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Factors associated with developing vaginal dryness symptoms in women transitioning through menopause: a longitudinal study

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Abstract

Objective: To evaluate factors associated with incident self-reported vaginal dryness and the consequences of this symptom across the menopausal transition in a multiracial/ethnic cohort of community-dwelling women.

Methods: We analyzed questionnaire and biomarker data from baseline and 13 approximately annual visits over 17 years (1996-2013) from 2,435 participants in the Study of Women's Health Across the Nation, a prospective cohort study. We used discrete-time Cox proportional-hazards regression to identify predictors of incident vaginal dryness and to evaluate vaginal dryness as a predictor of pain during intercourse and changes in sexual intercourse frequency.

Results: The prevalence of vaginal dryness increased from 19.4% among all women at baseline (ages 42-53 years) to 34.0% at the 13th visit (ages 57-69 years). Advancing menopausal stage, surgical menopause, anxiety, and being married were positively associated with developing vaginal dryness, regardless of partnered sexual activity. For women not using hormone therapy, higher concurrent levels of endogenous estradiol were inversely associated (multivariable-adjusted hazard ratio: 0.94 per 0.5 standard deviation increase, 95% confidence interval: 0.91-0.98). Concurrent testosterone levels, concurrent dehydroepiandrosterone sulfate levels, and longitudinal change in any reproductive hormone were not associated with developing vaginal dryness. Both vaginal dryness and lubricant use were associated with subsequent reporting of pain during intercourse, but not with a decline in intercourse frequency.

Conclusion: In these longitudinal analyses, our data support many clinical observations about the relationship between vaginal dryness, menopause, and pain during intercourse, and suggest that reporting of vaginal dryness is not related to androgen level or sexual intercourse frequency.

Key Words: Dyspareunia – Menopause – Sexual function – Vaginal dryness.

Vaginal dryness, a symptom of the genitourinary syndrome of menopause, increases with age, and advancing menopausal stage.[1,2] Vaginal dryness may be caused by reduced secretory function of the vaginal epithelium, which is associated with decreased vaginal blood flow, mucosal thinning, microbiome changes, and inflammation.[3,4] Women may report vaginal dryness as irritation, itching, or burning outside of sexual activities. Most women experience vaginal dryness a perceived reduction in lubrication during sexual activity. Vaginal dryness can lead to painful sex, low libido, and decreased sexual satisfaction.[5]

The menopause transition (MT) is an important time in genital tract aging. The cyclical, higher levels of estradiol (E2) of premenopause change to widely varying levels in perimenopause and to the more consistent, lower levels in postmenopause. In cross-sectional studies, low E2 levels and a decline in E2 are associated with a higher prevalence of vaginal dryness symptoms.[6] However, the longitudinal

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relationships between MT stages, reproductive hormone changes, the development of vaginal dryness, and this symptom's potential sexual consequences have not been well studied.

Our primary objective was to evaluate longitudinally, from pre- to postmenopause, factors associated with the development and consequences of reported vaginal dryness in a racially and ethnically diverse cohort of community-dwelling women enrolled in the Study of Women's Health Across the Nation (SWAN). We hypothesized that MT stage, lower serum levels of and a decline in E2, and psychosocial factors would be associated with incident vaginal dryness which would then precede new onset pain during intercourse and reduced sexual intercourse frequency.

METHODS

Study participants

This was a longitudinal analysis of an approximately annual questionnaire and biomarker data with repeated measures over 17 years (1996-2013) in SWAN, a multicenter, multiracial/ethnic cohort study of the MT.[7] The study began with a cross-sectional survey of 16,065 community-dwelling midlife women recruited by random–digit-dialing and/or list-based sampling. From this group, each of seven clinical sites recruited approximately 450 women for the prospective cohort study (3,302 women). Inclusion criteria for the cohort were (1) age 42 to 52 years and (2) self-identification of race or ethnicity as African-American (Detroit, MI; Chicago, IL; Pittsburgh, PA; and Boston, MA sites); Hispanic (Newark, NJ site), Japanese (Los Angeles, CA site), Chinese (Oakland, CA site), or white (all sites). Exclusion criteria were (1) inability to speak English, Spanish, Japanese, or Cantonese; (2) no menstrual period within 3 months before enrollment; (3) hysterectomy and/or bilateral oophorectomy before onset of study; (4) using any reproductive hormone therapy (HT) at enrollment; or (5) pregnant or lactating. All women consented for participation in SWAN, and the institutional review boards at each site approved the study.

Of the 3,302 enrolled participants at baseline, 24 were missing data on the frequency of vaginal dryness at baseline, and four reported use of antineoplastic medication which are known to cause vaginal dryness. We included the remaining 3,274 women in analyses of reported frequency of vaginal dryness at baseline. For our longitudinal analyses, we excluded 637 women who reported vaginal dryness at baseline, five women who initiated use of antineoplastic during follow-up, and 197 with no follow-up data, leaving a longitudinal analytic sample of 2,435 participants.

Measures

At baseline and at each of the 13 approximately annual follow-up visits, a self-administered questionnaire elicited recall of vaginal dryness frequency over the past 2 weeks on a five-point scale (responses were ''not at all,'' ''1-5 days,'' ''6-8 days,'' ''9-13 days,'' ''everyday''). Because frequency of vaginal dryness is not an indicator of perceived symptom severity, and may simply reflect frequency of sexual activity over the previous 2 weeks, we collapsed responses to this question into a dichotomous variable: any reported vaginal dryness (1 day to every day) versus none (not at all). We defined incident vaginal dryness as a new report of any vaginal dryness in women who had not previously reported this symptom. At baseline and annual follow-up visits 1 through 6, 8, 10, and 12, women were asked about frequency of lubricant use ''During the past 6 months how often have you used lubricants, such as creams or jellies, to make sex more comfortable?'' and pain during intercourse ''During the past 6 months, have you felt vaginal or pelvic pain during intercourse?'' Response options for both questions were ''never,'' ''almost never,'' ''sometimes'' ''almost always'' ''always.'' We defined sexually active as vaginal sexual activity with a partner for women who reported frequency of intercourse as ''once or twice a month,'' ''about once per week,'' ''more than once per week,'' or ''daily'' or reported any lubricant use or pain during intercourse. We categorized sexual frequency as ''less than monthly'' for women who answered ''none'' to frequency of intercourse but reported at least sometimes to lubricant use or pain during intercourse. Gender of sexual partners was assessed at baseline only.

SWAN annual serum measures of E2 (through visit 13), testosterone (T) and dehydroepiandrosterone sulfate (DHEAS) (through visit 10) were drawn in days 2 to 5 of the menstrual cycle for pre- and perimenopausal women and at any time for postmenopausal women. All endocrine assays were performed on the Automated Chemiluminesence System (ACS)-180 analyzer (Bayer Diagnostics Corporation, Tarrytown, NY) using a double-antibody chemiluminescent immunoassay with a solid phase anti-IgG immunoglobulin conjugated to paramagnetic particles, antiligand antibody, and competitive ligand labeled with dimethyl acridinium ester.[8] The E2 assay modified the rabbit anti-E2-6 ACS-180 immunoassay to increase sensitivity, with a lower limit of detection of 1.0 pg/mL. Duplicate E2 assays were conducted with results reported as the arithmetic mean for each participant, with a coefficient of variation of 3% to 12%. All other assays were single determinations. The T assay modified the rabbit polyclonal antitestosterone ACS-180 immunoassay. The DHEAS and sex hormone binding globulin assays were developed on site using rabbit anti-DHEAS and antisex hormone binding globulin antibodies.

SWAN classified menopausal status from menstrual bleeding patterns as: premenopausal—less than 3 months of amenorrhea and no menstrual irregularities in the previous year, early perimenopausal—less than 3 months of amenorrhea and some menstrual irregularities in the previous year, late perimenopausal—3 to 11 months of amenorrhea, and postmenopausal—at least 12 consecutive months of amenorrhea. Postmenopausal status was further subdivided by users and nonusers of exogenous systemic menopausal HT. Additional categories included unknown menopause status due to concurrent exogenous HT in women who were not known to be

postmenopausal and hysterectomy with and without bilateral oophorectomy (BSO), each subdivided by concurrent use of exogenous HT.

We calculated body mass index (BMI) as weight in kilograms/height in meters^2 based on measurements taken annually by certified staff using calibrated scales and stadiometers. At each visit, interviewers obtained smoking history[9] and medication use. In annual self-report questionnaires, information was elicited about general health, depressive symptoms,[10] and anxiety symptoms.[11]

Statistical analyses

We estimated the prevalence of any reported vaginal dryness in the past 2 weeks as a function of years before/after the final menstrual period in the subset of 1,593 women (19,119 observations) with the final menstrual period observed before initiation of HT, hysterectomy, or BSO. To allow for maximum flexibility in this trajectory, we used nonparametric locally weighted scatterplot smoothing.[12] We compared baseline demographic and sexual activity characteristics with any report of vaginal dryness in the past 2 weeks using analysis of variance or chi-square testing.

To identify predictors of incident vaginal dryness, we used discrete-time Cox proportional-hazards regression[13] to accommodate the approximately annual nature of longitudinal data collection. Analyses were conducted on three separate analytic samples. In our first analysis, we included all visits and all covariates except exogenous HT use and characteristics relevant only for visits when women reported sexual activity. Second, we estimated associations between reported vaginal dryness and endogenous hormones, restricting the analytic sample to visits with no exogenous HT use at the current or prior visit. Third, we analyzed associations with characteristics relevant only for sexually active women, restricting the analytic sample to visits with partnered vaginal sexual activity. All analyses omitted observations occurring on or after initiation of antineoplastic or fertility medications, and observations with concurrent pregnancy or lactation due to small numbers in these groups. We estimated unadjusted associations by including each covariate separately, and also assessed adjusted associations in a multivariate model using backward elimination ($P < 0.05$) to omit irrelevant predictors. We estimated separate models for each reproductive hormone due to collinearity of hormones. To allow the associations with incident vaginal dryness to vary by partner status, we tested the interaction of each covariate with partner status.

Because vaginal lubricants and vaginal estrogen are used frequently to manage vaginal dryness symptoms, and their use could alter the reporting of vaginal dryness symptoms, we ran sensitivity analyses including any lubricant or vaginal estrogen use as indicators of vaginal dryness. In addition, we compared analyses with and without imputation/interpolation of missing variables. In both cases, results were similar (data not shown); so, we have only shown those without imputation.

Since vaginal dryness, pain during intercourse, and decreasing intercourse frequency are clinically and behaviorally intertwined, we performed two additional analyses to investigate these relationships. First, we used discrete-time Cox regression to estimate hazard ratios (HRs) for reporting any incident pain during intercourse in relation to vaginal dryness alone, lubricant use alone, and vaginal dryness and lubricant use together as independent variables among the 1,551 sexually active women who reported no pain during intercourse at baseline. We also conducted binomial logistic regression[14] to examine whether reporting of vaginal dryness alone, lubricant use alone, or vaginal dryness and lubricant use together had preceded a decline in intercourse frequency among 2,551 sexually active women at two consecutive visits. All models included age, race/ethnicity, SWAN study site, and time-varying putative factors related to outcomes with a P value less than 0.05, including BMI, menopausal status, and HT use, as well as time-varying sexual activity factors. For all analyses, we selected covariates a priori based on the literature.[1,2,15] We used backward elimination ($P < 0.05$) to omit irrelevant or redundant predictors and selected our final models based on the Akaike Information Criterion for model fit.[16] All analyses were performed in SAS v9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Descriptive findings

Baseline characteristics of women who reported any versus no vaginal dryness in the previous 2 weeks are presented in Table 1. At baseline, when all participants were pre- or early perimenopausal, 13.1% of women who were not sexually active and 21.5% of sexually active women (19.6% of all women) recalled vaginal dryness occurring at least 1 day in the previous 2 weeks. Over the 17 years of SWAN, 1,470 women (60%) who had not reported vaginal dryness at baseline, reported vaginal dryness at least one study visit. By the end of the study period (visit 13) when 97% of participants were known to be postmenopausal (ages 57-69 years), 25.3% of women who were not sexually active and 47.0% of sexually active women (34.0% of all women) reported vaginal dryness. Vaginal dryness increased in prevalence as the MT progressed, with the most rapid rise around the final menstrual period (Fig. 1). None of the 44 women who reported generally having sex with a woman at the baseline assessment reported vaginal dryness during follow-up. Any lubricant use, measured among sexually active women only, also increased between baseline (25.2%) and visit 13 (63.5%), and frequent lubricant use (almost always/always) increased from 7.5% to 39.9%. For women who generally reported having sex with women, the median percent lubricant use for all visits was 9%. Women reported using vaginal estrogen infrequently over the 17 years, from 0% at baseline to 3.5% (5.9% for women engaged and 1.9% for women not engaged in sexual activity) at visit 13.

Unadjusted findings

In unadjusted analyses (Table 2), the HR of incident vaginal dryness increased through the MT, beginning in early perimenopause for both sexually active and sexually inactive women. Having a BSO (with or without HT) increased the HR

TABLE 1. *Study of Women's Health Across the Nation baseline characteristics by vaginal dryness frequency in past 2 weeks (1996-2013)*

Characteristic at baseline	% (N) or Mean (SD) None (N = 2,637)	Any (N = 637)	*P*
Partnered sexual activity in past 6 months	74.8 (1,925)	84.4 (528)	<0.0001
Married/living as married	64.5 (1,670)	73.3 (462)	<0.0001
Menopausal status			<0.0001
Premenopausal	55.9 (1,456)	46.4 (292)	
Early perimenopausal	44.1 (1,147)	53.6 (337)	
Age, y	46.3 (2.7)	46.5 (2.8)	0.104
Race/ethnicity			<0.0001
White	47.1 (1,241)	47.3 (301)	
African American	28.3 (746)	26.8 (171)	
Chinese	7.8 (205)	7.1 (45)	
Hispanic	7.5 (197)	13.8 (88)	
Japanese	9.4 (248)	5.0 (32)	
Current smoking	17.3 (453)	17.4 (110)	0.953
BMI, kg/m^2			0.856
<25	40.4 (1,051)	40.1 (252)	
25-29.9	26.9 (699)	26.1 (164)	
30+	32.8 (853)	33.9 (213)	
Self-reported health			0.001
Excellent	22.4 (581)	17.2 (108)	
Very good	37.0 (958)	33.8 (212)	
Good	28.3 (733)	32.6 (205)	
Fair/poor	12.4 (321)	16.4 (103)	
CES-D ≥16	22.4 (590)	31.5 (200)	<0.0001
Anxiety score ≥ 4	20.1 (524)	33.6 (212)	<0.0001
Symptom sensitivity score	10.1 (3.6)	10.5 (3.5)	0.043
Frequency of intercourse[a]			0.070
<Monthly	0.7 (13)	1.2 (6)	
1-2 Times/month	35.7 (678)	30.7 (160)	
At least weekly	63.7 (1,210)	68.1 (355)	
Frequency of pain with intercourse[a]			<0.0001
Never	61.7 (1,180)	13.3 (181)	
Almost never	22.2 (425)	23.7 (124)	
Sometimes	14.7 (281)	36.1 (189)	
Almost always	1.2 (22)	4.0 (21)	
Always	0.3 (5)	1.7 (9)	
Frequency of lubricant use[a]			<0.0001
Never	82.3 (1,576)	47.2 (248)	
Almost never	7.0 (133)	10.7 (56)	
Sometimes	6.7 (129)	21.9 (115)	
Almost always	2.0 (38)	11.8 (62)	
Always	2.0 (39)	8.6 (45)	

P values are from X^2 and *t* tests.
BMI, body mass index; CES-D, Center for Epidemiological Studies Depression Scale.
[a]Participants with partnered sexual activity in past 6 months only.

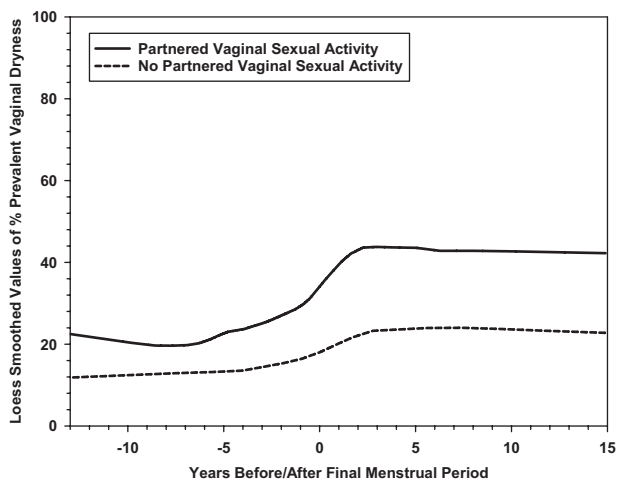

FIG. 1. LOESS plot of prevalence of any vaginal dryness in the prior 2 weeks in an 18-year period bracketing the final menstrual period. Figure represents 1,593 women (19,119 observations) with the final menstrual period observed before initiation of HT, hysterectomy, or bilateral oophorectomy. HT, hormone therapy; LOESS, locally weighted scatterplot smoothing.

significantly for women who were not sexually active. Compared with white women, Hispanic women had a higher HR of reporting vaginal dryness, regardless of sexual activity and adjustment for diabetes (data not shown). African Americans were more likely than white women to report onset of this symptom when not sexually active (*P* value for interaction of race/ethnicity with sexual activity: 0.03). Fair to poor health and depressive and anxiety symptoms were also positively associated with reporting incident vaginal dryness, regardless of sexual activity status. Concurrent higher E2 level was associated with a lower probability of incident vaginal dryness in sexually active women, whereas absolute T and DHEAS levels and change in E2, T, and DHEAS levels were not associated with vaginal dryness. For women engaged in sexual activity, more frequent use of sexual lubricants and more frequent pain during intercourse at both the prior and concurrent visit were associated with a higher HR of incident vaginal dryness.

Multivariable results

In adjusted analyses, we examined the relations between selected covariates and incident vaginal dryness in three

TABLE 2. *Unadjusted associations[a] with incidence of any vaginal dryness in Study of Women's Health Across the Nation by sexual activity with a partner status (1996-2013)*

	Not sexually active		Sexually active with partner		
Characteristic	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*	*P* value for interaction with sexual activity
Concurrent partnered sexual activity	Reference		1.87 (1.63, 2.15)		<0.001
Concurrent menopausal status/HT use		0.005		<0.001	0.163
Premenopausal	Reference		Reference		
Early perimenopausal	2.78 (1.49, 5.17)		1.60 (1.25, 2.05)		
Late perimenopausal	3.50 (1.73, 7.09)		3.16 (2.34, 4.27)		
Postmenopausal	4.25 (2.23, 8.12)		3.56 (2.64, 4.82)		
Postmenopausal-HT	2.76 (1.13, 6.72)		1.35 (0.77, 2.38)		
Bilateral salpingo-oophorectomy	3.80 (1.04, 13.87)		2.29 (0.99, 5.31)		
Bilateral salpingo-oophorectomy-HT	3.77 (1.20, 11.88)		2.12 (1.14, 3.91)		
Hysterectomy	1.82 (0.40, 8.23)		2.90 (1.63, 5.16)		
Hysterectomy-HT	3.90 (0.50, 30.28)		1.71 (0.24, 12.35)		
Not postmenopausal-HT	3.84 (1.88, 7.82)		1.79 (1.29, 2.49)		
Concurrent vaginal estrogen	6.05 (1.93, 18.99)	0.002	2.72 (1.40, 5.28)	0.003	0.270
Race/ethnicity		<0.001		0.003	0.027
White	Reference		Reference		
African American	1.41 (1.07, 1.85)		1.10 (0.93, 1.29)		
Chinese	0.94 (0.56, 1.56)		1.17 (0.93, 1.48)		
Hispanic	3.02 (2.06, 4.41)		1.69 (1.28, 2.23)		
Japanese	0.74 (0.47, 1.17)		0.94 (0.75, 1.18)		
Concurrent smoking	1.19 (0.85, 1.66)	0.309	1.01 (0.83, 1.22)	0.932	0.408
Concurrent BMI, kg/m^2		0.269		0.130	0.106
<25	Reference		Reference		
25-29.9	1.13 (0.81, 1.58)		0.85 (0.72, 1.00)		
30+	1.27 (0.95, 1.69)		0.90 (0.77, 1.06)		
Concurrent self-reported health		0.002		0.059	0.164
Excellent	Reference		Reference		
Very good	0.86 (0.57, 1.28)		1.13 (0.93, 1.36)		
Good	1.21 (0.82, 1.78)		1.18 (0.97, 1.44)		
Fair/poor	1.59 (1.05, 2.42)		1.40 (1.09, 1.78)		
Concurrent CES-D ≥16	1.81 (1.41, 2.33)	<0.001	1.29 (1.07, 1.54)	0.007	0.032
Concurrent anxiety ≥4	2.74 (2.15, 3.50)	<0.001	1.84 (1.56, 2.16)	<0.001	0.008
Symptom sensitivity per unit increase	1.03 (0.99, 1.06)	0.141	1.04 (1.02, 1.06)	<0.001	0.463
Currently married/partnered	1.29 (1.00, 1.65)	0.047	1.09 (0.92, 1.29)	0.313	0.278
Concurrent log hormones[b]					
E2	0.94 (0.88, 1.01)	0.090	0.95 (0.91, 0.99)	0.008	0.834
T	1.03 (0.95, 1.10)	0.502	1.02 (0.99, 1.07)	0.214	0.991
DHEAS	0.99 (0.93, 1.06)	0.754	0.99 (0.96, 1.03)	0.718	0.931
E2 change, before current visit[c]		0.450		0.129	0.842
Decrease	0.83 (0.58, 1.19)		0.93 (0.76, 1.13)		
Stable	Reference		Reference		
Increase	1.08 (0.73, 1.60)		1.18 (0.96, 1.46)		
T change, before current visit[c]		0.285		0.179	0.844
Decrease	1.38 (0.92, 2.06)		1.21 (0.98, 1.48)		
Stable	Reference		Reference		
Increase	1.21 (0.83, 1.76)		1.14 (0.94, 1.40)		
DHEAS change, before current visit[c]		0.910		0.643	0.964
Decrease	1.07 (0.74, 1.56)		1.04 (0.85, 1.27)		
Stable	Reference		Reference		
Increase	1.00 (0.69, 1.45)		0.95 (0.78, 1.15)		
Concurrent intercourse frequency				0.087	
<Monthly			Reference		
1-2 Times/month			0.76 (0.43, 1.36)		
≥Weekly			0.88 (0.50, 1.57)		
Concurrent lubricant use:				<0.001	
Never			Reference		
Sometimes/almost never			2.57 (2.20, 3.00)		
Always/almost always			4.18 (3.47, 5.05)		
Concurrent pain with intercourse:				<0.001	
Never			Reference		
Sometimes/almost never			2.83 (2.46, 3.25)		
Always/almost always			5.18 (3.81, 7.03)		

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TABLE 2 *(Continued)*

Characteristic	Not sexually active		Sexually active with partner		
	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*	*P* value for interaction with sexual activity
Prior-visit intercourse frequency				0.021	
None			Reference		
<Monthly			1.41 (0.64, 3.09)		
1-2 times/month			0.69 (0.51, 0.92)		
≥Weekly			0.82 (0.62, 1.08)		
Prior-visit lubricant use				<0.001	
No intercourse			1.49 (1.13, 1.96)		
Never			Reference		
Sometimes/almost never			1.59 (1.31, 1.94)		
Always/almost always			2.29 (1.74, 3.03)		
Prior-visit pain with intercourse				<0.001	
No intercourse			1.63 (1.23, 2.17)		
Never			Reference		
Sometimes/almost never			1.71 (1.46, 2.00)		
Always/almost always			2.38 (1.36, 4.14)		

A total of 2,435 participants in analytic sample: 9 excluded when initiated antineoplastic medication, 24 missing baseline vaginal dryness; 637 excluded who reported vaginal dryness at baseline, 197 dropped out after baseline.
BMI, body mass index; CES-D, Center for Epidemiological Studies Depression Scale; CI, confidence interval; DHEAS, dehydroepiandrosterone sulfate; E2, estradiol; HT, hormone therapy; T, testosterone.
[a]Models include baseline age and time since baseline.
[b]Visits with exogenous HT use excluded; hormones log-transformed; analyses with log E2 adjust for whether blood draw was in days 2 to 5 of menstrual cycle in pre- and perimenopause.
[c]Visits with concurrent or prior-visit exogenous HT use excluded; adjusted for current-visit log-transformed hormone; analyses with log E2 also adjust for blood draw in days 2 to 5 of menstrual cycle at current and prior visit in pre- and perimenopause; stable indicates change ≤0.5 SD.

TABLE 3. *Multivariable-adjusted associations with incident vaginal dryness in Study of Women's Health Across the Nation (1996-2013)*

Characteristic	Adjusted hazard ratio (95% CI)[a]	*P*
All women/all visits (N = 2,246 women/10,421 visits)		
Concurrent partnered sexual activity, stratified by concurrent anxiety[b]		
Anxiety symptom score <4	2.21 (1.81, 2.70)	<0.001
Anxiety symptom score ≥4	1.36 (1.03, 1.79)	0.029
Concurrent menopausal status/HT use		<0.0001
Premenopausal	Reference	
Early perimenopausal	1.67 (1.31, 2.13)	
Late perimenopausal	2.98 (2.21, 4.02)	
Postmenopausal	3.48 (2.57, 4.71)	
Postmenopausal-HT	1.57 (0.94, 2.61)	
Bilateral salpingo-oophorectomy	2.19 (0.99, 4.84)	
Bilateral salpingo-oophorectomy-HT	2.70 (1.56, 4.67)	
Hysterectomy	2.21 (1.19, 4.10)	
Hysterectomy-HT	2.74 (0.67, 11.20)	
Not postmenopausal, HT	2.03 (1.49, 2.77)	
Concurrent vaginal estrogen	2.97 (1.62, 5.45)	0.003
Race/ethnicity		0.101
White	Reference	
African American	1.08 (0.91, 1.29)	
Chinese	0.86 (0.64, 1.16)	
Hispanic	1.74 (1.08, 2.78)	
Japanese	1.11 (0.82, 1.51)	
Concurrent BMI, kg/m^2		0.011
<25	Reference	
25-29.9	0.82 (0.70, 0.96)	
30+	0.80 (0.68, 0.94)	
Concurrent anxiety ≥4 vs <4, stratified by concurrent partnered sexual activity[b]		
Not sexually active visit	2.56 (1.96, 3.35)	<0.001
Sexually active visit	1.57 (1.31, 1.89)	<0.001
Symptom sensitivity, 1-unit increase	1.02 (1.01, 1.04)	0.011
Currently married/partnered	1.20 (1.02, 1.40)	0.024

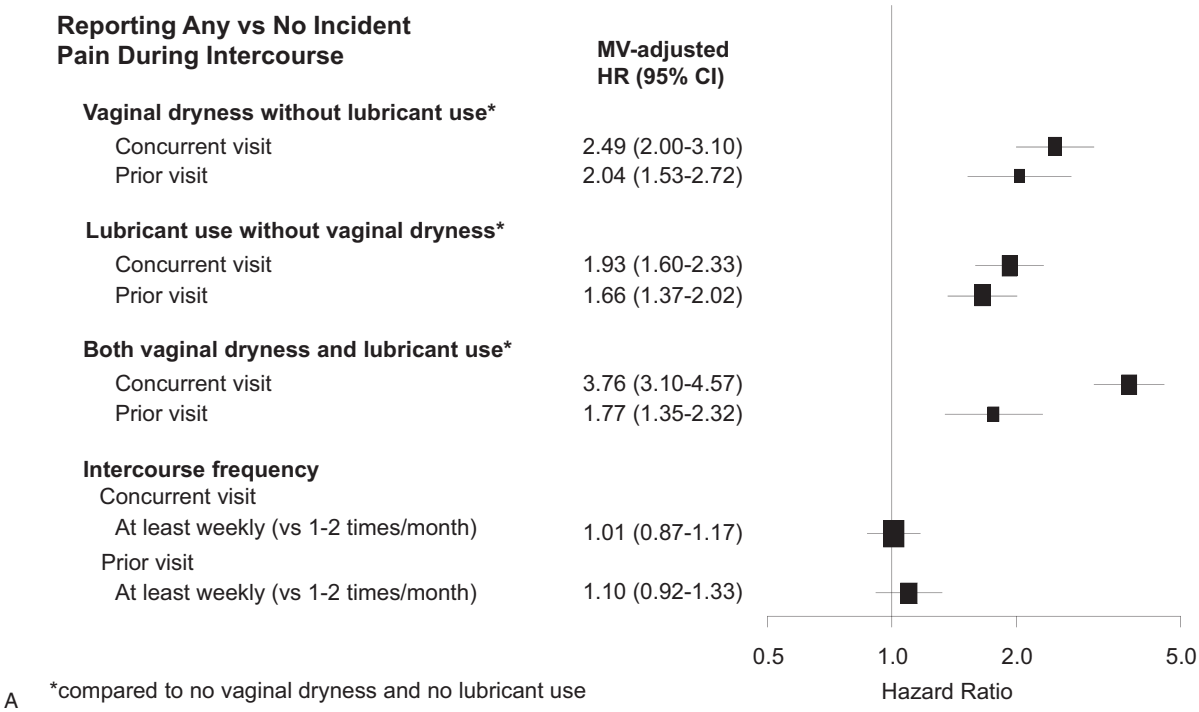
(Continued on next page)

TABLE 3 *(Continued)*

Characteristic	Adjusted hazard ratio (95% CI)[a]	*P*
Visits in which women report no hormone therapy use (N = 2,068-2,072 women/7,196-7,577 visits)		
Concurrent log hormones, 0.5 SD[c]		
E2	0.94 (0.91, 0.98)	0.002
T	1.02 (0.98, 1.05)	0.382
DHEAS	1.01 (0.98, 1.05)	0.555
E2 change, prior visit to current visit[d]		0.126
Decrease	0.89 (0.74, 1.06)	
Stable	Reference	
Increase	1.12 (0.92, 1.35)	
T change, prior visit to current visit[d]		0.134
Decrease	1.19 (0.99, 1.44)	
Stable	Reference	
Increase	1.16 (0.96, 1.40)	
DHEAS change, prior visit to current visit[d]		0.323
Decrease	1.01 (0.84, 1.21)	
Stable	Reference	
Increase	0.89 (0.75, 1.07)	
Visits in which women report partnered sexual activity[e] (N = 1,771 women/6,515 visits for concurrent-visit predictors, N = 1,745 women/5,532 visits for prior-visit predictors)		
Concurrent intercourse frequency		0.107
<Monthly	Reference	
1-2 Times/month	0.74 (0.41, 1.32)	
≥Weekly	0.86 (0.48, 1.53)	
Concurrent lubricant use		<0.001
Never	Reference	
Sometimes/almost never	2.53 (2.14, 3.00)	
Always/almost always	4.31 (3.53, 5.26)	
Concurrent pain with intercourse		<0.001
Never	Reference	
Sometimes/almost never	2.98 (2.56, 3.46)	
Always/almost always	4.68 (3.36, 6.50)	
Prior-visit intercourse frequency		0.412
None	Reference	
<Monthly	1.17 (0.46, 2.97)	
1-2 Times/month	0.81 (0.59, 1.12)	
≥Weekly	0.91 (0.67, 1.24)	
Prior-visit lubricant use		<0.001
No intercourse	1.30 (0.96, 1.76)	
Never	Reference	
Sometimes/almost never	1.64 (1.34, 2.01)	
Always/almost always	2.11 (1.58, 2.84)	
Prior-visit pain with intercourse		<0.001
No intercourse	1.44 (1.05, 1.96)	
Never	Reference	
Sometimes/almost never	1.73 (1.46, 2.04)	
Always/almost always	2.08 (1.16, 3.72)	

BMI, body mass index; DHEAS, dehydroepiandrosterone sulfate; E2, estradiol; HT, hormone therapy; T, testosterone.
[a]Also adjusted for site and baseline age.
[b]*P* value for sexual activity × anxiety = 0.003.
[c]Visits with exogenous HT use excluded; analyses with log E2 adjusted for blood draw in days 2 to 5 of menstrual cycle; adjusted for partnered sexual activity through marital status, site and baseline age.
[d]Visits with concurrent/prior-visit exogenous HT use excluded; adjusted for current-visit log-transformed hormone; analyses with log E2 adjusted for blood draw in days 2 to 5 of menstrual cycle; stable indicates change ≤0.5 SD; adjusted for partnered sexual activity through marital status, site and baseline age.
[e]Adjusted for variables menopause status through marital status, site, and baseline age.

analytic samples of SWAN women: all women eligible for this current analysis, women who did not use HT, and only women reporting sexual activity (Table 3). For all samples, advancing menopausal stage, surgical menopause, anxiety symptoms, and married status remained positively associated with developing vaginal dryness, regardless of sexual activity. Current anxiety symptoms were the only factor modified by sexual activity; the association between concurrent sexual activity and incident vaginal dryness was stronger in women with lower anxiety. Conversely current higher anxiety symptom score showed a stronger association with vaginal dryness in women reporting no sexual activity compared to sexually active women. Use of exogenous HT appeared to be associated with a smaller HR of incident vaginal dryness in women with natural postmenopausal status (covariate-adjusted $P = 0.001$ for HT), compared to women with BSO or hysterectomy (combining BSO and hysterectomy, covariate-adjusted $P = 0.49$ for HT, P value for interaction = 0.013). For women not using HT, higher levels of endogenous E2 in the concurrent visit remained inversely associated with the development of vaginal dryness in women at all menopausal stages (Table 3) and in a subanalysis of only postmenopausal



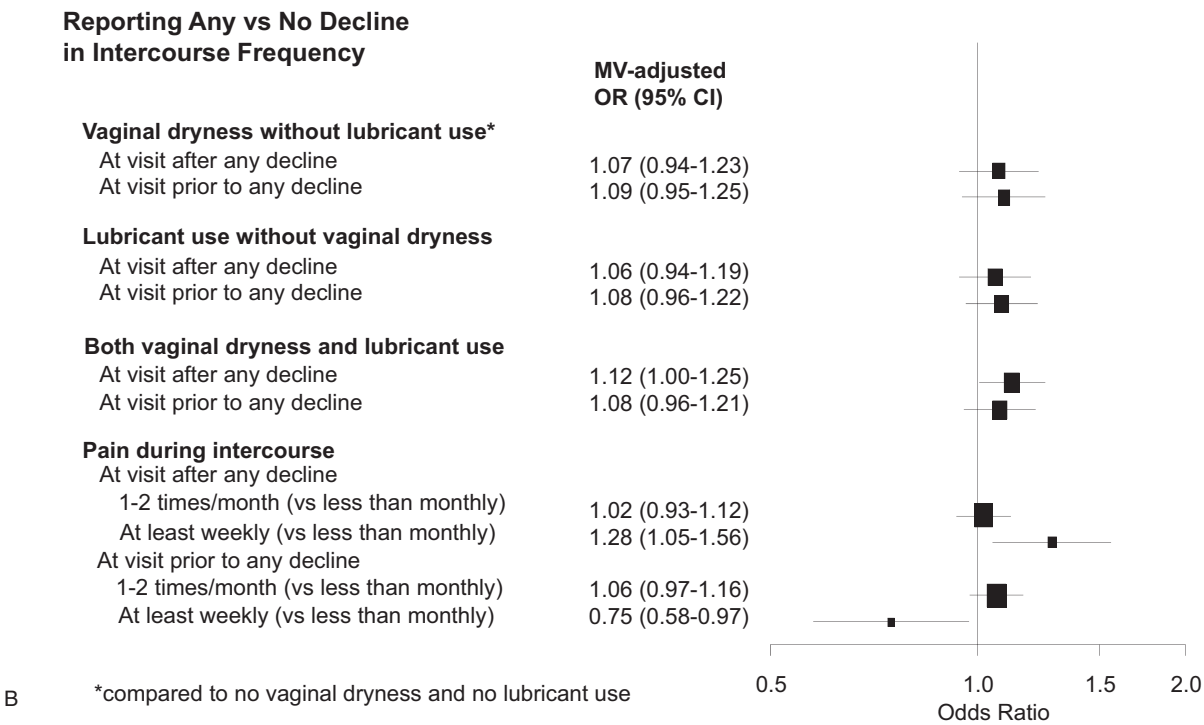


FIG. 2. A, Multivariable-adjusted hazard ratios for reporting incident pain during intercourse. Multivariable-adjusted hazard ratios for reporting incident pain during intercourse in relation to reporting of vaginal dryness alone, lubricant use alone, vaginal dryness and lubricant use together, and intercourse frequency in Study of Women's Health Across the Nation (SWAN) (1996-2013) among 1,474 women who reported having partnered sexual activity in 4,764 visits; excluding women who reported pain during intercourse at baseline and women with missing baseline partner status (and thus missing baseline pain). Models included variable of interest one at a time (eg, vaginal dryness at concurrent visit) and adjusted for age, race and ethnicity, site, menopausal status and hormone use, body mass index (BMI), anxiety (score $\geq$4), and symptom sensitivity score. Bracket size is proportional to sample size. **B**, Multivariable-adjusted odds ratio for reporting decline in intercourse frequency. Multivariable-adjusted odds ratio for reporting decline in intercourse frequency in relation to vaginal dryness, lubricant use, and pain during intercourse in SWAN (1996-2013) among 2,364 women who reported having sexual partners in 13,047 visits. Models included variables of interest one at a time (eg, vaginal dryness at concurrent visit) and adjusted for age at current visit, site, race and ethnicity, years between visits, menopausal status and hormone use, BMI, Center for Epidemiologic Studies Depression Scale (score $\geq$16), smoking, and marital status. Bracket size is proportional to sample size.

women, regardless of their BMI (data not shown). Neither concurrent T nor DHEAS levels nor change in any reproductive hormone from the prior visit predicted incident vaginal dryness. For women engaged in sexual activity, the more frequent use of lubricants or reports of pain during intercourse in the concurrent visit, the higher the HR of incident vaginal dryness, even after adjustment for other predictors. We found that HRs for developing vaginal dryness increased with higher frequency of lubricant use and pain during intercourse at the prior visit; the impact of adjustment for other predictors was minimal.

To examine the longitudinal relationship between vaginal dryness and lubricant use and the development of pain during intercourse, we used any reporting of vaginal dryness alone, lubricant use alone, and both vaginal dryness and lubricant use as independent variables among sexually active women. In women who did not report any pain during intercourse at baseline, we found that concurrent visit reporting of vaginal dryness and lubricant use were positively associated with incident pain during intercourse (Fig. 2A) regardless of age, menopausal status, BMI, and hormone use. Women who reported vaginal dryness with lubricant use together in the concurrent visit had the highest HR of reporting new onset pain during intercourse, likely representing severity of their vaginal dryness with their behavior of lubricant use to treat it. Meanwhile, developing pain with intercourse was not associated with intercourse frequency at the visit before or visit of reporting new-onset pain.

We also examined longitudinally whether reporting of vaginal dryness alone, lubricant use alone, and vaginal dryness and lubricant use together predicted a decline in intercourse frequency among women reporting sexually activity across the 13 years of follow-up. Regardless of age, menopausal status, BMI, and hormone use, only women reporting both vaginal dryness and lubricant use together had a decline in intercourse frequency from the previous visit. Interestingly, we found that at least weekly pain during intercourse was associated with an increased odds of decline in intercourse frequency from the previous visit, whereas at least weekly pain during intercourse reported before the measured change in intercourse frequency had a reduced odds of decline in intercourse frequency (Fig. 2B).

DISCUSSION

In this longitudinal study following a large multiracial and ethnic sample of community-dwelling women over 17 years across the MT, we found that, after controlling for age, advancing natural menopausal stage and surgical menopause were the factors most strongly associated with new reporting of any vaginal dryness within the previous 2 weeks. Higher concurrent endogenous levels of E2 were associated with a reduced probability of incident vaginal dryness, whereas neither concurrent endogenous T and DHEAS levels nor change in any reproductive hormone was associated with the development of this symptom.

Lower concurrent serum levels of estrogen have been associated with vaginal dryness in other studies,[15] whereas few studies have focused on the relationship between changes in serum E2 over time and incident vaginal dryness symptoms. Our somewhat surprising lack of association between declines in E2 and incident vaginal dryness could be explained by a number of factors. For example, declines between two measurements approximately 1 year apart may not represent the hormonal patterns over a longer time frame. A change in serum E2 may not correspond to changes in the hormone's effect on the vaginal epithelium. Early follicular phase pre- and peri-menopausal E2 levels may not be the best values for predicting effects on vaginal dryness. The strong association we found between incident vaginal dryness and advancing menopausal stage likely better reflects the complexity of factors involved in development of vaginal dryness, such as the psychosocial impact of menopause and variations in physiological change. Our finding that systemic HT may have differential effects on the development of vaginal dryness depending on a natural MT versus surgical menopause is novel. While we had small numbers in our surgical menopause group, other explanations include differences in type or dose of HT prescribed, different indications or timing for starting HT, or unclear biological factors.

Independent of menopausal stage and E2 level, we found several other factors associated with incident vaginal dryness, regardless of sexual activity. That Hispanic women were more likely to report incident vaginal dryness is consistent with prevalence estimates from SWAN cross-sectional reports[2,17,18] as well as other large studies.[19] In these studies, region of origin, but not primary language, immigrant status, or perceived quality of life were associated with vaginal dryness reporting.[18,19] Hispanic women have been noted to have higher reporting of vulvovaginal symptoms such as vulvodynia.[20]

We found that concurrent anxiety symptoms were independently related to the development of vaginal dryness, but there was a weaker relationship between concurrent anxiety and vaginal dryness in sexually active women compared to those who were not sexually active. Depressive symptoms have been associated with low libido, whereas anxiety symptoms have been linked to both higher subjective sexual arousal and vaginal lubrication[21] but also lower desire, emotional satisfaction, and physical pleasure.[2]

In SWAN, we were able to follow women's reporting of vaginal dryness, sexual intercourse frequency, lubricant use, and pain during intercourse longitudinally over 17 years and found bidirectional relationships. In addition to a strong co-occurrence of vaginal dryness, lubricant use, and pain during intercourse, we found vaginal dryness, lubricant use, and both vaginal dryness and lubricant use together were independently associated with the development of pain during intercourse. However, we also found that pain during intercourse preceded new reporting of vaginal dryness, suggesting that sexual pain leads to reduced vaginal lubrication during arousal. We also found that frequency of intercourse at the

prior visit, whether one to two times per month or more than weekly, was not associated with developing pain during intercourse.

Our study results should be interpreted in light of some limitations. First, without confirmation by a detailed history and physical examination, self-reported vaginal dryness is a nonspecific symptom that could represent a true reduction in vaginal fluid only or could be construed as a symptom of pathological vulvovaginal conditions. Second, our assessment of vaginal dryness asked the frequency of the symptom over the previous 2 weeks. Frequency of vaginal dryness within the previous 2 weeks is likely difficult to recall and may not reflect perceived severity because experience of the symptom may depend largely on frequency of sexual activity; for this reason, we did not analyze vaginal dryness by reported frequency and could not assess severity of the symptom. In addition, assessments of sexual intercourse, lubricant use, and pain during intercourse elicited perceived frequency over the previous 6 months, a different time frame from the vaginal dryness symptom question, and these time frame differences may lead to misclassification bias. Third, the strong association we found between vaginal dryness and lubricant use is likely because the symptom and behavior are inextricably intertwined—lubricant use may either mask awareness of or represent a response to vaginal dryness symptoms. To address this, we analyzed vaginal dryness and lubricant use alone and together as both predictors and outcomes. Fourth, we cannot assess whether participant responses to SWAN's sexual orientation-neutral sexual activity questions were influenced by a perception that they were heterosexual specific. Finally, although vaginal dryness is most often clinically associated with insertional dyspareunia, pain is not easy to localize. In this regard, our broader definition of pain during intercourse likely improves the generalizability of our results.

CONCLUSIONS

More than 50% of women with vaginal dryness do not report this symptom to their health care provider.[22] Although vaginal dryness can be treated successfully and safely in many women with vaginal estrogen tablets, creams and rings, less than 4% of SWAN participants reported using any of these medication by visit 13. In this unique longitudinal analysis, our data support many clinical observations, for example, that the incidence and prevalence of vaginal dryness, regardless of sexual activity, increased with progression through the MT and with lower E2 levels, and that reporting vaginal dryness both precedes and co-occurs with sexual intercourse pain. We also describe some new and clinically relevant findings. The development of any vaginal dryness does not appear to be related to androgen levels or sexual frequency. In sexually active women, less frequent (one to two times per month) intercourse compared to more frequent (at least weekly) intercourse does not appear to increase the risk of developing pain during intercourse. HT may be less effective in preventing the development of vaginal dryness in women after hysterectomy compared to women experiencing natural menopause.

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