

Relation between dietary n-3 and n-6 fatty acids and clinically diagnosed dry eye syndrome in women¹⁻³

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ABSTRACT

Background: Dry eye syndrome (DES) is a prevalent condition, but information on risk or protective factors is lacking.

Objective: We aimed to determine the association between the dietary intake and ratio of n-3 and n-6 fatty acids (FAs) and DES occurrence.

Design: Of the 39 876 female health professionals in the Women's Health Study (WHS), 32 470 women aged 45-84 y who provided information on diet and DES were cross-sectionally studied. We assessed FA intakes by using a validated food-frequency questionnaire and assessed DES by using self-reports of clinically diagnosed cases. Of the sample, 1546 (4.7%) subjects reported DES. We used logistic regression models to estimate the odds ratios (ORs) and 95% CIs to describe the relation of FA intake with DES.

Results: After adjustment for demographic factors, hormone therapy, and total fat intake, the OR for the highest versus the lowest quintile of n-3 FAs was 0.83 (95% CI: 0.70, 0.98; *P* for trend = 0.05). A higher ratio of n-6 to n-3 FA consumption was associated with a significantly increased risk of DES (OR: 2.51; 95% CI: 1.13, 5.58) for >15:1 versus <4:1 (*P* for trend = 0.01). In addition, tuna consumption [1 serving was 113 g (4 oz)] was inversely associated with DES (OR: 0.81; 95% CI: 0.66, 0.99 for 2-4 servings/wk; OR: 0.32; 95% CI: 0.13, 0.79 for 5-6 servings/wk versus ≤1 serving/wk; *P* for trend = 0.005).

Conclusions: These results suggest that a higher dietary intake of n-3 FAs is associated with a decreased incidence of DES in women. These findings are consistent with anecdotal clinical observations and postulated biological mechanisms. *Am J Clin Nutr* 2005; 82:887-93.

KEY WORDS Epidemiology, dry eye syndrome, diet, n-3 fatty acids, n-6 fatty acids, risk factors, women

INTRODUCTION

Dry eye syndrome (DES) is one of the most prevalent ocular conditions in the United States and a frequent reason that people seek eye care (1). Ocular discomfort is the most frequent patient complaint (2). In addition, DES commonly leads to lower functional visual acuity (3) and to problems in reading, using a computer, driving at night, and carrying out professional work (4, 5).

Despite progress in determining the etiology and pathogenesis of DES, current knowledge remains inadequate, and no preventive strategies have been found. Moreover, the most common therapy for DES—artificial tears—provides only temporary and

incomplete symptomatic relief. Therefore, identification of modifiable risk factors for DES may suggest avenues for investigation of novel preventive and treatment measures.

Inflammation of the lacrimal gland, the meibomian gland, and the ocular surface plays a significant role in DES (6, 7). Patients with DES have an increased concentration of inflammatory cytokines, such as interleukin 1, interleukin 6, and tumor necrosis factor α , in the tear film (8). Research has shown that dietary intake of n-3 fatty acids (FAs) and the ratio of their consumption to that of n-6 FA affects the overall amount of inflammatory activity in the body (9, 10). Anecdotal evidence has suggested a possible protective role of n-3 FA supplementation in the treatment of DES (11, 12), but this has not yet been established in a systematic study. Both n-3 and n-6 FAs are essential for human health and must be consumed directly in the diet. Therefore, we investigated the relation of dietary intake of n-3 and the ratio of n-3 FA to n-6 FA with DES incidence in a large, well-characterized population of women participating in the Women's Health Study (WHS).

SUBJECTS AND METHODS

Study population

The WHS is a randomized, double-blind, placebo-controlled trial of 39 876 female health professionals that is assessing the benefits and risks of low-dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer (13). At baseline, all of the participants, who were aged 39-90 y, were free of cancer (except nonmelanoma skin cancer), myocardial infarction, stroke, transient cerebral ischemia, liver disease, renal disease, peptic ulcer, and gout. Women using corticosteroids, anticoagulants, or vitamin A and E supplements were excluded.

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For the purpose of the current analysis, we excluded WHS participants who did not provide information on diet or DES, which left 32 470 women.

Ascertainment of diet

A semiquantitative food-frequency questionnaire (SFFQ), administered at baseline, captured information on 134 commonly consumed food items. For each item, a portion size was specified and each woman was asked how often, on average, during the past year she had consumed that amount. Nine responses were possible, ranging from “never or less than once a month” to “6 times a day.” A detailed description of the SFFQ and the procedures used for calculating nutrient intake, as well as data on reproducibility and validity, have been published previously (14). We computed nutrient scores by multiplying the frequency of consumption of each unit of food from the SFFQ by the nutrient content of that specific portion size of the food according to food composition tables from the US Department of Agriculture (15) and other sources (14, 16).

We obtained information on n-6 FA consumption, mostly linoleic acid (18:2n-6; LA), primarily via questions on the consumption of margarine, butter, mayonnaise or other creamy salad dressing, peanuts, and other nuts; the type of cooking oil used at home in the preparation of foods; and the type of fat used for frying, sautéing, and baking. In the typical American diet, n-3 FAs are primarily derived from seafood sources, which contain the long-chain n-3 FA eicosapentanoic acid (20:5n-3; EPA) and docosahexanoic acid (22:5n-3; DHA). The SFFQ included questions on the intake of canned tuna fish (85–113 g portion size); other dark-flesh fish such as mackerel, salmon, sardines, bluefish, and swordfish (85–142 g portion size); light-flesh fish (85–142 g portion size); and shrimp, lobster, or scallops (or all 3) (as a main dish). We calculated the intake of EPA and DHA by assigning grams per serving as follows: 1.51 g for dark-flesh fish, 0.42 g for canned tuna fish, 0.48 g for light-flesh fish, and 0.32 g for shrimp, lobster, or scallops. These n-3 FA values were derived by weighting the mean values of n-3 FA for the most commonly caught types of fish in US catches in 1984 (according to the US Department of Commerce), described elsewhere (17). Intake of the n-3 FA α -linolenic acid (18:3n-3; ALA), obtained primarily from plant sources, and of other n-3 FAs were also estimated and used to calculate total n-3 FA intake.

Ascertainment of dry eye

We assessed the history of DES on the 4-y follow-up questionnaire by asking participants “Have you ever been diagnosed, by a clinician, with dry eye syndrome?” If they answered yes, we requested the date of diagnosis. For the current study, we considered a woman to have DES if she reported a clinical diagnosis of DES. We used clinically diagnosed cases because, in a validation study in which we examined 53 subjects, that endpoint was a sensitive and specific predictor of the presence of a clinical finding of DES (18). For example, the sensitivity of this question was 77% with a specificity of 83% for clinical DES as defined by a Schirmer test score of ≤ 10 mm in ≥ 1 eye or tear break-up time of < 10 s in ≥ 1 eye, 2 commonly used clinical tests for diagnosis of DES. A total of 1546 (4.7%) of the 32 470 women in the current study reported having clinically diagnosed DES.

Statistical analysis

We categorized energy-adjusted total n-3 FA, EPA, DHA, and total n-6 FA consumption by using quintile cutoffs of intake based on the distribution of these FAs among all subjects. We categorized n-6:n-3 FA into 4 categories: $< 4:1$, $\geq 4:1$ to $< 10:1$, $\geq 10:1$ to $< 15:1$, and $\geq 15:1$. These ranges approximately correspond to a theoretically ideal intake, the World Health Organization’s recommended intake, an approximately average intake in a typical Western diet, and a high but still prevalent ratio in a typical American diet, respectively (9).

We initially examined the distribution of potential confounders according to the dietary intake of n-3 and n-6 FAs and n-6:n-3. We then used logistic regression models to estimate the odds ratios (OR) and 95% CIs, for the relations of n-3 FA, EPA, DHA, n-6 FA, and n-6:n-3 with DES. In an initial set of models, we controlled for age, randomized aspirin and vitamin E assignments, hormone therapy, race, education, household income level, frequency of eye examination, US census region, and total fat intake. In a second set of models, we also controlled for history of diabetes mellitus, hypertension, and any connective tissue diseases (eg, lupus or rheumatoid arthritis), because these variables are potential risk factors for DES and may be related to diet.

Because fish and seafood intakes account for such a large proportion of the total n-3 FA intake in a typical American diet, we also specifically examined the association of fish and seafood intakes with DES. In this analysis, we categorized average daily tuna fish consumption into 3 categories: ≤ 1 , 2–4, and ≥ 5 –6 servings/wk (a serving = 113 g, or 4 oz). Intakes of the less commonly consumed dark-flesh fish (besides tuna), light-flesh fish, and seafood were each divided into 2 categories: ≤ 1 and ≥ 2 –4 servings/wk. We used logistic regression models to assess the relations of fish and seafood consumption with DES and to obtain OR and 95% CI estimates for these associations.

RESULTS

The mean daily intake of n-3 FA was 1.40 g [roughly equal to eating three 113-g (4-oz) portions of canned tuna/wk], and the range was 0.27–4.63 g. Mean daily intakes of n-6 FA were 10.82 g (roughly equal to eating just < 2 T mayonnaise/d), and the range was 2.04–36.80 g. The mean n-6:n-3 FA was 7.97, and the range was 1.01–32.93. Baseline characteristics of the study participants distributed by quintiles of n-3 and n-6 FA intake and by n-6:n-3 are shown in **Table 1**. Older women were more likely than were younger women to have higher intakes of n-3 and n-6 FA and a lower n-6:n-3. In addition, there was a direct relation of total fat with n-3 and n-6 FA intakes and with n-6:n-3. Women with history of diabetes mellitus had higher intakes of n-3 and n-6 FAs than did women without such a history, and women with hypertension and those with higher body mass index also had a slightly higher intake of both n-3 and n-6 FAs than did women without hypertension and those with lower body mass index. Neither n-3 nor n-6 FA intake differed significantly between the categories of hormone therapy users.

In the initial set of logistic regression models after adjustment for age, randomized aspirin and vitamin E assignments, demographic factors, postmenopausal hormone therapy, and total fat intake, women with a higher intake of n-3 FA tended to have a lower risk of DES than did women with a lower intake (**Table 2**).



TABLE 1

Baseline characteristics of subjects by quintiles of dietary intake of n-3 and n-6 fatty acids and the ratio of n-6 to n-3

	Quintile					P for trend
	1	2	3	4	5	
n-3 Fatty acid intake						
Range (g)	0.27-1.07	1.08-1.25	1.26-1.43	1.44-1.67	1.68-4.63	
Subjects (n)	6473	6396	6606	6572	6423	
n-3 Intake (g)	0.92 ± 0.12 [†]	1.17 ± 0.05	1.34 ± 0.05	1.55 ± 0.07	1.99 ± 0.33	< 0.0001
n-6 Intake (g)	8.38 ± 2.11	9.69 ± 1.95	10.62 ± 2.07	11.66 ± 2.19	13.72 ± 3.31	< 0.0001
n-6:n-3	9.2	8.3	7.9	7.5	6.9	< 0.0001
Age (y)	57.35 ± 6.84	57.51 ± 6.85	57.80 ± 6.90	58.17 ± 7.04	58.63 ± 7.09	< 0.0001
BMI (kg/m ²)	26.29 ± 5.16	26.58 ± 5.22	26.55 ± 5.07	26.77 ± 5.29	26.83 ± 5.32	< 0.0001
Total fat intake (g)	54.33 ± 12.7	56.29 ± 11.35	57.44 ± 11.01	58.82 ± 10.43	61.71 ± 11.71	< 0.0001
Postmenopausal hormone therapy (%)						
None	20.62	19.84	20.11	19.79	19.65	
Estrogen	18.78	19.57	20.58	20.73	20.33	
Estrogen and progesterone	20.07	19.62	20.46	20.42	19.43	0.25
Diabetes mellitus (%)						
Absent	20.15	19.73	20.41	20.14	19.57	
Present	15.36	18.92	18.99	22.42	24.30	< 0.0001
Hypertension (%)						
Absent	20.49	19.90	20.74	19.77	19.12	
Present	19.05	19.38	19.72	21.00	20.85	< 0.0001
Any connective tissue disease (%)						
Absent	19.93	19.71	20.39	20.22	19.75	
Present	20.27	19.13	18.79	20.96	20.84	0.56
n-6 Fatty acid intake						
Range (g)	2.04-8.36	8.37-9.81	9.82-11.19	11.20-12.99	13.00-36.80	
Subjects (n)	6447	6498	6512	6516	6497	
n-3 Intake (g)	1.09 ± 0.3	1.24 ± 0.27	1.36 ± 0.28	1.49 ± 0.28	1.78 ± 0.43	< 0.0001
n-6 Intake (g)	7.15 ± 0.97	9.12 ± 0.42	10.49 ± 0.40	12.03 ± 0.52	15.25 ± 2.33	< 0.0001
n-6:n-3	6.9	7.6	8.0	8.3	9.0	< 0.0001
Age (y)	57.69 ± 6.88	57.82 ± 6.95	57.63 ± 6.83	57.98 ± 6.98	58.33 ± 7.13	< 0.0001
BMI (kg/m ²)	26.09 ± 4.95	26.39 ± 5.13	26.75 ± 5.17	26.86 ± 5.33	26.93 ± 5.44	< 0.0001
Total fat intake (g)	47.48 ± 10.90	54.43 ± 9.56	58.06 ± 9.07	61.35 ± 9.04	67.17 ± 9.78	< 0.0001
Postmenopausal hormone therapy (%)						
None	20.35	19.96	19.93	19.85	19.91	
Estrogen	19.22	19.74	20.15	19.98	20.91	
Estrogen and progesterone	19.76	20.36	20.15	20.47	19.26	0.73
Diabetes mellitus (%)						
Absent	20.01	20.02	20.09	19.99	19.88	
Present	16.41	19.76	19.20	21.79	22.84	< 0.0001
Hypertension (%)						
Absent	20.37	20.29	19.93	19.65	19.77	
Present	19.03	19.57	20.26	20.75	20.39	0.0004
Any connective tissue disease (%)						
Absent	19.84	20.03	20.03	20.09	20.02	
Present	20.50	19.48	20.96	19.36	19.70	0.66
n-6:n-3						
Range	1.01-6.59	6.60-7.45	7.46-8.20	8.21-9.17	9.18-32.93	
Subjects (n)	6528	6457	6472	6503	6510	
n-3 Intake (g)	1.6 ± 0.45	1.48 ± 0.37	1.42 ± 0.38	1.32 ± 0.32	1.16 ± 0.29	< 0.0001
n-6 Intake (g)	9.02 ± 2.45	10.41 ± 2.65	11.08 ± 2.93	11.37 ± 2.77	12.19 ± 3.08	< 0.0001
n-6:n-3	5.7	7.0	7.8	8.6	10.6	< 0.0001
Age (y)	58.56 ± 7.07	58.02 ± 6.97	57.82 ± 6.93	57.44 ± 6.73	57.61 ± 7.03	< 0.0001
BMI (kg/m ²)	26.21 ± 5.01	26.58 ± 5.11	26.63 ± 5.12	26.87 ± 5.34	26.74 ± 5.46	< 0.0001
Total fat intake (g)	49.29 ± 10.77	55.39 ± 10.32	58.58 ± 10.42	61.02 ± 10.38	64.32 ± 10.79	< 0.0001
Postmenopausal hormone therapy (%)						
None	19.87	19.74	20.15	19.66	20.57	
Estrogen	20.11	20.16	19.70	20.27	19.75	
Estrogen and progesterone	20.44	19.82	19.84	20.33	19.56	0.16
Diabetes mellitus (%)						
Absent	20.02	19.89	19.92	20.08	20.09	
Present	22.00	19.76	20.18	18.99	19.06	0.07
Hypertension (%)						
Absent	19.90	19.93	20.08	19.96	20.14	
Present	20.44	19.82	19.69	20.13	19.91	0.43
Any connective tissue disease (%)						
Absent	20.07	19.89	19.89	20.08	20.07	
Present	21.41	19.70	21.41	18.22	19.25	0.21

[†] $\bar{x} \pm SD$ (all such values).

TABLE 2

Relative risks (odds ratios) and 95% CIs of dry eye syndrome (DES) among 32 470 participants in the Women's Health Study, according to dietary intake of n-3 and n-6 fatty acids

Quintile of dietary intake (mean intake)	No. of subjects	No. with DES	Model 1: ¹ OR (95% CI)	Model 2: ² OR (95% CI)
	<i>n</i>	<i>n</i>		
n-3 Fatty acids				
Quintile 1 (0.92 g)	6473	329	1.0	1.0
Quintile 2 (1.17 g)	6396	296	0.89 (0.76, 1.05)	0.89 (0.76, 1.05)
Quintile 3 (1.34 g)	6606	318	0.92 (0.78, 1.08)	0.92 (0.78, 1.08)
Quintile 4 (1.55 g)	6572	314	0.90 (0.76, 1.06)	0.90 (0.76, 1.05)
Quintile 5 (1.99 g)	6423	289	0.83 (0.70, 0.98)	0.83 (0.70, 0.98)
<i>P</i> for trend			0.05	0.04
n-6 Fatty acids				
Quintile 1 (7.15 g)	6447	329	1.0	1.0
Quintile 2 (9.12 g)	6498	304	0.92 (0.78, 1.09)	0.93 (0.79, 1.09)
Quintile 3 (10.50 g)	6512	306	0.95 (0.80, 1.12)	0.94 (0.80, 1.12)
Quintile 4 (12.03 g)	6516	307	0.94 (0.78, 1.12)	0.94 (0.79, 1.12)
Quintile 5 (15.25 g)	6497	300	0.91 (0.75, 1.11)	0.92 (0.76, 1.12)
<i>P</i> for trend			0.72	0.74

¹ Odds ratios (OR) and 95% CIs are from logistic regression models (separate models for n-3 and n-6 fatty acids) after control for age (in 5-y categories); randomized assignments to aspirin, β -carotene, and vitamin E (each versus placebo); postmenopausal hormone therapy (none, estrogen only, or estrogen plus progesterone or progestins); race (white, black, Hispanic, Asian/Pacific Islander, Native American, or other); education [licensed practical or visiting nurse training, 2-y associate's degree for registered nurse (RN), 3-y RN diploma program, or 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, or \geq 100 000); an eye examination in the past 2 y; US census region [West, Midwest, Northeast, South, or outside the 50 states (Puerto Rico, Guam, and other US territories)]; and total fat intake (g).

² In addition to the variables in model 1, we controlled for diagnoses of diabetes mellitus, hypertension, and any connective tissue disease.

For the highest versus the lowest quintile of n-3 FA intake, the OR was 0.83 and the 95% CI was 0.70, 0.98 (*P* for trend = 0.05). In a second set of models, additional control for connective tissue diseases, diabetes mellitus, and hypertension did not appreciably modify these associations (Table 2). Similarly, women with the highest intake of DHA had a significantly lower risk of DES than did those with the lowest intake (OR: 0.88; 95% CI: 0.74, 1.04; *P* for trend = 0.01). The results for EPA did not differ significantly between the highest and lowest quintiles (OR: 0.87; 95% CI: 0.73, 1.03; *P* for trend = 0.08), but the estimated magnitude of that association also did not differ from that for DHA.

We observed no significant relation between n-6 FA intake and DES (Table 2). On the other hand, a higher n-6:n-3 FA was associated with a significantly greater risk of DES. The OR was

2.51 (95% CI: 1.13, 5.58) for comparison of extreme categories (\geq 15:1 versus <4:1; *P* for trend = 0.01) (Figure 1). Additional control for connective tissue diseases, diabetes mellitus, and hypertension had no important effect on these estimates.

In analyses examining the frequency of fish consumption in relation to DES, we observed a significant inverse association between tuna fish consumption and DES [OR: 0.81; 95% CI: 0.66, 0.99 for 2–4 servings/wk; OR: 0.32; 95% CI: 0.13, 0.79 for \geq 5–6 servings/wk compared with \leq 1 serving/wk (*P* for trend = 0.005)]. None of the other specific types of fish reached statistical significance. The OR for DES with seafood intake of \geq 2–4 servings/wk compared with \leq 1 serving/wk was 0.58 (95% CI: 0.27, 1.24). Consumption of dark-flesh fish other than tuna or of light-flesh fish also was not significantly related to the risk of

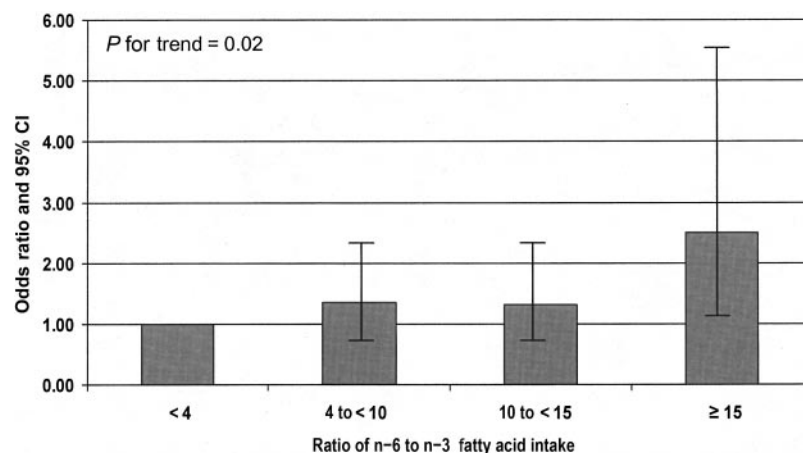


FIGURE 1. Odds ratios (ORs) and 95% CIs for the risk of dry eye syndrome (DES) according to categories of n-6:n-3 fatty acid intake. ORs and 95% CIs are from a logistic regression model after control for age, randomized aspirin and vitamin E assignments, postmenopausal hormone therapy, race, education, household income level, an eye examination in the past 2 y, US census region, and total fat intake.



TABLE 3

Relative risks of dry eye syndrome (DES) among 32 470 Women's Health Study participants, according to dietary intakes of fish and seafood

Diet variable ¹	No. of subjects	No. with DES	Model 1: ² OR (95% CI)	Model 2: ³ OR (95% CI)
	<i>n</i>	<i>n</i>		
Tuna fish				
≤1 serving/wk	29 424	1431	1.0	1.0
2–4 servings/wk	2728	110	0.81 (0.66, 0.99)	0.80 (0.65, 0.98)
≥5 servings/wk	318	5	0.32 (0.13, 0.79)	0.32 (0.13, 0.77)
<i>P</i> for trend			0.005	0.003
Other dark-flesh fish				
≤1 serving/wk	32 047	1530	1.0	1.0
≥2–4 servings/wk	423	16	0.70 (0.42, 1.17)	0.70 (0.42, 1.16)
Light-flesh fish				
≤1 serving/wk	30 816	1475	1.0	1.0
≥2–4 servings/wk	1654	71	0.84 (0.66, 1.07)	0.83 (0.65, 1.06)
Seafood				
≤1 serving/wk	32 226	1539	1.0	1.0
≥2–4 servings/wk	244	7	0.58 (0.27, 1.24)	0.58 (0.27, 1.23)

¹ Serving sizes were 85–113 g for tuna, 85–142 g for other dark-flesh fish and light-flesh fish, and “as a main dish” for seafood.

² Odds ratios (OR) and 95% CIs are from logistic regression models (separate models for each type of fish) after control for age (in 5-y categories); randomized assignments to aspirin, β -carotene, and vitamin E (each versus placebo); postmenopausal hormone therapy (none, estrogen only, or estrogen plus progesterone or progestins); race (white, black, Hispanic, Asian/Pacific Islander, Native American, or other); education [licensed practical or visiting nurse training, 2-y associate's degree for registered nurse (RN), 3-y RN diploma program, or 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, or ≥100 000); an eye examination in the past 2 y; US census region [West, Midwest, Northeast, South, or outside the 50 states (Puerto Rico, Guam, and other US territories)]; and total fat intake (g).

³ In addition to the variables in model 1, we controlled for diagnoses of diabetes mellitus, hypertension, and any connective tissue disease.

DES (OR: 0.70; 95% CI: 0.42, 1.17; OR: 0.84; 95% CI: 0.66, 1.07 for ≥2–4 servings/wk compared with ≤1 serving/wk of dark-flesh fish or of light-flesh fish, respectively). Results for the relations of fish consumption with DES were not affected by additional control for diabetes, hypertension, and connective tissue diseases (Table 3).

DISCUSSION

DES is a significant public health problem affecting more than 10 million Americans (19, 20). However, few risk or protective factors for DES have been identified, and, thus far, none of those identified relate to diet. The current study found that women with a higher dietary intake of n-3 FA have a lower prevalence of DES, including a 68% lower prevalence in women who consumed ≥5–6 servings/wk (a serving was 113 g, or 4 oz) compared with the women who consumed ≤1 serving/wk of tuna fish, one of the largest contributors of n-3 FA in the typical American diet. In contrast, we did not observe any independent relation of n-6 FA intake with DES; however, a high n-6:n-3 FA (ie, >15:1) was associated with a more than twofold greater prevalence of DES than was seen with a low ratio.

The central role of inflammation in the development of DES (21) and the known anti-inflammatory potential of n-3 FA are consistent with the correlations observed in the current study. Essential FAs are natural modulators of inflammatory activity via their metabolism to eicosanoids, locally acting hormone-like lipids involved in the control of inflammatory and immune responses. Eicosanoids are derived from 3 FA precursors, dihomogammalinoleic acid (20:3n-6 DGLA), arachidonic acid (20:4n-6 AA), and EPA. The modulation of inflammatory activity is based on the balance of these precursors. One of the possible ways in which n-3 FAs can reduce inflammatory activity is

through the suppression of the biosynthesis of AA-derived eicosanoids. Because the balance of n-3 and n-6 FAs in cellular membranes is largely dependent on dietary intake (22), high intakes of n-3 FAs result in replacement of the usually more abundant AA with EPA and DHA. Eicosanoids derived from AA, such as prostaglandin E₂ (PGE₂) and leukotriene B₄ (LTB₄), are vigorously proinflammatory, whereas the 3-series prostaglandins and 5-series leukotrienes from EPA are 10% to 90% less active biologically (23). A higher intake of n-3 FAs also reduces the desaturation and elongation of LA to AA (24, 25). Furthermore, n-3 FAs suppress cyclooxygenase-2 inhibitors and have greater affinity for enzyme substrates, which results in higher formation of EPA-derived than of AA-derived eicosanoids (26–28). When n-6:n-3 is ≈4:1 or lower, there is also competitive inhibition of the conversion of DGLA to AA (22), which results in the enhanced metabolism of DGLA to the 1-series prostaglandins including PGE₁, which has a number of anti-inflammatory actions (29).

Apart from the importance of FAs in modulating inflammatory response, their eicosanoid metabolites have a variety of other actions. Particularly salient to DES, PGE₁ appears to be an important stimulator of aqueous tear secretion (30). Early studies hypothesized that aqueous tear deficiency in Sjogren's-related DES was the result of PGE₁ precursor deficiency due to impaired δ -6 desaturase activity and a resultant reduction of the metabolism of LA to γ -linoleic acid (18:3n-6; GLA) (31). GLA is elongated to DGLA, which forms PGE₁. Investigators hypothesized that direct supplementation with GLA could correct this deficiency (31). However, a randomized trial comparing GLA and placebo in 90 Sjogren's syndrome patients found no significant difference in signs and symptoms of DES between the active treatment and placebo groups (32). In contrast, another randomized trial of 28.5 mg LA plus 15 mg GLA twice a day

compared with placebo in 26 patients with aqueous-deficient DES resulted in reported significant reductions in DES symptoms, lissamine green staining, and ocular surface inflammation (33). A trial with 60 subjects undergoing photorefractive keratectomy reported significant beneficial effects of a once-daily dose of 28.5 mg LA plus 15.1 mg GLA on tear function tests and ocular symptoms (34). Observational studies also suggested a link between n-3 FAs and DES in Sjogren's syndrome. In a cross-sectional study of 41 patients with primary Sjogren's syndrome (35), FA concentrations within erythrocyte phospholipids, plasma phospholipids, plasma triacylglycerols, and plasma cholesterol esters were investigated for associations with immunopathologic and clinical disease values. In that study, DHA was inversely correlated with the clinical DES status, a finding that is in general agreement with those of the current study. In a separate study, 68 women with Sjogren's syndrome were found to have a significantly lower dietary intake of n-3 FAs than did age-matched controls (36).


n-3 FAs may also have a direct effect on the polar portion of the lipid layer of tear film by increasing the amount of n-3 FAs present or by affecting n-6:n-3 FAs (37). Finally, n-3 FA intake may decrease endogenous estrogen production (38), which may affect the risk of DES (39).

One of the main limitations of our study lies in the questionnaire-based assessment of DES. Moreover, we could not differentiate between evaporative and aqueous-deficient subtypes of DES. However, previous studies suggested the validity of the type of assessment we used (19, 39, 40), and our own validation study of 53 patients showed good sensitivity and specificity as compared with commonly used clinical tests for DES (18). Although our classification of DES was certainly not perfect, misclassification would tend to bias estimates toward the null, unless the misclassification was associated with the exposure of interest. It is theoretically possible that women who consume higher amounts of n-3 FAs are less likely to receive a diagnosis of DES than are women who consume less n-3 FAs, but this seems particularly unlikely because higher consumption was correlated with factors such as older age and diabetes, which are associated with a higher risk of DES. Moreover, control for frequency of eye examinations (ie, the opportunity for diagnosis) did not eliminate the association between n-3 FAs and DES. Confounding by unmeasured factors, such as medication use, is another concern. Although we could not address this directly because information on medication use was not available, control for major diseases such as diabetes mellitus, hypertension, and connective tissue diseases did not alter the observed associations. Confounding due to differential use of contact lenses or artificial tears across levels of FA intake is also unlikely, given that neither of these factors was related to FA intake in a subgroup of 341 women for whom we had this information (P for trend > 0.6 for each; data not shown). Nonetheless, as in any epidemiologic study, it remains possible that the relations we observed could be explained by other differences between the women who consumed greater amounts of n-3 FAs and those who consumed lesser amounts.

Our study has several significant advantages including a large sample size, nationwide sampling of the study participants, control for most known or potential confounders, and use of a well-validated means of assessing dietary intake of essential FAs. Studies have shown that estimates of nutrient intake derived from

the SFFQ are reflective of long-term dietary intake (14). In addition, a positive association between n-6:n-3 and DES in the setting of a healthy population such as the WHS—in which 99% of participants had an n-6:n-3 below the mean for a typical Western diet (41), and 90% had a ratio below current recommendations (42)—may point to an even greater influence of FA imbalances on DES in the general population.

To our knowledge, this is the first study of dietary intake of n-3 or n-6 FAs (or both) as it may relate to the prevention of DES. Historically, appreciable amounts of n-3 FAs in the diet were provided by wild plants and wild game, and humans are thought to have evolved by eating an n-6:n-3 FA of close to 1:1. Many natural sources of n-3 FA have now been depleted from the diet, and this change is coupled with an oversupply of n-6 FA, particularly in last half-century, which has resulted in a distortion of n-6:n-3 to current levels, typically in the range of 12–16:1. Given the biology and importance of these FAs and their opposing biological effects, it seems quite likely that such an imbalance would be related to a pathologic condition (22).

In the current study, women with a higher intake of n-3 FAs appear to have a lower risk of DES than do women with a lower intake. Furthermore, a high n-6:n-3 is associated with a greater risk of DES. This is the first report of such an association. In light of the plausibility of hypothesized biological mechanisms, these findings suggest that increasing dietary intake of n-3 FAs may reduce the risk of DES, an important and prevalent cause of ocular complaints. 

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