American Journal of Epidemiology
Vol 145, No 3

Printed in U.S.A.

Hormone Replacement Therapy, Reproductive Factors, and Cataract

The Blue Mountains Eye Study

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The relation between estrogen (endogenous and exogenous) and cataract is unclear, with one large population-based study recently suggesting a protective effect of estrogen replacement therapy. The study reported in this paper, the Blue Mountains Eye Study, was conducted in Australia in 1992–1993 and involved 2,072 women aged 49–97 years. Subjects were recruited from a defined geographic area; the participation rate was 83 percent. Eye examination included photographs of the lens, which were graded for presence and severity of cortical, nuclear, and posterior subcapsular cataracts. Later age at menarche was associated with increased prevalence of all three types of cataract, but there were no associations with age at menopause, number of children, or use of the oral contraceptive pill. Among all women, there was no association between hormone replacement therapy and cataract. However, current users of hormone replacement therapy aged 65 years and over, among whom the duration of use was likely to have been longer than in younger current users, had lower prevalence of cortical cataract than did never users, the odds ratio adjusted for numerous potential confounders was 0.4 (95 percent confidence interval 0.2–0.8). The prevalence of posterior subcapsular cataract was increased in current users of hormone replacement therapy who had had a nonsurgical menopause; the adjusted odds ratio was 2.1 (95 percent confidence interval 1.1–4.1). The results of this study support the hypothesis that estrogen and/or progestin may be involved in cataract development. The effect of hormone replacement therapy on the lens needs to be evaluated in the laboratory and in further observational epidemiologic studies. *Am J Epidemiol* 1997;145:242–9.

cataract; estrogen replacement therapy, menarche; menopause; risk factors

Observational epidemiologic studies suggest that estrogen replacement therapy reduces the risk of ischemic heart disease and hip fractures and increases the risk of endometrial and breast cancers (1). A recent report from the Beaver Dam Eye Study raised the possibility that estrogen replacement therapy may reduce the risk of some types of cataract (2). Cataracts are the most common eye disease in older people (3); a protective effect of hormone replacement therapy would have important public health and clinical implications.

The Blue Mountains Eye Study is a population-based study of 3,654 older Australians, designed to assess the prevalence, incidence, natural history, and etiology of a number of eye diseases (4). Baseline (cross-sectional) data were collected in 1992 and 1993. We have analyzed these data to assess the relation between prevalent cataracts (cortical, nuclear, and posterior subcapsular) and use of hormone replacement therapy. We also assessed the relations between cataract and ages at menarche and menopause, number of children, use of the oral contraceptive pill, and surgical (vs. natural) menopause.

Received for publication February 3, 1996, and in final form October 18, 1996.

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MATERIALS AND METHODS

The Blue Mountains Eye Study is a population-based survey of vision and common eye diseases in an urban population comprising two postal code areas in the Blue Mountains region west of Sydney, Australia. Details of recruitment methods are given elsewhere (4). In brief, after a door-to-door census of the region, all permanent residents with a birth date prior to January 1, 1943, were invited to attend a local clinic for a detailed eye examination. Nursing home residents are not included in this report. The number of eligible residents found by our census differed from the Australian Census, conducted 3 months earlier, by only six persons. Of the 2,498 eligible women identified at our

census, 2,072 women attended the study clinic between January 1992 and January 1994.

Ethical approval for the study was obtained from the Western Sydney Area Health Service Human Ethics Committee, and informed consent was obtained from all participants.

Eye examination and grading of cataracts

Subjects underwent a detailed eye examination, including subjective refraction using a LogMar chart. Photographs of the lens of each eye were taken after pupil dilatation with 1 percent tropicamide and 10 percent phenylephrine. The protocol for lens photography and grading closely followed the Wisconsin Cataract Grading System (5, 6) developed for the Beaver Dam Eye Study (2, 7–10).

Slit lamp photographs were taken to assess the severity of nuclear lens opacities using a Topcon SL-7E Photo Slit Lamp Camera (Topcon Optical Co., Tokyo, Japan). This camera was specially modified with the illumination beam fixed at 45° to the observation system and the slit-beam width and height set to 0.3 mm and 9.0 mm, respectively. A specially designed fixation target provided by Michael Neider of the University of Wisconsin at Madison, Madison, Wisconsin, ensured that a standard angle was used to photograph right and left eyes (5).

Retroillumination photographs of the anterior and posterior lens were taken to assess presence and severity of cortical and posterior subcapsular lens opacities. A Neitz Cataract CT-R Camera CT-R (Neitz Instruments Co., Tokyo, Japan) was used, modified according to the Wisconsin protocol, with fixation targets for each eye and a linear potentiometer to measure the distance between the anterior and posterior photographs (5).

The severity of nuclear cataract on a five-point scale was assessed by comparing photographs of subjects' eyes with a set of four standard photographs. The presence and severity of cortical cataract was graded by placing over the Neitz photographs a circular grid divided into eight equal wedges and a central circle. Graders estimated the percentage of the area of each of these nine segments that was involved by cataract. These percentages were summed to give an estimate of the total area of the lens affected by cataract. Posterior subcapsular cataract was graded similarly. Photographs taken with pupils less than 4 mm in either vertical or horizontal diameter were excluded from cortical cataract analyses. The nuclear cataract standard photographs and the grid were provided by Dr. Barbara Klein of the University of Wisconsin at Madison. All photographs were graded by one of two masked graders. Quadratic weighted kappas for intergrader reproducibility were 0.79 for nuclear cataract (n = 260 eyes), 0.78 for cortical cataract (n = 379 eyes), and 0.57 for posterior subcapsular cataract (n = 383 eyes).

Data on cortical and posterior subcapsular cataract were missing from about 3 percent of subjects because photographs were not gradable or were not taken. Because of camera malfunction, 615 subjects (30 percent) did not have photographs suitable for nuclear cataract grading. These subjects did not differ in any important way from subjects with gradable photographs. Mean ages were similar (66.4 years in those without photographs vs. 65.9 years in those with photographs), as were the percentages with a history of use of hormone replacement therapy (32 vs. 29 percent), cortical cataracts (26 percent in each group), and posterior subcapsular cataracts (6 percent of each group).

Questionnaire data

An interviewer-administered questionnaire was used to collect information on a wide range of possible risk factors for cataract. The reproductive history included questions about the ages when menstrual periods started and ended; the number of pregnancies and number of children; use of the oral contraceptive pill; history of hysterectomy and oophorectomy; and history of use of hormone replacement therapy, including the name(s) and duration(s) of currently used preparations. No data on type or duration of use were collected for hormone preparations used in the past.

There were 63 women who reported that they were current users of hormone replacement therapy but who did not know the name or type of preparation that they were using. These women were included in analyses involving all users of hormone replacement therapy, but had to be excluded from analyses involving unopposed estrogen and estrogen/progestin combinations.

Duration of exposure to endogenous estrogen was defined as the number of years between menarche and menopause. Surgical menopause was defined as cessation of menstrual periods due to hysterectomy and bilateral oophorectomy. The category natural menopause included women who did not cease menstruating because of hysterectomy and those who had had a hysterectomy without oophorectomy.

The questionnaire also included questions on smoking history and the frequency and quantity of current alcohol use. Higher educational achievement was defined as attainment of a qualification (a certificate, diploma, or degree) after leaving high school. Subjects were asked whether they had ever been told by a doctor that they had diabetes or high blood pressure. Systolic and diastolic blood pressures were measured

with a standard sphygmomanometer after the subject had been sitting for at least 5 minutes and before any eye drops were instilled. In this paper, hypertension was defined as a history of high blood pressure and/or a diastolic pressure over 95 mmHg and/or a systolic pressure over 160 mmHg. A detailed history of use of oral and inhaled steroids was obtained.

The percentages of subjects with missing data for study variables were: age at menarche, 5 percent; age at menopause, 10 percent; menopausal status, 1 percent; type of menopause, 12 percent; ever use of hormone replacement therapy, 4 percent; type of current hormone replacement therapy, 20 percent of current users; and duration of use of current hormone replacement therapy preparation, 5 percent of current users.

Statistical analysis

The main statistical method employed was ordinal regression, using the cumulative odds model (11). The cumulative odds model gives odds ratios that represent the probability of having a cataract of a particular severity (or greater) compared with the probability of having a less severe cataract. Nuclear cataract was modeled as a five-level variable, while both cortical and posterior subcapsular cataracts were included as three-level variables. Cortical cataract levels were: less than 5 percent of lens involved (n = 1,437), 5–24 percent of lens involved (n = 348), and 25 percent or more of lens involved (n = 154). Posterior subcapsular cataract levels were: 0 percent of lens involved (n = 1,824), less than 5 percent of lens involved (n = 89), and 5 percent or more of lens involved (n = 31). Analyses involved data from the most severely affected eye only.

The assumption underlying the cumulative odds model is that odds ratios do not differ markedly according to outcome levels being compared. This proportional odds assumption held in all models except the multivariate models for posterior subcapsular cataract.

Potential confounders included in multivariate ordinal regression models were age (as a continuous variable), educational achievement, current alcohol consumption (number of drinks per week), smoking (ever vs. never), history of diabetes, hypertension (as defined above), and ever use of oral or inhaled steroids. These variables were selected because 1) they have been shown in other studies to be related to risk of at least one type of cataract; 2) they were related to at least one type of cataract in our data; and 3) most were unevenly distributed in our data across categories of use of hormone replacement therapy.

Stratified analyses were done to check the validity of the findings from analyses based on cumulative odds models. These analyses involved dichotomized cataract variables: For cortical cataract, the two levels were less than 5 percent and 5 percent or more of lens involved; for nuclear cataract, the levels were grade 3 or less and more than grade 3; and for posterior subcapsular cataract, the levels were 0 percent and more than 0 percent of lens involved.

We categorized duration of use of hormone replacement therapy, duration of exposure to endogenous estrogen, and ages at menarche and menopause. We tested for trends in duration by modeling the median durations (in years) in each category as a single continuous variable.

Interactions between exposure variables and age and type of menopause (surgical or natural) were assessed by using the Breslow-Day test for heterogeneity in stratified analyses and by including interaction terms in cumulative odds models.

All analyses were done using SAS statistical software (SAS Institute, Inc., Cary, North Carolina). A p value of less than 0.05 was taken to indicate statistical significance.

RESULTS

There were 2,072 female subjects in the Blue Mountains Eye Study, 1,953 of whom were postmenopausal. The participation rate was 83 percent. Subjects ranged in age from 49 to 97 years; the median age was 65 years. Sixty-two women were aphakic and/or had intraocular lenses in both eyes. The distribution of cortical, nuclear, and posterior subcapsular cataract in phakic women is shown in table 1.

Use of hormone replacement therapy was reported by 555 postmenopausal women: 312 were currently using hormone replacement therapy, and 243 were ex-users. The mean ages of current and past users were 60.4 and 64.0 years, respectively; never users had a mean age of 68.7 years. Table 2 shows the relations between use of hormone replacement therapy and some risk factors for cataract. Current users tended to be better educated than ex- or never users. Compared with women who had never used hormone replacement therapy, current users were more likely to drink alcohol and use inhaled steroids and less likely to have hypertension. Ex-users tended to have risk factor levels intermediate between current and never users.

The results in table 3 raise the possibility that current use of hormone replacement therapy might be associated with increased prevalence of posterior subcapsular cataract. Compared with never users, age-adjusted odds ratios for current use of hormone replacement therapy and more severe cortical, nuclear,

TABLE 1. Prevalence of cataract in the most affected eye, female subjects, Blue Mountains Eye Study, Australia, 1992–1993

Age group (years)	No of subjects (n = 2,072)	Type of cataract*					
		Cortical (n = 1,939)		Nuclear (n = 1,395)		Posterior subcapsular (n = 1,944)	
		No	%	No	%	No	%
49–54	270	13	5	3	2	7	0.3
55–64	659	89	14	16	4	27	4
65–74	682	210	32	115	24	40	6
75–84	374	152	48	112	49	34	11
≥85	87	38	63	26	67	12	20
All ages		502	26	272	19	120	6
Missing data†		133	6	677	33	128	6

* Definition of cataract: cortical cataract, ≥5% of lens involved, nuclear cataract, presence of grade 4 or 5 opacity; posterior subcapsular cataract, >0% of lens involved.

†Missing data on cataract severity because of bilateral aphakia (n = 61) or because of missing or ungradable photographs (n = 72 for cortical cataract, n = 560 for nuclear cataract, and n = 67 for posterior subcapsular cataract).

TABLE 2. Characteristics of postmenopausal study subjects according to history of use of hormone replacement therapy, Australia, 1992–1993

Characteristic	Hormone replacement therapy		
	% of current users (n = 312)	% of past users (n = 243)	% of never users (n = 1,319)
Education			
Post-high school qualifications	58	55	50
Alcohol consumption (drinks/week)			
No alcohol	32	34	44
<7	38	39	34
≥7	29	28	22
Smoking			
Never smoked	60	60	63
Ex-smoker	28	25	26
Current smoker	11	15	12
Medical conditions*			
Diabetes	4	4	6
Hypertension	46	51	56
Steroid use (ever)			
Oral steroids	10	14	9
Inhaled steroids	15	10	8

* Diabetes was self-reported, hypertension was defined as systolic blood pressure >160 mmHg and/or diastolic blood pressure >95 mmHg and/or a self-reported history of high blood pressure

and posterior subcapsular cataracts were 0.8, 1.1 and 1.5, respectively. None of these odds ratios were statistically significant. There was some suggestion that longer duration of use of current hormone preparation was associated with increased prevalence of more severe posterior subcapsular cataract (p for trend = 0.09).

Users of hormone replacement therapy differed from nonusers on several risk factors for cataract. To adjust for any confounding by these factors, we constructed ordinal regression models that included age, education (attainment of a post-high school qualification), smoking history, alcohol consumption, self-reported diabetes, hypertension (see Materials and Methods for definition), and use of oral or inhaled steroids. Odds ratios for cataracts and hormone replacement therapy were essentially the same as in the age-adjusted models (table 4).

For cortical cataract, there was a statistically significant interaction between age and use of hormone replacement therapy (p = 0.04). Relations between hormone replacement therapy and cataract according to age group are shown in table 5. In women aged 65 years or more, there was a statistically significant association between current use of hormone replacement therapy (any type) and cortical cataract (adjusted odds ratio = 0.4, 95 percent confidence interval 0.2–0.8). Current use of combined estrogen and progestin and posterior subcapsular cataract was also strongly associated in women aged 65 years or more (adjusted odds ratio = 4.3, 95 percent confidence interval 1.3–14.4).

For posterior subcapsular cataract, there was some suggestion of interaction (p = 0.09) between type of menopause and use of hormone replacement therapy. In women with a natural menopause (n = 1,536), the adjusted odds ratios for current use of hormone replacement therapy was 2.1 (95 percent confidence interval 1.1–4.1), with no difference between estrogen alone and combination therapy. There were insufficient data to assess the relation between cataract and hormone replacement therapy in the 186 women with a surgical menopause.

TABLE 3. Age-adjusted odds ratios and 95 percent confidence intervals from ordinal regression models for the association between hormone replacement therapy and cataract, Australia, 1992–1993

	No of subjects	Cortical cataract			Nuclear cataract			Posterior subcapsular cataract		
		No in model	Odds ratio	95% confidence interval	No. in model	Odds ratio	95% confidence interval	No. in model	Odds ratio	95% confidence interval
Ever users		1,776			1,272			1,780		
Never users	1,319		1.0	Referent		1 0	Referent		1 0	Referent
Ex-users	243		1.0	0 7–1.4		1.4	1.0–2.0		1.4	0.8–2.5
Current users	312		0.8	0.5–1.1		1.1	0.8–1.5		1.5	0.8–2 6
Current users*		1,484			1,062			1,488		
Never users	1,319		1.0	Referent		1.0	Referent		1.0	Referent
Estrogen only	144		0.7	0 4–1.1		1.4	0.9–2 1		1.8	0.9–3 6
Combined estrogen and progestin	105		0.7	0.4–1 3		0.9	0.6–1.4		1 8	0 7–4 4
Duration of currently used preparation (years)		1,532			1,105			1,536		
Never users	1,319		1.0	Referent		1 0	Referent		1.0	Referent
<5	175		0.8	0.5–1.3		1.2	0.8–1.8		1.1	0.5–2.6
5–9	53		0.7	0.3–1.8		1.3	0.6–2.8		2.7	0 9–7 8
≥10	69		0.7	0.3–1.3		0.7	0.4–1.2		1 9	0.7–4 9
Test for trend			$p = 0.19$			$p = 0.94$			$p = 0.09$	

* Excludes 63 current users who did not know the name or type of the hormone preparation they were taking.

There was a statistically significant association between prior cataract surgery (reported by 119 women) and past use of hormone replacement therapy: an adjusted odds ratio of 2.4 (95 percent confidence interval 1.2–4.5). Current use of hormone replacement therapy was not associated with a history of cataract surgery.

In this study, type of menopause, age at menopause, use of oral contraceptives, number of children, and total years of menstruation were not associated with any type of cataract (table 6). However, late age at menarche was associated with increased prevalence of cortical and nuclear cataracts (table 6). Compared with those who reported that they began menstruating at age 12 years or earlier, women whose menarche was at age 15 years or later had increased prevalence of more severe cortical cataract (age-adjusted odds ratio = 1.4, 95 percent confidence interval 1.0–1.9) and nuclear cataract (age-adjusted odds ratio = 1.6, 95 percent confidence interval 1.2–2.2). Although not statistically significant, odds ratios for age at menarche and posterior subcapsular cataract were of similar magnitude to odds ratios for the two more common types of cataract. Results were essentially the same after adjustment for multiple potential confounders (data not shown).

Women who are told that they have a cataract might alter their hormone replacement therapy status. Recall of ages at menarche and menopause might also be influenced by knowledge of cataract presence. Hence, all analyses were repeated after exclusion of women who said they knew that they had a cataract. The results were essentially the same in this subgroup (data not shown).

All analyses were repeated with each cataract type as a dichotomous, rather than a multilevel, variable. (Cutpoints are defined in Materials and Methods.) There were no differences between these two sets of analyses (data not shown).

DISCUSSION

In a large cross-sectional study of older Australians, we found some evidence that long-term users of hormone replacement therapy might be protected against cortical cataract and might be at increased risk of posterior subcapsular cataract. Our findings need cautious interpretation because of the exploratory nature of our study, the potential for unadjusted confounding, the multiple statistical tests, and the lack of previous studies of these associations.

In contrast to our study, the Beaver Dam Eye Study found that users of hormone replacement therapy had lower prevalence of nuclear cataract (2). The Study found no association between hormone replacement therapy and cortical cataract, and no findings were reported for posterior subcapsular cataract. The only other relevant epidemiologic study was concerned mainly with steroids and cataract in patients with asthma (12). The authors of that small study noted,

TABLE 4. Multivariable-adjusted odds ratios and 95 percent confidence intervals from ordinal regression models for the association between hormone replacement therapy and cataract*, Australia, 1992–1993

	Cortical cataract			Nuclear cataract			Posterior subcapsular cataract		
	No. in model	Odds ratio	95% confidence interval	No. in model	Odds ratio	95% confidence interval	No. in model	Odds ratio	95% confidence interval
Ever users	1,562			1,098			1,564		
Never users		1.0	Referent		1.0	Referent		1.0	Referent
Ex-users		1.0	0.7–1.4		1.4	1.0–2.0		1.3	0.7–2.4
Current users		0.7	0.5–1.1		1 0	0.7–1.5		1.4	0.7–2 5
Current users†	1,313			922			1,315		
Never users		1.0	Referent		1.0	Referent		1 0	Referent
Estrogen only		0.6	0.4–1.1		1.3	0.8–2.1		1.5	0.7–3.2
Combined estrogen and progestin		0 7	0.4–1 4		0 9	0.5–1.5		2 0	0.8–5.1
Duration of currently used preparation (years)	1,349			964			1,351		
Never users		1.0	Referent		1.0	Referent		1.0	Referent
<5		0 7	0.4–1.2		1.1	0 7–1 7		0 9	0.3–2.2
5–9		0.8	0.5–2.1		1.4	0.6–3.1		2.8	1.0–8.4
≥10		0.6	0.3–1.3		0.7	0.4–1.4		2 1	0.8–5 5
Test for trend		p = 0 19			p = 0.44			p = 0.07	

* Adjusted for age, age at menarche, education, smoking history, alcohol consumption, self-reported diabetes, hypertension (defined as systolic blood pressure >160 mmHg and/or diastolic blood pressure >95 mmHg and/or a self-reported history of high blood pressure), oral steroid use (ever), and inhaled steroid use (ever)

† Excludes 63 current users who did not know the name or type of the hormone preparation they were taking.

TABLE 5. Multivariable-adjusted odds ratios and 95 percent confidence intervals from ordinal regression models for the association between hormone replacement therapy and cataract, according to age group*, Australia, 1992–1993

Age group (years)	Cortical cataract		Nuclear cataract		Posterior subcapsular cataract	
	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval
<65 (n = 929)						
Never users	1.0	Referent	1.0	Referent	1.0	Referent
Current users†	1.3	0 7–2.2	1.1	0.7–1.8	1.3	0.5–3 3
Estrogen only	0 8	0.3–1.9	1.1	0.6–2.1	2.0	0.7–6.1
Combined estrogen and progestin	1 4	0 6–3 4	1.0	0.5–2 0	0.9	0.2–4.7
≥65 (n = 1,143)						
Never users	1.0	Referent	1.0	Referent	1.0	Referent
Current users†	0.4	0.2–0.8	1.0	0.5–1.7	1.5	0 7–3 5
Estrogen only	0.6	0 3–1.2	1.9	0.9–4.0	1.0	0.3–3.3
Combined estrogen and progestin	0.2	0 1–1 1	0.8	0.3–2 1	4.3	1.3–14 4

* Adjusted for age, age at menarche, education, smoking history, alcohol consumption, self-reported diabetes, hypertension (defined as systolic blood pressure >160 mmHg and/or diastolic blood pressure >95 mmHg and/or a self-reported history of high blood pressure), oral steroid use (ever), and inhaled steroid use (ever).

† Analyses for type of current hormone replacement therapy excludes 63 current users who did not know the name or type of the hormone preparation they were taking.

without any discussion, that use of progesterone-estrogen was statistically significantly associated with posterior subcapsular cataract.

Our study has several important limitations. First, our data are cross-sectional, making it difficult to assess the temporal relation between medication use and cataract development. Second, we had only limited data on past use of hormone replacement therapy, and so duration of use of hormone replacement therapy in this study concerns only currently used medications. For women who started on one type of preparation at the menopause and switched to another type several years later, we collected data only on the second hormone preparation. Finally, 20 percent of

TABLE 6. Age-adjusted odds ratios and 95 percent confidence intervals from ordinal regression models for the association between cataract and variables related to reproduction, Australia, 1992–1993

	No. of subjects	Cortical cataract			Nuclear cataract			Posterior subcapsular cataract		
		No. in model	Odds ratio	95% confidence interval	No. in model	Odds ratio	95% confidence interval	No. in model	Odds ratio	95% confidence interval
Contraceptive pill		1,865			1 329			1,869		
Never users	1,311		1.0	Referent		1.0	Referent		1.0	Referent
Ever users	649		0.8	0.6–1 1		1.2	0.9–1 6		1.0	0.6–1 6
Type of menopause		1,629			1,168			1,633		
Natural	1,536		1.0	Referent		1.0	Referent		1 0	Referent
Surgical	186		1.0	0.7–1.4		1.1	0.7–1.5		0 9	0.5–1 8
Age at menarche (years)		1,858			1,323			1,869		
≤12	691		1.0	Referent		1 0	Referent		1 0	Referent
13	440		0.9	0.7–1 3		1 2	0.9–1 6		1 2	0 7–2 1
14	474		1.1	0 9–1 5		1.3	1.0–1 7		1 1	0 7–1 9
≥15	351		1.4	1.0–1.9		1.6	1.2–2 2		1 4	0 8–2 4
Test for trend			$p = 0.02$			$p < 0.01$			$p = 0.16$	
Age at menopause (years)		1,732			1,291			1,736		
≤44	505		1.0	Referent		1.0	Referent		1 0	Referent
45–49	502		0.8	0 6–1.2		0.7	0.5–0 9		1 0	0.6–1.6
50–54	663		1.1	0 8–1 5		0.9	0.7–1 2		1 1	0 7–1 9
≥55	154		0.8	0 5–1 3		0.8	0.5–1 2		0 9	0 4–2.0
Test for trend			$p = 0.97$			$p = 0.35$			$p = 0 81$	
No of children		1,878			1,341			1,882		
0	399		1.0	Referent		1.0	Referent		1.0	Referent
1	254		0.9	0.6–1.3		1.1	0 8–1.6		1.5	0 8–3 0
2	493		0.8	0.6–1.1		1.1	0 8–1.5		1.4	0.8–2 5
3	415		0.9	0 7–1.3		1.0	0.7–1 4		1.2	0.6–2 2
4	228		0.9	0 6–1.4		1.3	0.9–1.9		1.2	0.5–2 5
≥5	193		1.3	0.9–1.9		1.2	0 8–1.8		1.5	0.7–3 2
Test for trend			$p = 0.33$			$p = 0.33$			$p = 0.47$	
Duration of exposure to endogenous estrogen (years)		1,720			1,230			1,724		
≤24	192		1.0	Referent		1.0	Referent		1.0	Referent
25–29	232		0.9	0 6–1.4		1.1	0 7–1.7		1.7	0.8–3 9
30–34	412		0.8	0 5–1.2		0.9	0 6–1.3		1.2	0 5–2 6
35–39	665		0.9	0 6–1 3		0.8	0.6–1.2		1.1	0 5–2 3
≥40	410		0.8	0.5–1.3		0.8	0.5–1.3		1.4	0 6–3.2
Test for trend			$p = 0.50$			$p = 0.25$			$p = 0.97$	

current users did not know the type of hormone preparation they were using. We assumed that they were taking estrogen of some sort, but this may have been incorrect. Excluding these subjects strengthened observed associations (data not shown).

Strengths of our study include high participation rate, large sample size, control for important confounders, and careful assessment of cataract type and severity using an established grading protocol (5).

We found stronger associations between current hormone replacement therapy and cataract in women age 65 years and over than in younger postmenopausal women. This is a finding similar to that of a recent study of the protective effect of hormone replacement therapy on risk of hip fracture (13). These findings are probably explained, at least in part, by longer use among older current users, many of whom would have started around the menopause, than among younger current users. This may not be the only explanation, as there is evidence that the association between hormone replacement therapy and breast cancer is stronger in older than in younger women, even if they have used hormone replacement therapy for the same length of time (14).

The positive association between hormone replacement therapy and posterior subcapsular cataract appeared to be stronger among women who had had a natural menopause. A hypothesis to explain the weaker association in women who had had a surgical menopause is their likely infrequent use of progestins. A recent meta-analysis of hormone replacement therapy and breast cancer also found much stronger associations in women who had had a natural, rather than a surgical, menopause (15).

A protective effect of hormone replacement therapy on cataractogenesis could be explained by the known antioxidant activity of estrogen (16). The biologic mechanism by which hormone replacement therapy might increase risk of posterior subcapsular and nuclear cataract is unknown. Interestingly, a recent randomized trial conducted in China found that subjects given a combination of niacin and riboflavin (which helps maintain levels of the antioxidant glutathione) were at increased risk of posterior subcapsular cataract (17). A small study in rats found that a combination of estrogen and progestin led to increased cataract formation (18). Further basic biologic research is needed on the effect of estrogen on the lens.

Late age at menarche was associated with increased prevalence all three types of cataract in our study; in the Beaver Dam Eye Study, late age at menarche was associated with nuclear cataract (2). These findings suggest that longer exposure to endogenous estrogens might protect the lens against cataract development; however, we found no association between age at menopause or total duration of menstruation and any type of cataract.

A fundamental problem in observational studies of the long-term effects of hormone replacement therapy is that women who choose to use these medications tend to differ from nonusers in many important ways. Although we tried to minimize this selection bias by controlling for a number of confounders, we acknowledge that other factors (known and unknown) could be the cause of the associations that we found.

Two large, cross-sectional, population-based studies have now found associations between use of hormone replacement therapy and cataract. More observational studies of these relations, particularly longitudinal studies involving incident cataract, are certainly warranted. Basic biologic research is also needed. The ultimate test of the beneficial and adverse effects of postmenopausal estrogen and progestin, however, will come from randomized trials. Investigators planning trials of hormone replacement therapy should consider including careful assessment of the lens of the eye.

ACKNOWLEDGMENTS

Supported by the Australian Department of Health, Housing, and Community Services (RADGAC Grant) and the Save Sight Institute, University of Sydney.

The authors thank Michael Neider and Paula Cisternas for their valuable assistance with this study.

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