potential case and control participants were selected from the registry at approximately monthly intervals. Potential participants were sent a letter of invitation with telephone followup beginning 1 week later to ascertain eligibility and willingness to participate. Recruitment protocols required calling potential participants 12 or more times at different times of day on weekdays and weekends. Exclusion criteria were kept to a minimum. Potential participants were excluded from study if they could not urinate on their own or were not ambulatory. Potential rUTI cases or controls who reported diagnoses of pyelonephritis or kidney infections were enrolled in the pyelonephritis case group. We excluded potential controls from study who reported any other UTI diagnoses. Women who were willing to participate were scheduled for a clinic visit. The appointment materials asked women to discuss UTI histories with available female relatives before the visit.

The final study group consisted of 1,261 participants, including 431 rUTI and 400 pyelonephritis case women, and 430 control women. Of 877 potential rUTI participants 431 (59%) were found to be eligible and willing to participate, and completed clinic appointments, 144 were ineligible, 256 declined and 46 could not be reached. Of 673 potential pyelonephritis participants 400 (69%) identified as eligible completed appointments, 89 were ineligible, 155 declined and 29 could not be reached. Of 1,923 potential control women selected 430 (47%) completed appointments, 999 were ineligible largely due to having a cystitis history, 440 declined and 54 could not be reached.

Data Collection

Participants visited the Seattle Group Health Research Clinic and completed 2 study questionnaires. Survey 1 was self-administered, and included items on demographics, medical history, family and personal history of genitourinary infections, and behavioral risk factors. This survey also ascertained the history of UTI in first-degree female relatives (mother, sister[s], daughter[s]). Participants were asked about bladder and/or kidney infections, and the number of such infections in each relative. Survey 2 was an in-person interview focused on events near the reference date, and included questions about risk factors (sexual behaviors, spermicidal products, incontinence) within 6 months and 30 days of the reference date. A life events calendar was used to help with recall.16,17 Participants also were asked if they had queried female relatives about UTI histories. Participants were reimbursed $100.

Statistical Analysis

The 2 case groups and the control group were characterized with regard to demographics and other variables of interest. For each case group we examined associations with behavioral and demographic risk factors using contingency table analysis and logistic regression to compute ORs and 95% CIs. UTI history in first-degree female relatives was evaluated in greater detail by examining a history of any UTI, multiple UTIs and pyelonephritis. To enhance recall validity and address possible differential recall by cases and controls we also evaluated mother and daughter UTI histories in the subgroup of women who reported asking their relatives about these exposures. Subsequently among women providing complete data for all relatives we calculated a variable for total number of UTI affected first-degree female relatives. Conditional logistic regression was used to calculate age adjusted risk estimates for women with 1, or 2 or more affected relatives, stratifying by the number and type of female relatives. Lastly we examined the joint association of family history and behavioral exposures by looking at strata of UTI history in a relative (none vs

any relative) and intercourse frequency 30 days before the reference date (less than 3 vs 3 or more episodes per week). All analyses were performed using SAS®.

RESULTS

Women in the 2 case groups were similar to controls with respect to age and race/ethnicity. Case women were less likely to be currently married, and more likely to have smoked and to have a pregnancy history than control women. Pyelonephritis cases also reported less education and income than controls, and were more likely to report fair or poor health.18

Many of the previously identified risk factors for these 2 outcomes were confirmed in this study sample (table 1). A history of sexual intercourse, frequency of intercourse episodes and new sex partner close to the reference date, and multiple partners increased risk for both outcomes. Odds ratios ranged from approximately 1.5 to 6.0. A chlamydia/sexually transmitted disease history also significantly increased risk. Generally associations with sexual and contraceptive behavior were stronger for rUTI than for pyelonephritis. Pyelonephritis risk was significantly increased for 2 or more births, incontinence and chronic diseases.

A UTI history in a first-degree female relative also revealed strong associations for both case groups (table 2). For participants whose mother had any UTI history (cystitis and/or pyelonephritis) the OR for rUTI was 2.5 (95% CI 1.9, 3.4) relative to controls, and for pyelonephritis the OR was 3.3 (95% CI 2.4, 4.5). Risk also was significantly increased when sisters or daughters were affected, with ORs ranging from 2.6 to 4.1. Generally we also observed increased risk when a first-degree relative had frequent UTIs (5 or more) or a pyelonephritis history (table 2).

A total of 983 participants (77%, 80% and 77% of rUTI cases, pyelonephritis cases and controls, respectively) reported ascertaining UTI history in their first-degree relatives. In this subgroup the associations between study outcomes and UTI in first-degree relatives, although generally somewhat lower, remained significantly increased for all but 1 of the significant associations (pyelonephritis history and risk of rUTI) reported for the overall study group in table 2.

Risk of rUTI as well as pyelonephritis increased with increasing numbers of affected first-degree relatives. In those women with no missing information on UTI history in any of their relatives (838, 66%) the age adjusted risks for rUTI with 1 and 2 or more affected relatives were OR 3.1 (95% CI 2.1, 4.7) and OR 5.0 (95% CI 3.1, 8.1), respectively. For pyelonephritis the risks were OR 3.3 (95% CI 2.2, 5.0) and OR 5.5 (95% CI 3.4, 9.0), respectively.

We also examined risks associated with family history of UTI (no affected relatives vs any) in strata of a strongly associated behavioral variable, the frequency of intercourse within 30 days of the reference date (less than 3 vs 3 or more times per week). Using the referent category of no affected relatives/less frequent intercourse we observed significantly increased risks in the intermediate strata (ORs ranging from 2.1 to 3.7). In the stratum positive for family history/more frequent intercourse risk estimates were notably higher (OR 12.6; 95% CI 6.8, 23.3 for rUTI and OR 9.6; 95% CI 5.1, 18.0 for pyelonephritis).

DISCUSSION

In this sizeable population based study of community dwelling women we examined risk factors for recurrent cystitis and pyelonephritis using a shared control group with no UTI history. UTI histories in first-degree female relatives were strong and consistent risk factors

for both conditions. We noted substantially increased risk for each type of relative and higher risk with greater numbers of infections. We also observed higher risk for both conditions with greater numbers of affected relatives. Evaluation of family UTI history in conjunction with a strong behavioral risk factor, intercourse frequency, showed that risk in women with combined exposures was considerably higher than with either exposure category alone.

These results build on several earlier studies. Hopkins et al found that 65.5% of mothers, 61% of daughters and 49% of sisters of 41 adult women with rUTI had similar recurrence histories.13 In our prior case-control study of rUTI in 482 young adult women 18 to 30 years old we noted a 2.3-fold increased risk with a history of UTI in subjects' mothers.7 A family study of children prone to pyelonephritis revealed that 15% of 130 relatives of case children but only 3% of 101 relatives of controls had a UTI history ($p < 0.002$).19 Our previous population based case-control study of risk factors for pyelonephritis in 788 adult women revealed increased risks for women with affected mothers, sisters or daughters.8

These familial variables likely reflect complex, multifocal genetic impacts on host defenses that may differ for rUTI vs pyelonephritis.13,20,21 Murine models of UTI indicate that increased host susceptibility to bladder and kidney infections is a complex, multigenic process involving several pathways. 20,22,23 These pathways include initial recognition of Escherichia coli by innate immune receptors on hematopoietic and uroepithelial cells, recruitment of neutrophils to the bladder, and later effects of T cells and B cells. In human populations previous studies of genetics and infectious disease susceptibility suggest a role for genetic factors but few diseases with complex inheritance patterns have been examined in detail. In considering UTI pathogenesis several studies have suggested the ABH blood group nonsecretor status may increase the risk of rUTI in some women22,24–27 but this association has been inconsistent.

In a family study of children prone to pyelonephritis expression of CXCR1 (interleukin-8 receptor) was significantly lower in case patients and their family members compared to age matched controls.19 Two polymorphisms in the CXCR1 gene that may predispose to pyelonephritis by disarming neutrophil dependent host response to UTI were identified.28 Toll-like receptors also appear relevant to UTI risk in mouse and human studies. TLR2 and TLR4 polymorphisms have been associated with susceptibility to UTIs in children,29,30 and we found associations of TLR1, TLR4 and TLR5 with UTI susceptibility in adults.18 Ongoing work in these areas of inquiry is likely to yield more specific and/or stronger genetic associations with host immune response to common UTI pathogens.

Our study had several limitations. As our participants were asked to remember some information around a reference date that was sometimes years past, there is the potential for recall bias. However, the distribution of reference dates was similar for cases and controls, and we used a life events calendar to assist with recall.16,17 Our family history information, the focus of these analyses, did not rely on the reference date. Our data on family history of UTI relied on participant self-report and case women may have better recall of relatives' histories than controls. However, the proportion of missing data was less for controls than cases. In addition, in the subgroup who reported ascertaining UTI history in their female relatives all risk estimates except 1 remained strongly and significantly associated. We also had more difficulty enrolling eligible control participants (response rates of 59% to 69% for cases vs 47% for controls). We still enrolled similar age groups, thus allowing similar opportunity for the exposures to occur. In addition, prior UTI history was the major reason for control ineligibility and many of those included in the response rate denominator as refusal/unable to locate were likely negligible. If we apply the proportion of control women

ineligible due to prior UTI from our completed and ineligible groups (41%) to our refusal/unable to locate groups our control response rate is 60%.

The current study also has a number of strengths. The study group size and the data collection focus allowed us to evaluate risks associated with family UTI history in greater detail than reports to date, including intensity of UTI history and familial factors in conjunction with behavioral variables. The use of a shared control group allowed us to efficiently evaluate risks for 2 related conditions. The inclusion of a comparison group drawn from the same defined population also reduced the potential biases of hospital or clinic based controls.

CONCLUSIONS

Studies of host related risk factors for cystitis and related outcomes have focused largely on behavioral and acquired factors. Our results suggest that a range of family UTI history exposures also increases predisposition to rUTI and pyelonephritis in women, that the risk increases with the intensity of these exposures, and that the risk from common behavioral exposures may be increased if women have a family UTI history. These findings, in conjunction with efforts to identify causal genetic variants, can further illuminate steps in pathogenesis as well as inform counseling, prevention and management strategies for these common conditions.

Acknowledgments

Patricia Yarbro assisted with study protocols and project management; Jane Grafton, study programming; Kelli O'Hara, Holly Roberts and Linda Wehnes, study recruitment and data collection; Yin Yang and Hongwei Wang, data management and analyses; and Cate Coughlin, manuscript preparation.

Abbreviations and Acronyms

rUTI	recurrent cystitis
TLR	toll-like receptor
UTI	urinary tract infection

REFERENCES

1. Hooton TM, Scholes D, Hughes JP, et al. Prospective study of risk factors for symptomatic urinary tract infection in young women. N Engl J Med. 1996; 335:468. [PubMed: 8672152]
2. Brown PD, Foxman B. Pathogenesis of urinary tract infection: the role of sexual behavior and sexual transmission. Curr Infect Dis Rep. 2000; 2:513. [PubMed: 11095901]
3. Foxman B, Chi J. Health behavior and urinary tract infection in college-aged women. J Clin Epidemiol. 1990; 43:329. [PubMed: 2324774]
4. Ikaheimo R, Siitonen A, Heiskanen T, et al. Recurrence of urinary tract infection in a primary care setting: analysis of a 1-year follow-up of 179 women. Clin Infect Dis. 1996; 22:91. [PubMed: 8824972]
5. Foxman B, Klemstine KL, Brown PD. Acute pyelonephritis in US hospitals in 1997: hospitalization and in-hospital mortality. Ann Epidemiol. 2003; 13:144. [PubMed: 12559674]
6. Hooton T, Stamm W. Diagnosis and treatment of uncomplicated urinary tract infection. Infect Dis Clin North Am. 1997; 11:551. [PubMed: 9378923]
7. Scholes D, Hooton TM, Roberts PL, et al. Risk factors for recurrent urinary tract infection in young women. J Infect Dis. 2000; 182:1177. [PubMed: 10979915]
8. Scholes D, Hooton TM, Roberts PL, et al. Risk factors associated with acute pyelonephritis in healthy women. Ann Intern Med. 2005; 142:20. [PubMed: 15630106]

9. Strom BL, Collins M, West SL, et al. Sexual activity, contraceptive use, and other risk factors for symptomatic and asymptomatic bacteriuria. A case-control study. Ann Intern Med. 1987; 107:816. [PubMed: 3688674]
10. Cooke GS, Hill AV. Genetics of susceptibility to human infectious disease. Nat Rev Genet. 2001; 2:967. [PubMed: 11733749]
11. Casanova JL, Abel L. Genetic dissection of immunity to mycobacteria: the human model. Annu Rev Immunol. 2002; 20:581. [PubMed: 11861613]
12. Hill AV. The genomics and genetics of human infectious disease susceptibility. Annu Rev Genomics Hum Genet. 2001; 2:373. [PubMed: 11701655]
13. Hopkins WJ, Uehling DT, Wargowski DS. Evaluation of a familial predisposition to recurrent urinary tract infections in women. Am J Med Genet. 1999; 83:422. [PubMed: 10232756]
14. Saint S, Scholes D, Fihn SD, et al. The effectiveness of a clinical practice guideline for the management of presumed uncomplicated urinary tract infection in women. Am J Med. 1999; 106:636. [PubMed: 10378621]
15. Rubin RH, Shapiro ED, Andriole VT, et al. Evaluation of new anti-infective drugs for the treatment of urinary tract infection. Infectious Diseases Society of America and the Food and Drug Administration. Clin Infect Dis. 1992; 15:S216. [PubMed: 1477233]
16. Armstrong, BK.; White, E.; Saracci, R. Principles of Exposure Measurement in Epidemiology. New York: Oxford University Press; 1992.
17. Marcus AC. Memory aids in longitudinal health surveys: results from a field experiment. Am J Public Health. 1982; 72:567. [PubMed: 7072873]
18. Hawn TR, Scholes D, Li SS, et al. Toll-like receptor polymorphisms and susceptibility to urinary tract infections in adult women. PLoS One. 2009; 4:e5990. [PubMed: 19543401]
19. Lundstedt AC, Leijonhufvud I, Ragnarsdottir B, et al. Inherited susceptibility to acute pyelonephritis: a family study of urinary tract infection. J Infect Dis. 2007; 195:1227. [PubMed: 17357062]
20. Hopkins WJ, Elkahwaji JE, Heisey DM, et al. Inheritance of susceptibility to induced Escherichia coli bladder and kidney infections in female C3H/HeJ mice. J Infect Dis. 2003; 187:418. [PubMed: 12552425]
21. Finer G, Landau D. Pathogenesis of urinary tract infections with normal female anatomy. Lancet Infect Dis. 2004; 4:631. [PubMed: 15451491]
22. Hopkins WJ, Heisey DM, Lorentzen DF, et al. A comparative study of major histocompatibility complex and red blood cell antigen phenotypes as risk factors for recurrent urinary tract infections in women. J Infect Dis. 1998; 177:1296. [PubMed: 9593015]
23. Frendeus B, Godaly G, Hang L, et al. Interleukin 8 receptor deficiency confers susceptibility to acute experimental pyelonephritis and may have a human counterpart. J Exp Med. 2000; 192:881. [PubMed: 10993918]
24. Tomisawa S, Kogure T, Kuroume T, et al. P blood group and proneness to urinary tract infection in Japanese children. Scand J Infect Dis. 1989; 21:403. [PubMed: 2587941]
25. Sheinfeld J, Schaeffer A, Cordon-Cardo C, et al. Association of the Lewis blood-group phenotype with recurrent urinary tract infections in women. N Engl J Med. 1989; 320:773. [PubMed: 2922027]
26. Ishitoya S, Yamamoto S, Mitsumori K, et al. Nonsecretor status is associated with female acute uncomplicated pyelonephritis. BJU Int. 2002; 89:851. [PubMed: 12010227]
27. Kinane DF, Blackwell CC, Brettle RP, et al. ABO blood group, secretor state, and susceptibility to recurrent urinary tract infection in women. Br Med J (Clin Res Ed). 1982; 285:7.
28. Lundstedt AC, McCarthy S, Gustafsson MC, et al. A genetic basis of susceptibility to acute pyelonephritis. PLoS One. 2007; 2:e825. [PubMed: 17786197]
29. Tabel Y, Berdeli A, Mir S. Association of TLR2 gene Arg753Gln polymorphism with urinary tract infection in children. Int J Immunogenet. 2007; 34:399. [PubMed: 18001294]
30. Karoly E, Fekete A, Banki NF, et al. Heat shock protein 72 (HSPA1B) gene polymorphism and Toll-like receptor (TLR) 4 mutation are associated with increased risk of urinary tract infection in children. Pediatr Res. 2007; 61:371. [PubMed: 17314700]

J Urol. Author manuscript; available in PMC 2013 May 28.

Table 1

Association of selected behavioral and other variables with recurrent cystitis and pyelonephritis

	No. rUTI Cases (%)	No. Pyelonephritis Cases (%)	No. All Controls (%)	rUTI OR (95% CI)	rUTI p Value	Pyelonephritis OR (95% CI)	Pyelonephritis p Value
Not married at enrollment *	226 (52.4)	221 (55.3)	199 (46.4)	1.3 (0.97, 1.7)	0.08	1.4 (1.1, 1.9)	0.01
Parity:					0.25		0.02
1 (vs 0)	80 (18.6)	62 (15.5)	63 (14.7)	1.4 (0.94, 2.0)		1.3 (0.85, 1.9)	
2 or More (vs 0)	133 (30.9)	156 (39.0)	130 (30.9)	1.1 (0.82, 1.5)		1.6 (1.1, 2.1)	
Sexual intercourse:							
Ever	427 (99.8)	390 (98.0)	400 (93.9)	27.8 (3.8, 205.5)	<0.001	3.2 (1.4, 7.1)	0.003
6 Mos before reference date †	390 (90.9)	306 (79.7)	280 (65.7)	5.2 (3.6, 7.7)	<0.001	2.1 (1.5, 2.8)	<0.001
30 Days before reference date							
Any to less than 3 episodes/wk (vs 0)	165 (45.0)	122 (37.1)	165 (39.5)	3.2 (2.2, 4.6)	<0.001	1.4 (1.0, 2.0)	<0.001
3 or More episodes/wk (vs 0)	146 (39.8)	114 (34.7)	75 (17.9)	6.2 (4.1, 9.3)		2.9 (2.0, 4.3)	
More than 5 lifetime sex partners	255 (60.9)	227 (59.4)	190 (49.7)	1.6 (1.2, 2.1)	0.002	1.5 (1.1, 2.0)	0.007
New partner 6 mos before reference date	147 (34.3)	105 (27.4)	70 (16.4)	2.7 (1.9, 3.7)	<0.001	1.9 (1.4, 2.7)	<0.001
Any spermicide use 6 mos before reference date †	113 (27.1)	58 (15.5)	46 (11.2)	3.0 (2.0, 4.3)	<0.001	1.5 (0.96, 2.2)	0.08
Diabetes	8 (1.9)	23 (5.8)	10 (2.3)	0.79 (0.31, 2.0)	0.63	2.6 (1.2, 5.5)	0.01
Difficulty holding urine 6 mos before reference date:							
Any (stress, urge, neither)	103 (24.1)	116 (30.9)	80 (18.8)	1.4 (0.99, 1.9)	0.06	1.9 (1.4, 2.7)	<0.001
Stress	81 (19.2)	91 (24.6)	64 (15.2)	1.3 (0.92, 1.9)	0.13	1.8 (1.3, 2.6)	<0.001
Urge	54 (12.8)	68 (18.5)	31 (7.3)	1.9 (1.2, 3.0)	0.01	2.9 (1.8, 4.6)	<0.001
Chlamydia infection	48 (11.3)	48 (12.2)	26 (6.1)	2.0 (1.1, 3.2)	0.01	2.1 (1.3, 3.5)	0.002
Other sexually transmitted disease ‡	98 (22.8)	85 (21.4)	45 (10.5)	2.5 (1.7, 3.7)	<0.001	2.3 (1.6, 3.4)	<0.001
Hypertension	28 (6.5)	54 (13.5)	35 (8.1)	0.78 (0.47, 1.3)	0.36	1.8 (1.1, 2.8)	0.01

Data were missing in less than 1% to 6% of subjects for most variables with the exception of data for sexual intercourse 30 days before reference date, which were missing for 12% of subjects.

* Includes never married, widowed, separated, divorced and living as married.

† Reference date is date of first UTI for case women and randomly assigned date for control women.

‡ Includes trichomonas, gonorrhea, herpes or genital warts. No participants reported HIV positivity.

Table 2

History of UTI in first-degree female relatives, and associations with recurrent cystitis and pyelonephritis

	% rUTI Cases	% Pyelonephritis Cases	% Controls	rUTI OR (95% CI)	rUTI p Value	Pyelonephritis OR (95% CI)	Pyelonephritis p Value
History of UTI in mother:							
Any UTI *	55.3	61.9	32.9	2.5 (1.9, 3.4)	<0.001	3.3 (2.4, 4.5)	<0.001
5 or More UTIs *	26.5	26.7	11.0	2.9 (1.9, 4.4)	<0.001	3.0 (2.0, 4.5)	<0.001
Pyelonephritis	9.4	20.7	5.1	2.0 (1.1, 3.6)	0.03	4.9 (2.8, 8.5)	<0.001
History of UTI in sister (in 875 subjects with sister[s]):							
Any UTI *	68.1	64.3	34.0	4.1 (2.8, 6.0)	<0.001	3.5 (2.4, 5.1)	<0.001
5 or More UTIs *	26.4	28.0	7.3	4.6 (2.6, 8.1)	<0.001	5.0 (2.8, 8.7)	<0.001
Pyelonephritis	13.6	21.3	6.1	2.4 (1.3, 4.6)	0.006	4.2 (2.3, 7.7)	<0.001
History of UTI in daughter (in 439 subjects with daughter[s]):							
Any UTI *	34.0	36.2	16.4	2.6 (1.5, 4.7)	<0.001	2.9 (1.6, 5.1)	<0.001
5 or More UTIs *	9.7	3.3	1.5	7.1 (1.6, 31.9)	0.01	2.2 (0.43, 11.8)	0.33
Pyelonephritis	3.5	9.3	3.0	1.2 (0.31, 4.5)	0.81	3.3 (1.1, 10.3)	0.03

Ascertainment was most complete in daughters' history variables (2% to 3% missing) and least complete in mothers' history variables (14% to 22% missing). Ascertainment for sisters (17% to 20% missing) was similar to that of mothers.

* Includes cystitis and pyelonephritis.