ORIGINAL INVESTIGATION

Postmenopausal Estrogen Use, Type of Menopause, and Lens Opacities

The Framingham Studies

Katherine Worzala, MD, MPH; Rita Hiller, MS; Robert D. Sperduto, MD; Karen Mutalik, BS; Joanne M. Murabito, MD, MPH; Mark Moskowitz, MD, MPH; Ralph B. D'Agostino, PhD; Peter W. F. Wilson, MD

Background: Previous studies of estrogen replacement therapy and lens opacities have not reported consistent findings.

Objective: To investigate whether postmenopausal estrogen use is associated with the occurrence of age-related lens opacities (nuclear, cortical, and posterior subcapsular).

Methods: Surviving members of the original cohort of the Framingham Heart Study who also participated in the Framingham Eye Study (1986-1989) were examined for the absence or presence of lens opacities. Data from the Framingham Heart Study, including information on menopausal status (collected biennially from approximately 1948) and use of estrogen replacement therapy (collected biennially from approximately 1960) were used to examine associations between lens opacities and duration of postmenopausal estrogen use, type of menopause, and age at menopause. Five hundred twenty-nine women, aged 66 to 93 years, were included. Multivariable-adjusted odds ratios of specific types of lens opacities were calculated for (1) duration of estrogen use (never and 1-2, 3-9, and ≥10 years), (2) surgical vs natural menopause, and (3) age at menopause.

Results: Longer duration of postmenopausal estrogen therapy was inversely associated with the presence of nuclear lens opacities in an adjusted model. Women who had taken estrogen for 10 years or longer had a 60% reduction in risk compared with nonusers (odds ratio, 0.4; 95% confidence interval, 0.2-1.01). Longer duration of estrogen use was associated with fewer posterior subcapsular opacities at a borderline level of significance. No association was noted for cortical opacities. The risk of posterior subcapsular opacities was significantly increased for women who had undergone surgical menopause compared with women with natural menopause (odds ratio, 2.2; 95% confidence interval, 1.1-4.3). No association was noted for lens opacities and age at menopause.

Conclusion: Data from our study and other studies suggest that a reduction in the risk of lens opacities may be an additional benefit of postmenopausal estrogen use.

Arch Intern Med. 2001;161:1448-1454

From the Section of General Internal Medicine, University of Minnesota School of Medicine, Minneapolis Veterans Affairs Medical Center, Minneapolis (Dr Worzala); Division of Epidemiology and Clinical Research, National Eye Institute, Bethesda, Md (Ms Hiller and Dr Sperduto); National Heart, Lung, and Blood Institute, Framingham, Mass (Ms Mutalik and Drs Murabito and Wilson); Sections of General Internal Medicine (Drs Murabito and Moskowitz) and Endocrinology (Dr Wilson), Boston University School of Medicine, Boston, Mass; and Department of Mathematics and Statistics, Boston University (Dr D'Agostino).

AGE-RELATED cataract is a major cause of visual impairment and blindness throughout the world. In the United States, cataract surgery is the most frequently performed surgical procedure in the Medicare program, with about 1.35 million cataract operations done each year.[1] Nuclear and cortical cataracts are by far the most common types of cataract in the general population, but posterior subcapsular and nuclear cataracts are the predominant types in surgical series.[2] Histologic, biochemical, and physiologic differences in the 3 major types of cataract suggest that risk factors for cataract be investigated separately for the 3 types. Factors that may predispose to cataract formation include aging, diabetes mellitus, cigarette smoking, elevated body mass index (BMI), UV light, alcohol use, and perhaps a history of systemic hypertension.[3-11] A protective role of micronutrients in the development of cataracts has attracted much recent interest, but studies to date have been inconclusive.[3,4,12]

Previous studies have demonstrated that men and premenopausal women have similar prevalences of cataract; however, in postmenopausal women the prevalence of cataracts is increased relative to men of equivalent age.[13-17] The increased prevalence of cataracts in postmenopausal women suggests a possible role for estrogen in retarding cataract formation. Two population-based cross-sectional studies have reported beneficial effects of estrogen replacement therapy on specific types of cataract.[18,19] A third population-based cross-sectional study reported no protective association between hormone

SUBJECTS AND METHODS

The Framingham Heart Study consists of a cohort that has been examined approximately every 2 years since 1948.[20] Eye examinations were conducted on 2675 persons (1117 men and 1558 women) between 1973 and 1975, at approximately the time of the 12th biennial heart study examination.[13,21] Of the 2675 Framingham subjects, 2670 were white.[22] Survivors of the Framingham Eye Study (FES I) were reexamined between 1986 and 1989.[23] The dates of the second Framingham Eye Study (FES II) correspond to the 19th to 20th heart study biennial examination. Of the 1558 women examined during FES I, 565 had died by the time of FES II and 340 were unavailable for the examination, leaving 653 women eligible for the study. The 340 women who were not available for the FES II eye examination were similar to the 653 women with respect to diabetes, hypertension, smoking history, and BMI measurement at the time of FES I.

LENS OPACITY CLASSIFICATION

Participants in FES II were examined by 2 certified, experienced examiners who evaluated lens status at the slit lamp through a dilated pupil by means of a standardized grading system described by Taylor and West.[24] For nuclear cataract, 3 standard photographs of lenses with increasing levels of nuclear opalescence were used to grade nuclear status on a scale of 0 to 3. We considered a nuclear opacity to be present if the grade was 2 or 3. Cortical opacities were graded by estimating the cumulative number of one-eighth wedges of the retroilluminated lens affected by cortical opacities. A cortical opacity was judged to be present if the opacity affected at least one eighth the area of the lens cortex. Posterior subcapsular opacity was present when either the vertical or horizontal width of a posterior subcapsular opacity seen on retroillumination was at least 1 mm. A person was considered to have a specific type of lens opacity when the opacity was present in either eye, regardless of the presence or absence of other opacity types.

MENOPAUSAL STATUS AND POSTMENOPAUSAL ESTROGEN USE

Age and type of menopause were ascertained through 1978, ie, about the time of Framingham Heart Study examination 14. At biennial examinations 1 through 14, women were asked if they were still menstruating. If menses had ceased for 1 year or more, their age at the time of cessation of menses and the cause of cessation (natural, surgical, or other) were recorded. The date of menopause assigned for women with natural cessation was 1 year after the last menstruation. Surgical menopause was defined as the cessation of menstrual periods because of hysterectomy and bilateral oophorectomy. Cases of surgical menopause were confirmed by examining the surgeons' operative notes and pathology reports. For the purposes of this study, women who underwent hysterectomy but not oophorectomy were classified as having natural menopause, and the average age of menopause in the cohort was assigned.

Since 1960 (the seventh biennial examination), women were asked about postmenopausal estrogen hormone use since their last examination. Charts were reviewed to verify estrogen use. Estrogen use of less than 1 year was categorized as 1 year of use, and estrogen use of 1 year or more, as 2 years of use. Lifetime duration of postmenopausal estrogen use was determined by summing the estrogen use from the 7th through the 20th biennial examinations. Almost all women who used estrogen took the oral conjugated form at a dosage of 0.625 mg or more daily.[25-27] Reported use of progesterone was rare in the early cohort examinations. The use of estrogen in combination with progesterone did not become widespread until the early 1980s.[28,29] Only 7% of women attending examinations 19 and 20 who reported estrogen use also reported progesterone use.

OTHER FACTORS

Other potential risk factors for cataract were included in the analyses. Examination 20 data were used except for subjects who did not attend examination 20; for them, examination 19 data were used. Women were considered to have diabetes mellitus if they had a random blood glucose determination of greater than 8.3 mmol/L (150 mg/dL) on at least 2 examinations, abnormal results of a glucose tolerance test, or a history of treatment by a physician for diabetes mellitus. The mean of 2 blood pressures taken by a physician was used to determine the presence of hypertension. Hypertension was defined as a systolic blood pressure of greater than 160 mm Hg or diastolic blood pressure of greater than 95 mm Hg. Data on smoking status in the previous year were collected at each biennial examination. Women who reported cigarette smoking at either examination 19 or 20 were considered current smokers. Women who did not smoke at examination 19 or 20 but had been smokers at preceding examinations were considered past smokers, and women who did not smoke at any of the examinations were categorized as never smokers. Body mass index was computed as weight in kilograms divided by the square of height in meters.

STATISTICAL METHODS

Six hundred fifty-three women were examined in FES II. We excluded 114 women who had missing data on estrogen use on 3 or more Framingham Heart Study examinations. Furthermore, we excluded 7 women for whom type of menopause (natural or surgical) could not be determined, 2 women who had menopause from other causes, and 1 woman for whom the presence or absence of lens opacity or aphakia was not coded. The study population thus consisted of 529 women for whom estrogen use, natural or surgical menopause, and presence or absence of lens opacities could be determined. The 529 women in the study group were on average about 2.5 years older at the time of the eye examination than the 124 excluded women (75.5 years in the study group vs 73.0 years in the excluded group). The prevalences of lens opacities, diabetes, hypertension, and smoking history were similar in both groups.

Multivariable logistic regression was used to assess the association of lens opacities with duration of postmenopausal estrogen use, age at menopause, and type of menopause (surgical or natural). Adjustments were made for potential confounders: age at eye examination, diabetes, BMI, cigarette smoking, and hypertension. All P values were 2-sided and were obtained, except where noted, by likelihood ratio tests.[30]

Table 1. Characteristics of Postmenopausal Study Subjects

	No. (%)†
Total	**529 (100)**
Age, y	
66-74	257 (49)
75-93	272 (51)
Lens opacities without regard to type (including aphakia)	
Yes	395 (75)
No (clear lenses)	134 (25)
Nuclear lens opacities*	
Yes (nuclear alone or in combination with other lens opacities)	269 (51)
No (clear lenses, or cortical, or posterior subcapsular)	201 (38)
Unknown (aphakia in both eyes, or aphakia in one eye and clear lens in the other eye)	59 (11)
Cortical lens opacities*	
Yes (cortical alone or in combination with other lens opacities)	172 (33)
No (clear lenses, or nuclear, or PSC)	281 (53)
Unknown (aphakia in both eyes, or aphakia in one eye and clear lens in the other eye)	76 (14)
PSC lens opacities*	
Yes (PSC alone or in combination with other lens opacities)	77 (15)
No (clear lenses, or nuclear, or cortical)	368 (70)
Unknown (aphakia in both eyes, or aphakia in one eye and clear lens in the other eye)	84 (16)
Duration of postmenopausal hormone use, y	
0	338 (64)
1-2	75 (14)
3-9	73 (14)
≥10	43 (8)
Type of menopause	
Natural	415 (78)
Surgical	114 (22)
Age at menopause, y	
Normal (45-53)	358 (68)
Early (23-44)	126 (24)
Late (≥54)	45 (8)
Diabetes	
Yes	55 (10)
No	474 (90)
Body mass index, kg/m^2	
<22.0	88 (17)
22.0-27.7	269 (51)
≥27.8	169 (32)
Unknown	3 (1)
Hypertension	
Yes	326 (62)
No	200 (38)
Unknown	3 (1)
Cigarette smoking	
Never	263 (50)
Past	205 (39)
Current	60 (11)
Unknown	1 (<1)

*Specified lens opacity in at least 1 eye. PSC indicates posterior subcapsular.
†Because of rounding, percentages may not all total 100.

Table 2. Adjusted Odds Ratios for Lens Opacities Without Regard to Type (Including Aphakia)*

	Age-Adjusted† OR (95% CI)	Multivariable‡ OR (95% CI)
Duration of estrogen use, y		
0	1.0	1.0
1-2	0.8 (0.4-1.5)	0.8 (0.4-1.5)
3-9	0.8 (0.4-1.4)	0.7 (0.3-1.3)
≥10	0.5 (0.2-1.1)§	0.4 (0.2-0.9)‖
P¶	.07	.02
Type of menopause		
Natural	1.0	1.0
Surgical	1.1 (0.7-1.9)	1.5 (0.8-2.9)
P	.68	.21
Age at menopause		
Normal	1.0	1.0
Early	1.1 (0.6-1.8)	1.1 (0.6-1.8)
Late	0.9 (0.4-2.1)	1.0 (0.4-2.4)
P	.94	.95
Diabetes		
No	1.0	1.0
Yes	1.1 (0.5-2.2)	1.0 (0.5-2.0)
P	.87	.97
Body mass index, kg/m^2		
<22.0	1.0	1.0
22.0-27.7	0.8 (0.5-1.6)	0.9 (0.5-1.6)
≥27.8	1.2 (0.6-2.3)	1.1 (0.5-2.1)
P	.41	.74
Hypertension		
No	1.0	1.0
Yes	1.2 (0.8-1.9)	1.2 (0.7-1.9)
P	.37	.46
Cigarette smoking		
Never	1.0	1.0
Past	1.1 (0.7-1.7)	1.2 (0.7-1.9)
Current	0.9 (0.5-1.9)	1.0 (0.5-1.9)
P	.91	.74

*OR indicates odds ratio; CI, confidence interval.
†Sample sizes varied for the risk factors depending on the availability of the data. Of the 395 cases, the number included in the analysis ranged from 392 to 395. Of the 134 controls, the number ranged from 133 to 134.
‡Odds ratio adjusted for age at eye examination (years), and the variables shown in the table. The multivariable model included 392 subjects with lens opacities and 133 with clear lenses.
§P<.10 (Wald test).
‖P<.05 (Wald test).
¶P values were computed as χ^2 tests for trend with 1 df for all variables, except for age at menopause and cigarette smoking. Because age at menopause and cigarette smoking (see Table 1) do not have a natural ordering, a χ^2 test with 2 df was used.

replacement therapy and cataract.[17] We had the opportunity to study women participating in the Framingham Heart Study, who have provided information on hormone use at each biennial examination since about 1960 and who participated in the Framingham Eye Study from 1986 to 1989. Our primary goal was to examine the relationship between age-related lens opacities, in particular the specific types of opacity, and the use of estrogen replacement therapy. A second aim was to evaluate the relationship between lens opacities and age and type (surgical vs natural) of menopause.

RESULTS

Table 1 shows the characteristics of the 529 study participants. Lens opacities, including aphakia, were present in 395 women. Nuclear, cortical, and posterior subcapsular opacities, each with or without other lens opacities, occurred in 269, 172, and 77 women, respectively.

The women's ages ranged from 66 to 93 years; mean age was 75.5 years. Three hundred thirty-eight (64%) of the 529 participants were nonestrogen users. Among the 191 estrogen users, 43 (23%) had used them for 10 years or more (Table 1). Only 35 women were current postmenopausal estrogen users; 21 of them (60%) had taken the preparation for 10 years or more (data not shown).

Tables 2, **3**, **4**, and **5** provide results of the multivariable logistic regression. For each lens opacity type, we initially evaluated the 1 three-way and 3 two-way interactions of duration of postmenopausal estrogen use,

Table 3. Adjusted Odds Ratios for Nuclear Lens Opacities*

	Age-Adjusted† OR (95% CI)	Multivariable‡ OR (95% CI)
Nuclear Lens Opacities		
Duration of estrogen use, y		
0	1.0	1.0
1-2	0.9 (0.5-1.6)	0.8 (0.4-1.6)
3-9	0.7 (0.4-1.2)	0.6 (0.3-1.2)
≥10	0.5 (0.3-1.1)§	0.4 (0.2-1.01)§
P‖	.04	.02
Type of menopause		
Natural	1.0	1.0
Surgical	0.9 (0.5-1.4)	1.3 (0.7-2.4)
P	.58	.36
Age at menopause		
Normal	1.0	1.0
Early	0.9 (0.5-1.4)	0.9 (0.6-1.5)
Late	1.2 (0.6-2.7)	1.3 (0.6-2.9)
P	.68	.77
Diabetes		
No	1.0	1.0
Yes	0.6 (0.3-1.1)	0.6 (0.3-1.1)
P	.10	.12
Body mass index, kg/m^2		
<22.0	1.0	1.0
22.0-27.7	0.6 (0.3-1.03)	0.6 (0.3-1.1)
≥27.8	0.5 (0.3-1.03)	0.6 (0.3-1.2)
P	.10	.21
Hypertension		
No	1.0	1.0
Yes	0.9 (0.6-1.3)	0.9 (0.6-1.5)
P	.44	.82
Cigarette smoking		
Never	1.0	1.0
Past	1.2 (0.8-1.9)	1.3 (0.8-2.1)
Current	1.6 (0.8-3.1)	1.5 (0.8-3.0)
P	.36	.35

*OR indicates odds ratio; CI, confidence interval.

†Sample sizes varied for the risk factors depending on the availability of the data. Of the 269 cases, the number included in the analysis ranged from 268 to 269. Of the 201 controls, the number ranged from 199 to 201.

‡Odds ratio adjusted for age at eye examination (years), and the variables shown in the table. The multivariable model included 268 subjects with nuclear lens opacities and 199 nonnuclear controls.

§P<.10 (Wald test).

‖P values were computed as χ^2 tests for trend with 1 df for all variables, except for age at menopause and cigarette smoking. Because age at menopause and cigarette smoking (see Table 1) do not have a natural ordering, a χ^2 test with 2 df was used.

Table 4. Adjusted Odds Ratios for Cortical Lens Opacities*

	Age-Adjusted† OR (95% CI)	Multivariable‡ OR (95% CI)
Duration of estrogen use, y		
0	1.0	1.0
1-2	0.9 (0.5-1.7)	0.9 (0.5-1.7)
3-9	1.1 (0.6-2.0)	1.2 (0.6-2.2)
≥10	0.8 (0.4-1.7)	0.8 (0.4-1.8)
P§	.82	.81
Type of menopause		
Natural	1.0	1.0
Surgical	1.3 (0.8-2.0)	1.3 (0.7-2.2)
P	.33	.43
Age at menopause		
Normal	1.0	1.0
Early	1.0 (0.6-1.6)	0.9 (0.5-1.4)
Late	0.8 (0.4-1.6)	0.8 (0.4-1.7)
P	.80	.81
Diabetes		
No	1.0	1.0
Yes	0.8 (0.4-1.6)	0.7 (0.4-1.4)
P	.61	.32
Body mass index, kg/m^2		
<22.0	1.0	1.0
22.0-27.7	1.4 (0.8-2.5)	1.3 (0.7-2.4)
≥27.8	2.4 (1.3-4.5)‖	2.2 (1.1-4.2)‖
P	.002	.008
Hypertension		
No	1.0	1.0
Yes	1.5 (0.98-2.3)	1.3 (0.9-2.0)
P	.06	.22
Cigarette smoking		
Never	1.0	1.0
Past	0.9 (0.6-1.3)	0.9 (0.6-1.4)
Current	0.9 (0.5-1.8)	1.1 (0.5-2.1)
P	.79	.90

*OR indicates odds ratio; CI, confidence interval.

†Sample sizes varied for the risk factors depending on the availability of the data. Of the 172 cases, the number included in the analysis ranged from 170 to 172. Of the 281 controls, the number ranged from 280 to 281.

‡Odds ratio adjusted for age at eye examination (years), and the variables shown in the table. The multivariable model included 170 subjects with cortical lens opacities and 280 noncortical controls.

§P values were computed as χ^2 tests for trend with 1 df for all variables, except for age at menopause and cigarette smoking. Because age at menopause and cigarette smoking (see Table 1) do not have a natural ordering, a χ^2 test with 2 df was used.

‖P<.05 (Wald test).

age at menopause, and type of menopause. None of the interactions were significant at the $P<.05$ level. After adjustment for age at menopause, type of menopause, age at the eye examination, BMI, diabetes, hypertension, and cigarette smoking, we found that longer duration of estrogen use was inversely associated with risk of lens opacities without regard to type. For categories of increasing duration of estrogen use (never and 1-2, 3-9, and ≥10 years), the odds ratios were 1.0, 0.8, 0.7, and 0.4, respectively (test for trend, $P=.02$). In particular, women who had taken estrogen preparations for 10 years or more were at significantly lower risk of having lens opacities than the non–estrogen takers (odds ratio, 0.4; $P=.03$). Increasing duration of postmenopausal estrogen use was strongly associated with a decreased prevalence of nuclear lens opacities (test for trend, $P=.02$), borderline associated with decreased risk for posterior subcapsular lens opacities (test for trend, $P=.06$), and not associated with cortical lens opacities (test for trend, $P=.81$).

The risk of posterior subcapsular opacities was significantly increased for women who had undergone surgical menopause (odds ratio, 2.2; 95% confidence interval, 1.1-4.3) compared with women who had undergone natural menopause (Table 5).

Age at menopause ranged from 26 to 58 years; mean age was 47 years (data not shown). Compared with normal age at menopause (45 to 54 years), neither early nor late age at menopause was associated with lens opacities (Tables 2-5).

The multivariable logistic regression analysis found that posterior subcapsular lens opacities were more common in diabetic subjects (Table 5) and that larger values

Table 5. Adjusted Odds Ratios for Posterior Subcapsular Lens Opacities*

	Age-Adjusted† OR (95% CI)	Multivariable‡ OR (95% CI)
Duration of estrogen use, y		
0	1.0	1.0
1-2	0.3 (0.1-0.9)§	0.3 (0.1-0.8)§
3-9	1.2 (0.6-2.4)	0.8 (0.4-1.8)
≥10	0.6 (0.2-1.7)	0.3 (0.1-1.1)
P‖	.37	.06
Type of menopause		
Natural	1.0	1.0
Surgical	1.7 (0.97-3.0)	2.2 (1.1-4.3)
P	.07	.02
Age at menopause		
Normal	1.0	1.0
Early	1.3 (0.7-2.3)	1.3 (0.7-2.4)
Late	0.9 (0.4-2.4)	1.3 (0.5-3.4)
P	.63	.69
Diabetes		
No	1.0	1.0
Yes	2.7 (1.4-5.3)	2.4 (1.2-5.0)
P	.006	.008
Body mass index, kg/m^2		
<22.0	1.0	1.0
22.0-27.7	0.9 (0.5-1.9)	0.8 (0.4-1.7)
≥27.8	0.9 (0.4-1.8)	0.6 (0.3-1.4)
P	.67	.17
Hypertension		
No	1.0	1.0
Yes	1.5 (0.9-2.7)	1.6 (0.9-2.8)
P	.11	.14
Cigarette smoking		
Never	1.0	1.0
Past	1.1 (0.6-1.8)	1.1 (0.6-1.9)
Current	0.6 (0.2-1.6)	0.6 (0.2-1.7)
P	.47	.39

*OR indicates odds ratio; CI, confidence interval.

†Sample sizes varied for the risk factors depending on the availability of the data. All 77 cases were included in the analysis. Of the 368 controls, the number ranged from 365 to 368.

‡Odds ratio adjusted for age at eye examination (years), and the variables shown in the table. The multivariable model included 77 subjects with posterior subcapsular lens opacities and 365 non–posterior subcapsular controls.

§P<.05 (Wald test).

‖P values were computed as χ^2 tests for trend with 1 df for all variables, except for age at menopause and cigarette smoking. Because age at menopause and cigarette smoking (see Table 1) do not have a natural ordering, a χ^2 test with 2 df was used.

of BMI were associated with the presence of cortical opacities (Table 4).

COMMENT

Increasing duration of estrogen use was associated with a decreased prevalence of nuclear opacities in the Framingham Eye Study cohort. Posterior subcapsular opacities were also less common in estrogen users, but this finding was at a borderline level of significance. No association was noted for cortical lens opacities. Our finding that estrogen use had a protective effect for lens opacities without regard to type is probably explained by the fact that 85% of the "any" opacity group had either nuclear or posterior subcapsular opacities. These results again stress the need for studying specific types of lens opacities when assessing risk factors for cataract.

Other studies have noted associations between postmenopausal estrogen use and lens opacities. The Beaver Dam Eye Study reported a decreased risk of more severe nuclear sclerosis in current users of postmenopausal estrogen.[18] Younger age at menarche and older age at menopause were also associated with decreased risk of lens opacities, further suggesting hormonal influences on cataractogenesis. No association was found for cortical opacities and no results were reported for posterior subcapsular opacities. The Melton Eye Study found that "ever" use of oral contraceptives resulted in reduced nuclear opalescence but had no effect on cortical opacities.[31] The similarity of findings in these studies with different definitions of opacity and different definitions of hormone use strengthens the likelihood that the relationship between estrogen use and nuclear opacity is real. However, 2 studies reported dissimilar findings. The Blue Mountains Eye Study found that current estrogen users older than 65 years had fewer cortical lens opacities than women who had never used estrogen therapy.[19] In the subset of women with natural rather than surgical menopause, current users of hormone replacement therapy in the Blue Mountains Eye Study had an increased prevalence of posterior subcapsular opacity. The population-based Melbourne Visual Impairment Project reported no associations between hormone replacement therapy and cataract.[17]

In our fully adjusted models, surgical menopause was associated with an increased prevalence of posterior subcapsular opacities. This seems consistent with a hypothesis of a beneficial hormonal effect, since surgical menopause results in a more abrupt decline in levels of endogenous estrogen than does natural menopause. However, the Beaver Dam Eye Study noted a higher prevalence of less severe nuclear sclerosis in women with hysterectomy than in women with natural menopause.[18] The authors suggested that this might reflect the use of estrogen replacement therapy started soon after surgery in women with complete hysterectomies. In our study, with adjustment for estrogen therapy in the model, rates of posterior subcapsular opacity were still higher with surgical menopause. The Blue Mountains Eye Study reported no association between type of menopause and risk of any type of lens opacity.[19]

The mechanism by which estrogen replacement therapy might protect against lens opacities is unclear. In an animal model of age-related cataract, estrogen has been shown to reduce the incidence of methylnitrosourea-induced cataracts in rats subjected to ovariectomy.[32] Since reverse transcription polymerase chain reaction has demonstrated that lens cells express both α and β types of estrogen receptors, it has been suggested that the protective effect of estrogen may be a direct, receptor-mediated one. Other investigators have suggested that estrogen may confer protection against cataracts by affording protection against the effect of transforming growth factor β.[33,34] Transforming growth factor β has been demonstrated to be present in the eye and is capable of inducing opacities in cultured rat lenses. Lenses from rats subjected to ovariectomy are sensitive to the

damaging effects of transforming growth factor β, but in vivo or in vitro estrogen replacement restores resistance. Finally, it has been suggested[19] that the reported antioxidant activity of estrogen[35] may have a beneficial effect on cataractogenesis.

Several potential risk factors for cataract were included in the multivariable analyses. The findings for these factors were generally consistent with previous reports. In particular, the associations between diabetes and posterior subcapsular cataract[5,36] and between higher BMI and cortical cataract[9,37] have been reported. Earlier reports have consistently linked smoking and increased risk of nuclear cataract.[10,11] The odds ratio for current smoking and nuclear cataract was 1.5 in our study, but not significant, perhaps because of low statistical power to examine the relationship in this cohort of women.

A strength of the current report is the prospective design of the Framingham Study, which allowed for ascertainment of estrogen use and menopausal status at each examination (up to 39 years preceding the eye examination). In addition, surgical notes and pathology reports were used to substantiate menopausal status. Previous studies that collected data with a single interview were more likely to have been hampered by inaccurate recall of estrogen use and self-report of details about menopause. For example, women may be aware of their hysterectomy but are less likely to be certain about whether they underwent bilateral oophorectomy. The collection of reliable data on duration of estrogen use was also important because it allowed us to examine the effect of long-term therapy. Other studies of the role of estrogen in disease prevention have suggested that disease prevention is most manifest when estrogen therapy has been used for an extended period. For example, in some[38,39] but not other[40] studies, mortality was reduced in women with longer vs shorter duration of estrogen use. Also, women who had taken estrogen for at least 7 years had significantly higher bone mineral density than those who had taken it for shorter periods.[25] Another strength of the study was the independent collection of estrogen data in the Framingham Heart Study and eye data in the Framingham Eye Study. This eliminated important potential sources of bias in ascertainment of exposure and outcome status.

Our study had some limitations. The original Framingham Eye Study cohort included only 5 nonwhites, so the results cannot necessarily be generalized to nonwhite populations. Also, the study was not designed to investigate dose-response relationships, as estrogen dose was not recorded uniformly during the exposure period. In addition, the study did not address the influence of progesterone on lens opacities. However, recent studies suggest that progesterone does not eliminate the beneficial effects of estrogen on lipid or fibrinogen levels.[41] Another limitation of the study is that lens status was not determined before initiation of estrogen treatment, and therefore some women may have had opacities before treatment. It is reassuring that the associations were strongest for women with longest duration of estrogen treatment and, particularly for this group, it is likely that the treatment began before development of lens opacities. As with other observational studies, the results could also have been affected by uncontrolled confounding. If women who decided to take estrogen replacement therapy were different from the women who did not use estrogen and these differences were related to their risk of lens opacities, the results could have been affected. Adjustments were made in the analyses for known confounders, but the possibility of uncontrolled confounding remains.

Our data suggest a beneficial effect of long-term estrogen replacement therapy on lens opacities. The strength of the association, the dose-response nature of the association, the consistency of the finding across several epidemiologic studies, and the biological plausibility of the association suggest that it is real. Thus, our findings suggest a possible additional benefit of postmenopausal estrogen use. Whether the findings should influence a woman's decision about estrogen replacement therapy should take into account the widespread availability of an effective treatment for cataract and the other potential risks and benefits of such therapy.

Accepted for publication December 4, 2000.

The Framingham Eye Study I and the Framingham Eye Study II were supported by contracts N01-EY-2-2112 and N01-EY-6-2105, respectively, from the National Eye Institute, National Institutes of Health, Bethesda, Md. The Framingham Heart Study is supported by contract NO1-HC-38083.

Corresponding author and reprints: Rita Hiller, MS, Division of Epidemiology and Clinical Research, National Eye Institute, Bldg 31, Room 6A52, 31 Center Dr MSC 2510, Bethesda, MD 20892-2510.

REFERENCES

1. Steinberg EP, Javitt JC, Sharkey PD, et al. The content and cost of cataract surgery. *Arch Ophthalmol.* 1993;111:1041-1049.
2. Adamsons I, Munoz B, Enger C, Taylor HR. Prevalence of lens opacities in surgical and general populations. *Arch Ophthalmol.* 1991;109:993-997.
3. West SK, Valmadrid CT. Epidemiology of risk factors for age-related cataract. *Surv Ophthalmol.* 1995;39:323-334.
4. Hodge WG, Whitcher JP, Satariano W. Risk factors for age-related cataracts. *Epidemiol Rev.* 1995;17:336-346.
5. Hiller R, Sperduto RD, Ederer F. Epidemiologic associations with nuclear, cortical, and posterior subcapsular cataracts. *Am J Epidemiol.* 1986;124:916-925.
6. Hankinson SE, Seddon JM, Colditz GA, et al. A prospective study of aspirin use and cataract extraction in women. *Arch Ophthalmol.* 1993;111:503-508.
7. Glynn RJ, Christen WG, Manson JE, Bernheimer J, Hennekens CH. Body mass index: an independent predictor of cataract. *Arch Ophthalmol.* 1995;113:1131-1137.
8. Klein BEK, Klein R, Moss SE. Incident cataract surgery: the Beaver Dam Eye Study. *Ophthalmology.* 1997;104:573-580.
9. Hiller R, Podgor MJ, Sperduto RD, et al. A longitudinal study of body mass index and lens opacities: the Framingham Studies. *Ophthalmology.* 1998;105:1244-1250.
10. Hiller R, Sperduto RD, Podgor MJ, et al. Cigarette smoking and the risk of development of lens opacities. *Arch Ophthalmol.* 1997;115:1113-1118.
11. Solberg Y, Rosner M, Belkin M. The association between cigarette smoking and ocular diseases. *Surv Ophthalmol.* 1998;42:535-547.
12. Sperduto RD, Ferris FL III, Kurinij N. Do we have a nutritional treatment for age-related cataract or macular degeneration? *Arch Ophthalmol.* 1990;108:1403-1405.
13. Kahn HA, Leibowitz HM, Ganley JP, et al. The Framingham Eye Study, I: outline and major prevalence findings. *Am J Epidemiol.* 1977;106:17-32.
14. Sperduto RD, Hiller R. The prevalence of nuclear, cortical, and posterior subcapsular lens opacities in a general population sample. *Ophthalmology.* 1984;91:815-818.

15. Klein BEK, Klein R, Linton KLP. Prevalence of age-related lens opacities in a population: the Beaver Dam Eye Study. *Ophthalmology*. 1992;99:546-552.
16. Mitchell P, Cumming RG, Attebo K, Panchapakesan J. Prevalence of cataract in Australia: the Blue Mountains Eye Study. *Ophthalmology*. 1997;104:581-588.
17. McCarty CA, Mukesh BN, Fu CL, Taylor HR. The epidemiology of cataract in Australia. *Am J Ophthalmol*. 1999;128:446-465.
18. Klein BEK, Klein R, Ritter LL. Is there evidence of an estrogen effect on age-related opacities? The Beaver Dam Eye Study. *Arch Ophthalmol*. 1994;112:85-91.
19. Cumming RG, Mitchell P. Hormone replacement therapy, reproductive factors, and cataract: the Blue Mountains Eye Study. *Am J Epidemiol*. 1997;145:242-249.
20. Dawber TR, Meadors GF, Moore FE Jr. Epidemiological approaches to heart disease: the Framingham Study. *Am J Public Health*. 1951;41:279-286.
21. Leibowitz HM, Krueger DE, Maunder LR, et al. The Framingham Study monograph: an ophthalmological and epidemiological study of cataract, glaucoma, diabetic retinopathy, macular degeneration, and visual acuity in a general population of 2631 adults, 1973-1975. *Surv Ophthalmol*. 1980;24(suppl):335-610.
22. Ederer F, Hiller R, Taylor HA. Senile lens changes and diabetes in two population studies. *Am J Ophthalmol*. 1981;91:381-395.
23. Podgor MJ, Hiller R, and the Framingham Eye Studies Group. Associations of types of lens opacities between and within eyes of individuals: an application of the second-order generalized estimating equations. *Stat Med*. 1996;15:145-156.
24. Taylor HR, West SK. The clinical grading lens opacities. *Aust N Z J Ophthalmol*. 1989;17:81-86.
25. Keil DP, Felson DT, Anderson JJ, Wilson PWF, Moskowitz MA. Hip fracture and the use of estrogens in postmenopausal women: the Framingham Study. *N Engl J Med*. 1987;317:1169-1174.
26. Felson DT, Zhang Y, Hannan MT, Kiel DP, Wilson PWF, Anderson JJ. The effect of postmenopausal estrogen therapy on bone density in elderly women. *N Engl J Med*. 1993;329:1141-1146.
27. Wilson PWF, Garrison RJ, Castelli WP. Postmenopausal estrogen use, cigarette smoking, and cardiovascular morbidity in women over 50: the Framingham Study. *N Engl J Med*. 1985;313:1038-1043.
28. Kuller LH. Hormone replacement therapy and coronary heart disease: a new debate. *Med Clin North Am*. 2000;84:181-198.
29. Grady D, Rubin SM, Petitti DB, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann Intern Med*. 1992;117:1016-1037.
30. Dixon WJ, ed. *BMDP Statistical Software Manual*. Berkeley: University of California Press; 1990.
31. Thompson JR, Deane JS, Hall AB, Rosenthal AR. Oestrogen and lens opacities in the Melton Eye Study [abstract]. *Invest Ophthalmol Vis Sci*. 1996;37:S585.
32. Bigsby RM, Cardenas H, Caperell-Grant A, Grubbs CJ. Protective effects of estrogen in a rat model of age-related cataracts. *Proc Natl Acad Sci U S A*. 1999;96:9328-9332.
33. Hales AM, Schulz MW, Chamberlain CG, McAvoy JW. TGF-β 1 induces lens cells to accumulate α-smooth muscle actin, a marker for subcapsular cataracts. *Curr Eye Res*. 1994;13:885-890.
34. Hales AM, Chamberlain CG, Murphy CR, McAvoy JW. Estrogen protects lenses against cataract induced by transforming growth factor-β (TGFβ). *J Exp Med*. 1997;185:273-280.
35. Niki E, Nakano M. Estrogens as antioxidants. *Methods Enzymol*. 1990;186:330-333.
36. Leske MC, Chylack LT, Wu SY, the Lens Opacities Case-Control Study Group. The Lens Opacities Case-Control Study: risk factors for cataract. *Arch Ophthalmol*. 1991;109:244-251.
37. Caulfield LE, West SK, Barron Y, Cid-Ruzafa J. Anthropometric status and cataract: the Salisbury Eye Evaluation Project. *Am J Clin Nutr*. 1999;69:237-242.
38. Ettinger B, Friedman GD, Bush T, Quesenberry CPJ. Reduced mortality associated with long-term postmenopausal estrogen therapy. *Obstet Gynecol*. 1996;87:6-12.
39. Henderson BE, Paganini-Hill A, Ross RK. Decreased mortality in users of estrogen replacement therapy. *Arch Intern Med*. 1991;151:75-78.
40. Stampfer MJ, Colditz GA, Willett WC, et al. Postmenopausal estrogen therapy and cardiovascular disease: ten-year follow-up from the Nurses' Health Study. *N Engl J Med*. 1991;325:756-762.
41. The Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women: the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *JAMA*. 1995;273:199-208.