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Context Postmenopausal hormone replacement therapy (HRT) use is common in the United States. Some research suggests that estrogen may have detrimental effects on the tear film and could influence the development of dry eye syndrome, but few data are available on this relationship.

Objective To determine the relationship of HRT and dry eye syndrome.

Design, Setting, and Participants The Women's Health Study, a large cohort study in which 25 665 postmenopausal women provided information about use of HRT at baseline (1992), 12, and 36 months and dry eye syndrome at 48 months.

Main Outcome Measures (1) Clinically diagnosed dry eye syndrome, as reported by participants; (2) severe symptoms (both ocular dryness and irritation either constantly or often); and (3) either clinically diagnosed dry eye syndrome or severe symptoms, compared between women who used HRT vs those who did not.

Results For the combined end point of either clinically diagnosed dry eye syndrome or severe symptoms, the multivariable-adjusted odds ratios were 1.69 (95% confidence interval [CI], 1.49-1.91) for estrogen use alone and 1.29 (95% CI, 1.13-1.48) for estrogen plus progesterone/progestin use compared with no HRT use. Each 3-year increase in the duration of HRT use was associated with a significant 15% (95% CI, 11%-19%) elevation in risk of clinically diagnosed dry eye syndrome or severe symptoms. Results were similar for the combined end point of clinically diagnosed dry eye syndrome and severe symptoms.

Conclusions These data suggest that women who use HRT, particularly estrogen alone, are at increased risk of dry eye syndrome. Physicians caring for women who are taking or considering HRT should be apprised of this potential complication.

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Dry eye syndrome, or keratoconjunctivitis sicca, damages the ocular surface and can cause debilitating symptoms of dryness and irritation, which may result in psychological comorbidity and reduced work capacity.[1-4] Dry eye syndrome is associated with an enhanced risk of corneal infection, and, when severe, can cause permanent visual impairment.[2,3] Treatments for dry eye syndrome are generally costly and inadequate, and many patients are unable to find satisfactory relief from their symptoms.[5] Finally, dry eye syndrome accounts for a substantial burden on the health care system,[5] comprising one of the leading causes of patient visits to both ophthalmologists and optometrists.[2]

Hormone replacement therapy (HRT) is used by an estimated 38% of postmenopausal women in the United States.[6] It has been shown to have a clear role in the treatment of a variety of menopausal symptoms,[7] and may confer other health benefits.[8-11] However, some deleterious effects of HRT are increasingly recognized,[12-14] and estrogen may have adverse effects on the ocular surface.[15-17] Despite this, virtually no data are available on the relationship of HRT and dry eye syndrome. Therefore, we examined this relationship in the Women's Health Study.

METHODS

Study Subjects

The Women's Health Study is a randomized trial among 39 876 health professionals (aged 45 to 84 years in 1992) to assess the benefits and risks of aspirin and vitamin E in the prevention of cardiovascular disease and cancer.[18] Women were also initially randomized to beta carotene, but this component of the trial was terminated after an average treatment time of 22.8 months. To be eligible for the Women's Health Study, women must have been postmenopausal or have no intention of becoming pregnant. At baseline, all participants were free of cancer (except possibly nonmelanoma skin cancer), myocardial infarction, stroke, transient cerebral ischemia, liver disease, renal disease, peptic ulcer, or gout. Women using anticoagulants, corticosteroids, or supplements of vitamins A, E, or beta carotene were also excluded. Participants completed annual questionnaires reporting health-related exposures and any health outcomes experienced over the previous year.

Risk Factor Information

At baseline, participants reported demographic information including age,

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race/ethnicity, educational level, and household income, as well as a detailed medical history and information on lifestyle factors. Women reported their HRT use at baseline and at 12 and 36 months of follow-up. We classified postmenopausal women by their use at 36 months as either never or ever users of HRT. We further classified ever users as using estrogen alone, or estrogen combined with progesterone/progestins based on their most recent use pattern.

Dry Eye Syndrome Ascertainment

On the 4-year follow-up questionnaire we included 3 questions to assess dry eye syndrome: How often do your eyes feel dry (not wet enough)? How often do your eyes feel irritated? and Have you ever been diagnosed by a clinician as having dry eye syndrome? The 2 questions pertaining to symptoms had possible answers of constantly, often, sometimes, or never. These 2 questions alone were previously found to have a sensitivity of 60% coupled with a specificity of 94% compared with clinical diagnosis of dry eye syndrome, and to provide nearly the same predictability as a 14-item questionnaire.[19]

We defined 3 outcome measures for dry eye syndrome. We defined clinically diagnosed dry eye syndrome as a self-reported diagnosis of dry eye syndrome by a clinician, and severe symptoms as a report of both dryness and irritation either constantly or often. We also formed a composite end point of either a previous clinical diagnosis or severe symptoms of dry eye syndrome.

Statistical Analysis

We used χ^2 tests to examine the relationship of HRT with several potential determinants of its use as well as with dry eye syndrome. We then constructed multivariable logistic regression models (separate models for each definition of dry eye syndrome) to obtain odds ratios (ORs) and 95% confidence intervals (CIs) to estimate the effects of estrogen use only, and estrogen plus progesterone/progestin. We initially adjusted for age in 5-year categories and, since subjects were participants in a randomized trial, randomized treatment assignments (aspirin vs placebo, vitamin E vs placebo, and beta carotene vs placebo). We then extended the models to account for predictors of HRT, as well as other medical conditions that may have influenced the prevalence of dry eye syndrome.

Although our primary analysis was restricted to postmenopausal women, we also fit models in which premenopausal women formed the reference group. In additional analyses, we fit models to examine whether the dose of estrogen or progesterone/progestin or duration of HRT were related to dry eye syndrome.

There is evidence that androgens are protective against dry eye syndrome.[20,21] Since women who had oophorectomy would be expected to have lower androgen levels[22] and to be more likely to take HRT, we also conducted separate analyses among women based on oophorectomy history.

Finally, to address the issue of the timing of the onset of dry eye syndrome relative to initiation of HRT, we conducted an additional analysis for the end point of clinically diagnosed dry eye syndrome, in which we excluded women who were diagnosed with dry eye syndrome prior to the initiation of HRT. In this analysis, we chose an index date of 10 years prior to our assessment of dry eye syndrome and excluded all women with a date of diagnosis prior to this index date. Beginning from the index date, we then constructed a series of consecutive 1-year intervals, which included data from all women who remained free of dry eye syndrome at the beginning of the interval. We used data on duration of HRT to estimate the time of initiation of therapy to determine each participants' HRT status at the beginning of each interval, and data on the date of diagnosis of dry eye syndrome to assign the diagnosis to the interval in which it occurred. We used Cox proportional hazards models to obtain estimates of the relative risk and 95% CI associated with HRT.

RESULTS

Information about dry eye syndrome was provided by 36995 (93%) of the 39876 women enrolled in the Women's Health Study. Among the women with data on dry eye syndrome, 25665 (69%) were postmenopausal. We excluded from further analyses 156 women who were taking either vaginal estrogen or progesterone alone, as well as 120 women for whom data on HRT were unavailable. Of the remaining 25389 women, 61.1% had ever taken HRT and 90% of these women were current users. As expected, HRT was related to a number of demographic and social characteristics, being more common among younger women, women who identified themselves as either white or Asian, and women with higher levels of education and household income (TABLE 1). Use of HRT also varied by geographic region with the highest prevalence in the West, and the lowest levels in the Northeast. Women who had taken HRT were also more likely to have had an eye examination in the past 2 years.

Use of HRT was significantly related to the prevalence of dry eye syndrome (FIGURE). Considering the prevalence of either clinically diagnosed dry eye syndrome or severe symptoms, women who never used HRT had the lowest prevalence (5.9%). Women who used estrogen alone had the highest prevalence (9.1%), and women who used a combination of estrogen plus progesterone/progestin had a prevalence that was intermediate between never users and users of estrogen alone (6.7%). Relationships were similar for severe symptoms and clinically diagnosed dry eye syndrome.

After adjusting for age and randomized treatment assignments, HRT was still significantly associated with clinically diagnosed dry eye syndrome for estrogen alone (OR, 1.70 [95% CI, 1.49-1.95] and for estrogen and progesterone/progestin OR, 1.30 [95% CI, 1.12-1.50]); severe symptoms (OR, 1.72

[95% CI, 1.46-2.03] and OR, 1.24 [95% CI, 1.04-1.48]); and the combined end point of either clinically diagnosed dry eye syndrome or severe symptoms (OR, 1.69 [95% CI, 1.51-1.90] and OR, 1.27 [95% CI, 1.12-1.44]), respectively. Further adjustment for race/ethnicity, geographic region, educational level, household income, and frequency of eye examinations had little impact on these findings. Additional adjustment for diabetes mellitus, hypertension, rheumatoid arthritis, and other connective tissue diseases also had no effect (TABLE 2). Compared with no HRT use, the multivariable-adjusted ORs for the combined end point of clinically diagnosed dry eye syndrome or severe symptoms were 1.69 (95% CI, 1.49-1.91) for estrogen use alone and 1.29 (95% CI, 1.13-1.48) for estrogen plus progesterone/progestin use.

In models that included premenopausal women as the reference group, the multivariable-adjusted ORs for clinically diagnosed dry eye syndrome or severe symptoms were 1.02 (95% CI, 0.86-1.22) for postmenopausal women who never used HRT; 1.71 (95% CI, 1.46-2.00) for postmenopausal women who used estrogen alone; and 1.29 (95% CI, 1.10-1.51) for postmenopausal women who used estrogen plus progesterone/progestin.

In models examining dose, the risk of dry eye syndrome was elevated compared with nonusers in all women who took estrogen, including women who used less than 1 mg/d, the lowest prescribed doses (multivariable-adjusted OR, 1.73 [95% CI, 1.25-2.41]), and there was no clear dose-response relationship. Use of progesterone/progestin in combination with estrogen resulted in lower risks of dry eye syndrome compared with those associated with use of estrogen alone regardless of progesterone dose. For example, in women taking the lowest doses of progesterone/progestin in combination with the lowest doses of estrogen, the multivariable-adjusted OR was reduced from 1.73 for estrogen alone to 1.31 (95% CI, 0.80-2.14) for the combination. Duration of HRT was significantly associated with a multivariable-adjusted 15% higher risk (95% CI, 11%-19%) of dry eye syndrome for each 3-year increase in the duration of HRT use.

Among the subgroup of postmenopausal women without a history of oophorectomy, the multivariable-adjusted ORs for the end point of clinically diagnosed dry eye syndrome or severe symptoms were 1.38 (95% CI,

Table 1. Relationship of Demographic Characteristics With Use of Hormone Replacement Therapy (HRT) Among Postmenopausal Women*

Characteristic	No. (%) Total	No. (%) HRT Users†
Age, y		
≤49	885 (3.5)	684 (77.3)
50-54	6316 (24.9)	4454 (72.1)
55-59	6710 (26.4)	4509 (67.2)
60-64	5411 (21.3)	3198 (59.1)
65-69	3553 (14.0)	1688 (47.5)
70-74	1834 (7.2)	695 (37.9)
≥75	680 (2.7)	192 (28.2)
Race/ethnicity		
White	23 906 (94.2)	14 726 (61.6)
Black	542 (2.1)	257 (47.4)
Asian/Pacific Islander	359 (1.4)	211 (58.8)
Hispanic	249 (1.0)	131 (52.6)
Native American/Alaskan Native	68 (0.3)	35 (51.5)
Other/unknown	44 (0.2)	21 (47.7)
Not indicated	221 (0.9)	132 (59.7)
Education		
Licensed practical nurse or licensed visiting nurse training	3398 (13.4)	1753 (51.6)
2-Year associate's degree (registered nurse)	2553 (10.1)	1705 (66.8)
3-Year diploma program (registered nurse)	8654 (34.1)	4993 (57.7)
Bachelor's degree	5521 (22.2)	3611 (65.4)
Master's degree	3599 (14.2)	2383 (66.2)
Doctoral degree (including medicine)	1253 (4.9)	818 (65.3)
Not indicated	411 (1.6)	252 (61.3)
Household income, $		
<10 000	270 (1.1)	78 (28.9)
10 000-19 999	1351 (5.3)	488 (36.1)
20 000-29 999	2805 (11.1)	1327 (47.3)
30 000-39 999	3740 (14.7)	2072 (55.4)
40 000-49 999	3926 (15.5)	2418 (61.6)
50 000-99 999	9110 (35.9)	6249 (68.6)
≥100 000	2651 (10.4)	1954 (73.7)
Not indicated	1536 (6.1)	928 (60.4)
Current residence, US Census region		
West	5494 (21.6)	3807 (69.3)
Midwest	7208 (28.4)	4325 (60.0)
Northeast	4815 (19.0)	2364 (49.1)
South	7793 (30.7)	4988 (64.0)
Outside of United States (Puerto Rico, Guam, and other US territories)	79 (0.3)	37 (46.8)
Frequency of eye examinations		
≥1 in 2 years	21 060 (83.0)	13 141 (62.4)
<1 in 2 years	4324 (17.0)	2417 (55.9)
Not indicated	5 (0)	3 (60.0)

*Total percentages across categories may be slightly higher or lower than 100 due to rounding.
†Includes both past and current users (as of the 3-year Women's Health Study follow-up questionnaire) of either estrogen alone or estrogen plus progesterone/progestin. Of all HRT users, 90% were current users.

1.04-1.83) for estrogen alone and 1.32 (95% CI, 1.14-1.54) for estrogen plus progesterone/progestin. Among postmenopausal women with a history of oophorectomy, the multivariable-adjusted ORs were 1.53 (95% CI, 1.24-1.89) for estrogen alone and 1.24 (95% CI, 0.79-1.94) for estrogen plus progesterone/progestin.

Finally, in models examining the timing of the initiation of HRT relative to the diagnosis of dry eye syndrome, we observed a higher incidence of clinically diagnosed dry eye syndrome among women who were free of clinically diagnosed dry eye syndrome at the time they began using HRT (multivariable-adjusted relative risk, 1.48 [95% CI, 1.27-1.72] for estrogen alone; relative risk, 1.15 [95% CI, 0.97-1.37] for estrogen plus progesterone/progestin).

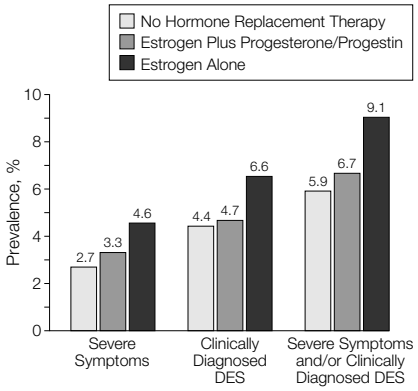
COMMENT

In this study, postmenopausal women who used HRT had higher prevalences of dry eye syndrome than never users (estrogen alone, 69%; estrogen plus progesterone/progestin, 29%). Adjusting for age and other factors, postmenopausal women who had never used HRT did not differ from premenopausal women in the prevalence of dry eye syndrome. The relationship of HRT and dry eye syndrome was consistent for all definitions of dry eye syndrome used in the present study, and held for clinically diagnosed cases diagnosed after the initiation of therapy. The longer the duration of HRT, the higher the risk of dry eye syndrome.

Since we were not able to determine if initiation of HRT preceded the onset of dry eye syndrome, the relationships we observed may reflect a higher tendency of women with dry eye syndrome to be prescribed HRT. However, given the lack of evidence of any beneficial effect of replacement hormones in this context, its prescription specifically for dry eye syndrome is not likely to be common and certainly cannot be considered a standard of practice. Moreover, when we excluded cases that were clinically diagnosed prior to the initiation of HRT, we continued to observe a significantly elevated risk of subsequent dry eye syndrome among women who took exogenous estrogen. Although we could not address the issue of timing for our analysis based on dry eye symptoms, the similarity of our findings for symptoms compared with clinically diagnosed cases as well as the consistently stronger relationship with estrogen alone and significant increased risk with longer duration HRT use argue against this as a major source of bias. These factors, and the fact that participants were unaware of our hypothesis when they provided information about HRT use and dry eye syndrome (collected at different times and on different questionnaires), also argue against the possibility that women taking HRT were more likely to think that such therapy caused dry eye syndrome and therefore were more likely to report dry eye symptoms.

Residual confounding is a concern in any epidemiological study. In the present study, we were not able to control for factors such as contact lens use or use of other medications that might lead to an increased frequency of dry eye syn-

Figure. Prevalence of Dry Eye Syndrome (DES), by Categories of Use of Hormone Replacement Therapy (HRT), Among 25 389 Postmenopausal Women



Users of HRT include both past and current users (90% of ever users were still using HRT), with the type of therapy assigned according to the type used most recently. Differences in the prevalence of DES by category of HRT were significant for each definition (each $P<.001$).

Table 2. Results of Logistic Regression Models Examining the Association of Hormone Replacement Therapy (HRT) With Dry Eye Syndrome (DES) Among Postmenopausal Women*

HRT Use†	Never	Estrogen Only	Estrogens Plus Progesterone/ Progestin
Model 1 (n = 25 389)‡			
Severe symptoms	1.00	1.72 (1.46-2.03)	1.24 (1.04-1.48)
Clinically diagnosed DES	1.00	1.70 (1.49-1.95)	1.30 (1.12-1.50)
Symptoms and/or clinically diagnosed DES	1.00	1.69 (1.51-1.90)	1.27 (1.12-1.44)
Model 2 (n = 23 269)§			
Severe symptoms	1.00	1.64 (1.37-1.95)	1.25 (1.03-1.50)
Clinically diagnosed DES	1.00	1.69 (1.47-1.96)	1.31 (1.12-1.53)
Symptoms and/or clinically diagnosed DES	1.00	1.65 (1.45-1.87)	1.27 (1.11-1.45)
Model 3 (n = 23 269)‖			
Severe symptoms	1.00	1.66 (1.40-1.97)	1.27 (1.05-1.53)
Clinically diagnosed DES	1.00	1.74 (1.50-2.00)	1.33 (1.14-1.56)
Symptoms and/or clinically diagnosed DES	1.00	1.69 (1.49-1.91)	1.29 (1.13-1.48)

*Values are expressed as odds ratios (95% confidence intervals) and are based on the results of separate multivariable regression models for each outcome (ie, severe symptoms, clinically diagnosed DES, symptoms and/or clinically diagnosed DES).
†Women who had ever used HRT were classified as users according to the type used most recently (either estrogen alone, or estrogen plus progesterone/progestin. Ninety percent of ever users were still using HRT.
‡Adjusted for age (5-year categories), and randomization assignments to aspirin, vitamin E, and beta carotene (each vs placebo).
§Excludes 2120 women with missing data on 1 or more covariates. Adjusted for age (5-year categories), race (white, black, hispanic, Asian/Pacific Islander, Native American, other) and randomization assignments to aspirin, vitamin E, and beta carotene (each vs placebo), education (licensed practical or visiting nurse training; 2-year associate's degree for registered nurse [RN]; 3-year RN diploma program; bachelor's, master's, or doctoral degree), household income level (≤$10 000, $10 000-$19 999, $20 000-$29 999, $30 000-39 999, $40 000-$49 999, $50 000-$99 999, ≥$100 000), frequency of eye examinations (≥1 every 2 years vs <1), and US Census region (West, Midwest, Northeast, South, outside of the United States [Puerto Rico, Guam, and other US territories]).
‖See the section symbol for the variables adjusted for. In addition, the following variables were adjusted for: a history of hypertension (yes vs no), diabetes mellitus (yes vs no), rheumatoid arthritis (yes vs no), and other connective tissue diseases (yes vs no).

drome. However, given the high prevalence of HRT and the magnitude of the observed effects, any extraneous factor would need to be prevalent as well as strongly related to both HRT and dry eye syndrome to explain the observed associations. With regard to contact lens use, in a subgroup of 393 women, we determined that HRT was not associated with contact lens use (26.8% of never users wore contact lenses vs 24.8% of HRT users), making residual confounding by this factor unlikely. Moreover, control for medical conditions such as hypertension, diabetes, rheumatoid arthritis, and other connective tissue diseases had little impact on our findings.

An additional consideration relates to our use of a questionnaire-based assessment of dry eye syndrome, although there is consensus among both researchers[2] and clinicians[23,24] that ascertainment of dry eye symptoms provides important information. In fact, assessment of symptoms was determined to be the single most important test for dry eye syndrome identified by clinicians in practice.[23,24] An expert panel also identified these symptoms to be the sine qua non of dry eye syndrome.[2] This seems appropriate since ocular surface damage rarely reaches clinical importance in the absence of symptoms,[25] and a major goal of therapy for dry eye syndrome is the relief of debilitating symptoms. Moss et al[26] identified expected relationships when using self-reported dry eye syndrome in epidemiological studies. In the present study, we used a validated questionnaire to assess symptoms of dry eye syndrome, and strict criteria to identify women as having dry eye syndrome based on symptoms alone. We also assessed previous clinical diagnoses of dry eye syndrome, which should have helped us identify participants with treated dry eye syndrome who had received some relief from their symptoms, as well as cases with only milder symptoms. Because we were not able to examine study participants, however, estimates could have been biased by a higher likelihood of diagnosis among women using HRT, although controlling for more frequent eye examinations did not have any impact on our findings. This explanation also seems unlikely given the significant relationship of HRT with symptoms alone, the stronger effect of estrogen taken alone, and the significant increase in risk with longer duration of HRT use.

Despite the common occurrence of dry eye syndrome, basic epidemiological data are limited. Clinical observations suggest, and most epidemiological studies[26-28] support, that dry eye syndrome is more common in women, a finding that would be consistent with either a detrimental effect of estrogen or a beneficial role of androgens,[1,21] or both. Indeed, it may be the balance of androgens and estrogen that is important in determining risk of dry eye syndrome. Since women with oophorectomy would be expected to have lower androgen levels[22] and are also more likely to be prescribed estrogen replacement, we were concerned that low androgen levels might have confounded the relationship of exogenous estrogen with dry eye syndrome. However, when we looked separately among the subgroups of women based on history of oophorectomy, we observed elevated risks of dry eye syndrome associated with estrogen in each subgroup, suggesting that these relationships were not likely to be purely a consequence of confounding by low androgen levels.

There are few epidemiological studies that directly assess the potential relationship of exogenous estrogen use with dry eye syndrome, and none that has examined the relationship in as much detail as the present study. Two studies[26,27] reported that there was no statistically significant relationship of HRT with the presence of self-reported dry eye symptoms. However, the data were not actually presented in either study, estrogen and estrogen plus progesterone/progestin were not examined separately, and it is unlikely that either study had sufficient statistical power to detect an association of the magnitude we observed.

Strengths of the present study include its large sample size and the prevalent use of HRT, which provided a high degree of precision for our estimates of an association with dry eye syndrome. We also used a validated questionnaire-based assessment of dry eye symptoms with high specificity for identifying subjects with dry eye syndrome. In addition, we obtained information on clinical diagnoses of dry eye syndrome from our population of knowledgeable female health professionals, and reporting of medical diagnoses has proven reliable among such populations.[29,30] Information on HRT was obtained without knowledge of dry eye status (and vice-versa). The results of the present study consistently showed a higher prevalence of dry eye syndrome among women who used HRT, regardless of the way in which we defined dry eye syndrome. As would be expected if the relationship were real rather than spurious, similar findings were observed for clinically diagnosed dry eye syndrome, severe symptoms, or either condition. Moreover, there was a significant trend of increasing prevalence of dry eye syndrome with longer duration of HRT use.

Basic research suggests that sex hormone levels may influence both the lacrimal and meibomian glands.[15,21] Laboratory and preliminary clinical studies suggest that whereas androgens have a beneficial influence on lacrimal and meibomian gland function,[15,21] estrogen may play a role in exacerbating dry eye syndrome.[15-17,21,31,32] Given our findings as well as the known inhibitory effects of estrogen on other sebaceous glands,[33] further study of the effects of estrogen on the function of the meibomian gland—a large sebaceous gland containing estrogen receptors[34]—would be interesting. Moreover, the apparently beneficial modifying effect of progesterone/progestin on the relationship of estrogen with dry eye syndrome requires further study.

In summary, the present study suggests that postmenopausal women who use HRT have a higher prevalence of dry eye syndrome compared with those who have never used HRT, and this is par-

ticularly true of women who used estrogen alone. Given these findings and the high prevalence of HRT in the United States, further studies of the effects of sex-steroid hormones on dry eye syndrome are recommended. Meanwhile, physicians caring for women who are taking or are considering HRT should be informed of the potential increased risk of dry eye syndrome with this therapy.

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