ARE SEX HORMONES ASSOCIATED WITH AGE-RELATED MACULOPATHY IN WOMEN? THE BEAVER DAM EYE STUDY

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INTRODUCTION

AGE-RELATED MACULOPATHY (ARM) IN ITS MOST SEVERE FORM IS OFTEN associated with legal blindness.[1-3] The lesions characterizing this condition are geographic atrophy and neovascularization of the macula. This latter manifestation of macular degeneration appears to occur more commonly in women.[4] A recent case-control study found a protective effect of reported use of estrogen replacement therapy.[5] In the Beaver Dam Eye Study, current estrogen replacement therapy was associated with less severe nuclear sclerosis.[6] Other markers of estrogen exposure were also associated with decreased frequencies of lens opacities. Therefore, because of the biologic plausibility of an association of estrogens and maculopathy and the availability of a unique data set from the Beaver Dam Eye Study, we explored the relationship of the range of maculopathy as it occurs in an unselected population of women and a variety of lifetime estrogen exposures.

METHODS AND MATERIALS

A private census of Beaver Dam was performed from September 15, 1987, to May 4, 1988. Details of the census enumeration have been previously published.[7] A total of 4,926 persons 43 to 84 years of age at the time of the census completed the study evaluation. The parts of the examination that are pertinent to this study consisted of height and weight measurement;

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measurement of blood pressure following the Hypertension Detection and Follow-up Program protocol[8]; a slit-lamp examination to determine anterior chamber depth; and pupillary dilation with 1% tropicamide and 2.5% phenylephrine if the chamber depth was judged to be adequately deep. A medical history was obtained as part of the study evaluation. Women were asked their age at menarche, whether they were still having menstrual periods and, if not, the age at which menses stopped; whether they had ever been pregnant and, if so, how many times; whether they had a hysterectomy; and whether they had had taken estrogen replacement therapy and, if so, for how long and were they currently taking this medication.[6] In addition, subjects were queried about smoking history. Pack-years smoked was computed as the number of packs of cigarettes (20 cigarettes per pack) smoked each day multiplied by the number of years smoked. Serum total[9] and high-density lipoprotein (HDL) cholesterol[10] were measured from a venous blood specimen. Informed consent was obtained from each study subject.

Photographs were taken of the macula of each eye according to protocol.[1] They were graded in masked fashion by graders who were specially trained for this project.[1] Grading procedures have been described in detail elsewhere. In brief, before grading, a grid consisting of three circles concentric with the center of the macula and four radial lines was superimposed over one member of the stereoscopic pair of field 2. Nine subfields were defined by the grid: the central subfield (within the inner circle); the inner superior, inner nasal, inner inferior, and inner temporal subfields (between the inner and middle circles); and the outer superior, outer nasal, outer inferior, and outer temporal subfields (between the middle and outer circles).

Assessment of the presence and severity of lesions associated with ARM was made in each subfield. More detailed descriptions of these lesions appear elsewhere.[1,4] For purposes of this paper, early ARM was defined as the presence in any subfield of the macular area of either (1) soft drusen or (2) hard or soft drusen plus pigmentary abnormalities (increased retinal pigment or retinal pigment epithelial [RPE] degeneration) in the absence of signs of late ARM. Late ARM was defined as the presence of signs of exudative age-related macular degeneration or pure geographic atrophy. Exudative macular degeneration was defined as the presence of an RPE detachment or serous detachment of the sensory retina, subretinal or sub-RPE-hemorrhage, and/or subretinal fibrous scars. Pure geographic atrophy was defined by the presence of geographic atrophy and the absence of exudative macular degeneration.

Wisconsin Information Storage and Retrieval (WISAR), an information processing system,[11] was used for processing all subject files. The Statistical

Analysis System (SAS) (Cary, NC) was used for calculating Spearman correlation coefficients, means, and chi-square statistics.[12] Odds ratios and confidence intervals were calculated by using multiple logistic regression analyses after adjusting for confounders.

RESULTS

Table I describes the distributions of three measures of premenopausal estrogen exposure by current age. There was a significant increase in both age at menarche and the number of years of having menstrual cycles with increasing age (by category). There was no evidence of a relationship between the mean number of pregnancies and age groups.

TABLE I: PREMENOPAUSAL ENDOGENOUS ESTROGEN EXPOSURES BY AGE: THE BEAVER DAM EYE STUDY, 1988-1990

CURRENT AGE (YR)	AGE AT MENARCHE		NO. OF YEARS OF MENSTRUAL CYCLES		NO. OF PREGNANCIES	
	NO.	MEAN ± SD	NO.	MEAN ± SD	NO.	MEAN ± SD
43-49	451	12.6 ± 1.5	192*	26.2 ± 6.9	452	3.1 ± 1.8
50-59	691	12.8 ± 1.6	590	32.9 ± 7.0	694	3.8 ± 2.4
60-69	744	13.0 ± 1.9	733	33.9 ± 7.3	749	3.4 ± 2.5
70+	839	13.2 ± 1.6	806	33.8 ± 7.0	866	2.8 ± 2.3
r†		.10		.27		.01
P		<.0001		<.0001		.68

*Excludes women currently having menstrual cycles.
†Spearman correlation coefficient with age as a categorical variable.

Exogenous estrogens were additional sources of exposure for some women in Beaver Dam. Table II describes the reported use of birth control pills and estrogen replacement therapy. There was a significant trend of decreasing past use of birth control pills in the older age groups with less than 1% in the oldest group reporting any past use. Use of estrogen replacement therapy was less variable between the age-groups, but there was a significant difference. Women who had undergone natural menopause were less likely (14.8%) to report such intake compared with those who had had hysterectomy (38.9%).

Table III describes the frequencies of some lesions of ARM by age category. There is a significant age trend for each category of maculopathy. The category "early ARM" is a composite category as described in the Methods section. We include this grouping because clinicians may be more likely to accept this classification as representative of a group of persons at

TABLE II: EXOGENOUS ESTROGEN EXPOSURES BY CURRENT AGE: THE BEAVER DAM EYE STUDY, 1988-1990

CURRENT AGE (YR)	BIRTH CONTROL USE		ESTROGEN REPLACEMENT	
	NO.*	% USERS	NO.*	% USERS
43-49	452	73.1	443	14.5
50-59	693	40.7	677	21.3
60-69	748	13.8	735	30.2
70+	861	0.5	840	20.1
Total	2,754	35.3	2,695	22.2
P†		<.0001		.03

*The history of estrogen use was missing for 67 women.
†Mantel-Haenzel chi-square.

TABLE III: AGE-RELATED MACULOPATHY (ARM) LESIONS BY AGE: THE BEAVER DAM EYE STUDY, 1988-1990

AGE (YR)	SOFT DRUSEN		PIGMENT ABNORMALITIES		EARLY ARM		PURE GEOGRAPHIC ATROPHY		EXUDATIVE MACULOPATHY		LATE ARM	
	NO. AT RISK	%	NO. AT RISK	%	NO. AT RISK	%	NO. AT RISK	%	NO. AT RISK	%	NO. AT RISK	%
43-49	446	4.5	446	6.1	4415	7.4	445	0.0	445	0.0	445	0.0
50-59	687	10.9	687	5.4	685	8.9	686	0.2	686	0.2	687	0.3
60-69	729	20.3	729	10.7	725	17.2	726	0.1	728	0.4	729	0.6
70+	785	38.2	786	23.8	741	30.5	748	1.0	777	4.6	784	5.5
P trend	<.0001		<.0001		<.0001		.004		<.0001		<.0001	

greater risk of experiencing subsequent loss of vision. Late maculopathy is a classificaton that encompasses pure geographic atrophy and exudative maculopathy. The larger sample size, which results when including either lesion, permits a more powerful test of significance of a relationship of a risk or protective factor and the end point. We give information regarding the specific lesions because for some risk-factor relationships the association may be specific for a given lesion.

To evaluate a potential association between the estrogen exposure variables and lesions of ARM, we performed logistic regression analyses. We included as covariates those characteristics that we had found on previous analyses to confound the associations between risk (or protective) factors and lesions of maculopathy. Such factors include age, systolic blood pressure, smoking history, and HDL-cholesterol. Table IV describes relationships between premenopausal estrogen exposure variables and lesions of maculopathy. The number of past pregnancies was significantly inversely related to soft drusen; the odds ratio was 0.94. A relationship with the number of pregnancies to any maculopathy was of borderline significance; the odds ratio was 0.96. Past use of birth control pills had no effect on lesions of maculopathy (data not shown).

Table V describes relationships between postmenopausal exposure variables and lesions of maculopathy. Number of years of use of estrogen replacement therapy was inversely associated with any maculopathy. The relationship was of borderline significance; the odds ratio was 0.98.

DISCUSSION

The strengths of this study derive from the population-based setting of a large sample of American women. Standardized procedures were used to obtain information about relevant exposures and outcomes. It has permitted the investigation of a variety of sources of biologic exposure to estrogen and the relationship of these exposures to the range of maculopathy as it occurs in an unselected population. Thus, from these data we can say that cross-sectionally there is little evidence to support the notion of important (protective) effects of estrogen exposure on maculopathy. The few relationships that border on or achieve statistical significance are unimpressive, and the significant *P* values may derive from chance.

It may be that failure to find strong evidence of an affect on maculopathy is due to the infrequency of some lesions in this relatively young cohort. Moreover, if genetic determinants are important,[13] it may be more difficult to demonstrate environmental effects. Also, measurement variability in both exposure and outcome may lessen our ability to demonstrate effects of low

TABLE IV: ODDS RATIOS OF PREMENOPAUSAL ESTROGEN EXPOSURE VARIABLES AND LESIONS OF ARM

LESIONS OF ARM	AGE AT MENARCHE			YEARS OF MENSTRUATION			NO. OF PREGNANCIES		
	OR*	95% CI	*P*	OR*	95% CI	*P*	OR*	95% CI	*P*
Soft drusen	1.01	0.95,1.07	.75	1.00	0.99,1.01	.92	0.94	0.90,0.98	.01
Pigment abnormalities	1.04	0.97,1.11	.31	0.99	0.97,1.00	.11	0.97	0.92,1.02	.21
Early ARM†	1.01	0.95,1.07	.84	1.00	0.98,1.01	.54	0.95	0.92,1.01	.12
Pure geographic atrophy	1.33	0.88,1.99	.17	1.01	0.91,1.12	.88	0.84	0.58,1.22	.37
Exudative maculopathy	0.94	0.76,1.17	.60	1.00	0.95,1.04	.85	1.02	0.89,1.17	.79
Late ARM†	1.01	0.85,1.21	.92	1.00	0.96,1.04	.98	0.99	0.87,1.12	.83
Any ARM‡	1.01	0.95,1.07	.80	1.00	0.98,1.01	.50	0.96	0.92,1.01	.10

OR, odds ratio; CI, confidence interval.
*Per one unit change in outcome variable.
†Includes both previous categories.
‡Includes early or late ARM.

TABLE V: ODDS RATIOS OF POSTMENOPAUSAL ESTROGEN EXPOSURE VARIABLES AND LESIONS OF ARM

LESIONS OF ARM	YEARS ON ESTROGEN REPLACEMENT			ESTROGEN REPLACEMENT (EVER,NEVER)			HYSTERECTOMY (EVER,NEVER)		
	OR*	95% CI	*P*	OR*	95% CI	*P*	OR*	95% CI	*P*
Soft drusen	0.99	0.97,1.01	.24	1.04	0.93,1.17	.49	1.00	0.90,1.11	.99
Pigment abnormalities	0.99	0.96,1.01	.25	0.91	0.78,1.06	.21	0.94	0.83,1.07	.35
Early ARM†	0.99	0.97,1.01	.18	0.97	0.85,1.10	.66	0.96	0.86,1.07	.44
Pure geographic atrophy	1.02	0.93,1.12	.66	1.28	0.56,2.92	.56	0.87	0.42,1.79	.70
Exudative maculopathy	0.92	0.80,1.06	.24	0.94	0.59,1.48	.78	0.87	0.62,1.22	.41
Late ARM†	0.96	0.88,1.04	.28	0.94	0.63,1.39	.75	1.01	0.99,1.02	.33
Any ARM‡	0.98	0.96,1.00	.09	0.96	0.85,1.09	.55	0.95	0.85,1.05	.31

OR, odds ratio; CI, confidence interval.
*Per one unit change in outcome variable.
†Includes both previous categories
‡Includes early or late ARM

orders of magnitude.

We cannot, with great certainty, negate the possibility of effects of these exposures on severe disease that is relatively rare in the general population. The power to test an effect of postmenopausal estrogen use on neovascular macular degeneration is low. Thus, we cannot refute the finding from the Eye Disease Case Control Study,[5] which had a larger sample of women with this lesion (n=236). Further research in this area is merited because prevention of this sight-devastating lesion is clearly preferable to the inadequate treatment that is available after its appearance.

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DISCUSSION

DR THOMAS C. BURTON. This impressive population based survey included nearly 5,000 inhabitants of Beaver Dam, Wisconsin. The authors have been unable to determine a relationship between estrogen exposure and various lesions associated with age-related macular degeneration, consisting of drusen, retinal pigment epithelial defects, geographic atrophy, and exudative maculopathy. We seem to be faced

with a dilemma, because the Eye Disease Case Control Study Group reported a strong protective effect on the neovascular form of macular degeneration associated with postmenopausal exogenous estrogen (*Arch Ophthalmol* 1992;110:1701-1708). The Beaver Dam survey included 2761 women aged 43 to 84 years, among whom there were only 40 cases of exudative macular degeneration, 36 (90%) of which occurred in the 70+ age-group. On the other hand the EDCCS survey included 236 women with subretinal neovascularization, 65% of whom were under age 75 years. The value of the authors' analyses with respect to exudative maculopathy may be undermined by inclusion of data from over 1,800 younger women, in whom the condition was virtually nonexistent.

The authors provided this reviewer with specific details for the oldest age-group, which contained 156 women with a history of estrogen use and 603 with no history of estrogen use. Of the estrogen users, five (3.2%) developed exudative maculopathy. Among the nonestrogen group, 29 (4.8%) developed exudative maculopathy. The *P* value of .39 was insignificant. However, it is possible that this actually represents a true difference and may indicate that estrogens have a protective influence. Assuming an actual difference of 2% and 4%, representing a doubling in rates of exudative maculopathy between estrogen users and non estrogen users, the older age cohort would need to be in the magnitude of 2,000 or greater to have confidence in determining whether a difference actually exists. Thus, in relatively rare disorders, a case-control study may be a more effective epidemiologic method.

By using the data provided for the older age-group, a different odds ratio of .66 can be calculated with a confidence interval of .26 to 1.67. On the basis of this calculation, the true value might be a fourfold protective factor or a two-thirds greater risk factor. The analysis, at least for the exudative maculopathy component and estrogen use, would be regarded as inconclusive, neither proving an association nor ruling out a strong association.

Population-based surveys and case-control studies seek associations and linkages, rather than demonstrating causality. Epidemiologic surveys can be compared, to a degree, to a fishing expedition. Some associations will be "found" on the basis of chance alone. Alternatively, there are undoubtedly numerous factors that influence age-related macular degeneration of which we are entirely unaware. It will remain for randomized trials to determine the impact of estrogen exposure on exudative maculopathy.

DR BARBARA E. R. Klein. I appreciate your thoughtful comments concernlng the differences between our findings in The Beaver Dam Eye Study and those reported by the Eye Disease Case-Control Study. The Eye Disease Case-Control Study enrolled 236 women with neovascular age-related macular degeneration and visual acuity poorer than 6/6 or distortion on Amsler grid, and drusen in either eye. They were matched (by frequency matching) with 356 controls on age (55 to 80 years of age), race (all were white), and service within each clinic. Cases were on average older than controls (data given for both sexes; 71 versus 68, respectively). In multivariate analyses, protective factors for both sexes were carotenoids, larger cup/

disc ratio, and myopia. In women, there was an apparent protective effect of reported use of estrogen categorized as never, former, or current user, but a deleterious affect, paradoxically, of ever having been pregnant. In the Beaver Dam Eye Study, there were only 41 cases of exudative macular degeneration in the population. We found an odds ratio for postmenopausal estrogen use that did not differ significantly from one. Similarly, we found no evidence of an effect of ever having been pregnant. Thus, The Beaver Dam data are consistent in finding no evidence of a protective effect of recent (estrogen use) or past (only as reflected in parity) estrogen exposure and age-related maculopathy.

Results of case-control studies are influenced by exposures within the case or control group. Thus, if cases systematically under report or controls over report exposure, biased conclusions can result. Also, if cases are less likely to be exposed (in this case, to take estrogen) than controls (perhaps due to health care patterns) even if the exposure is not causally related to the disease, an incorrect conclusion can result. It is of some concern that in the Eye Disease Case-Control Study, the controls were recruited from ophthalmology clinics and therefore their health care patterns may differ from the general population with regard to estrogen replacement (and other variables).

The Beaver Dam Eye Study and the Eye Disease Case-Control Study are only two epidemiologic studies that have begun to explore this relationship. One study has limited power due to a small number of cases, this other study depends on self-report and the possibility of bias of recall as well as the possibility of unusual frequencies of exposure in the case and control groups. When dealing with a relatively small beneficial effect, as may be true here, more studies and longitudinal follow-up is needed.

There currently are large clinical trials which have been initiated by those studying cardiovascular disease and osteoporosis. Women in those studies are randomly assigned to estrogen replacement therapy or placebo. It would be relatively easy to add eye examinations which could resolve some of these issues. As an epidemiologist, I am aware of the limitations of the data we obtain, but it is the totality of evidence from various epidemiological investigations that will further inform us about the disease etiology and prevention. I look forward to these studies with great enthusiasm and I thank you for your attention.