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Skin Disease and Age-related Cataract

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Dermatological conditions and treatments were analysed in a study comparing cataract patients and stringently matched controls.

One thousand patients were taken from the cataract waiting list of a specialist eye hospital. For each patient a matched control of the same gender, half-decade of age, and family doctor but without cataract was selected. Venepunctures and eye examinations were performed on both patients and controls; in addition, questionnaire information was obtained from each.

Age-related cataract is significantly associated with dermatological abnormality and its treatment, the former association being more significant and more pronounced after 69 years of age. The association of hydrocortisone use after 69 years of age and cataract, however, remains significant even after adjustments for dermatological abnormality and steroid use, suggesting that even among steroid medications hydrocortisone is particularly strongly associated with cataract. ***Key words: psoriasis; hydrocortisone; steroids.***

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Risk factors have been sought for senile or age-related cataract for more than a decade by our own group (1–4) and several others (see 5 for refs). This report presents results from our recently completed study of a large number of patients and closely matched controls, the first pair-matched epidemiological study of age-related cataract to examine dermatological disease and its treatment.

Some syndermatotic cataracts, bilateral and occurring at a young age, were noted long ago (6) and are well known although rare (7–11), for example in atopic dermatitis, Rothmund-Thomson syndrome and Werner's syndrome. The association is attributed to the common ectodermal origin of the eye lens and the skin. On that background, we investigated the associations between skin conditions and their treatments with age-related cataract.

MATERIALS AND METHODS

Two thousand individuals form the basis for this report, comprising 1,000 patients on the waiting list for cataract operations at the Princess Alexandra Eye Pavilion, Royal Infirmary, Edinburgh, and 1,000 controls. An individual without cataract of the same gender and the same half-decade of age as the patient was obtained from the list of the patient's general practitioner, thus ensuring that the patient and the control (who were unrelated either by consanguinity or marriage) resided in the same area of the city. Only one eye from each patient and control was included. At a home visit, one of eight ophthalmologists, randomly allotted, examined the eye. In patients, the pupil of the eye to be operated was dilated with 1% tropicamide and the cataract assessed with a direct ophthalomascope and a portable handheld slit-lamp microscope. The visual acuity of the patients' eyes was poor. To ensure the absence of significant cataract, controls had to have a visual acuity no worse than 6/9 with correction in both eyes, neither operated; also there had to be no evidence of clinically significant cataract in the eye with the pupil dilated or its fellow.

Of the 1,000 patient-control pairs, 358 were male and 642 were female. The age distribution is shown in Table I.

A detailed questionnaire on social and medical history, including medication taken continuously for 4 or more months, was administered at a home visit to patients and controls. Each study participant had been asked not to divulge whether or not a cataract patient during the interview, since the patient/control status was unknown to the four qualified nurses who conducted the interviews. Confirmation of diagnosis and treatment including medications was obtained in cases of doubt from the family doctor. In order to minimise possible reporting bias, the nurse examined and recorded details of all containers of medications in the individuals' homes.

When dermatological data are missing for any patient or control, that patient-control pair is excluded from this analysis. These deficits are also present in the multivariate analysis because the method of model selection demanded values for all of the variables considered in all patients and controls.

Fasting blood samples were obtained by venepuncture from both patients and controls at an early morning domiciliary visit. All participants had been asked to ingest only water after the midnight previous to the appointed morning. No participants admitted noncompliance with the requirement. The analysis of plasma samples was undertaken in the Department of Clinical Chemistry, Royal Infirmary, Edinburgh, using a Technicon SMAC analyser for the majority of tests. Plasma cortisol was measured by radioimmunoassay.

Separate conditional logistic regression models were used to assess the independent associations with cataract of the presence of any dermatological conditions and the use of any medication for dermatological conditions. Odds ratio estimates and the corresponding confidence intervals were calculated based on the conditional logistic regression models. Multivariate analyses were performed to test the effects of nine categories of dermatological conditions simultaneously and the effects of six categories of medications for dermatological conditions simultaneously. A step-up conditional logistic regression analysis was conducted on the data, incorporating sequentially the next most significant effect until none of the remaining effects increased the overall significance of the multivariate model. In order to perform this method of model selection, it is necessary for all patient-control pairs analysed to have complete data for the variables under consideration.

Tests for the homogeneity of odds ratios across the strata were performed for nuclear colours, cataract locations and opacity types.

RESULTS

The cataract group showed significantly higher prevalence of dermatological conditions ($p=0.005$). The simultaneous test of equal prevalence of nine categories of conditions in patients and controls was not significant ($p=0.167$); however, there was weak evidence that the prevalence of psoriasis was greater in patients than in controls ($p=0.041$ for the one degree of freedom test) (Table II).

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Table I. *Age distribution of matched patient and controls*

Age in years	20–29	30–39	40–49	50–59	60–69	70–79	80–89	90+
Number of pairs	2	4	17	55	196	429	278	19

Table II. *Estimated odds ratios (OR) and the corresponding 95% confidence intervals (CI) for the presence of any dermatological condition and separately for the presence of specific dermatological conditions*

	Patient	Control	Total	OR	95% OR CI	*p*-value
Presence of any dermatological condition						
No	835	878	1713	1		
Yes	155	112	267	1.44	(1.11, 1.87)	$p=0.005$
Total	990	990	1980			
Dermatological condition present						
None	835	878	1713	1		
Psoriasis	24	13	37	2.02	(1.00, 4.08)*	
Eczema	19	18	37	1.07	(0.56, 2.04)	
Contact dermatitis	17	12	29	1.52	(0.70, 3.29)	
Allergy/Rash	23	15	38	1.61	(0.82, 3.15)	
Cancers	7	11	18	0.67	(0.26, 1.73)	
Infection (Bacterial/Fungal/Microbial)	12	8	20	1.59	(0.64, 3.93)	
Ulcers/Lesions	19	13	32	1.53	(0.75, 3.11)	
Other	31	21	52	1.54	(0.88, 2.68)	
Multiple	3	1	4	3.00	(0.31, 28.84)	
Total	990	990	1980			
For the simultaneous test of all odds ratios equal 1 $p=0.167$						

* For psoriasis separately $p=0.041$.

There was significantly more use of medication for dermatological conditions in patients than controls ($p=0.020$). The simultaneous test for equal use of six categories of medications in patients and controls was not significant ($p=0.193$). There was, however, some evidence that the use of ointment/tar/lotion was more common in patients than controls ($p=0.032$ for the one degree of freedom test) (Table III).

The presence of dermatological conditions and the use of medication for them are, of course, highly correlated. As a result, after adjustment for the presence of any dermatological condition, no other effects were significant.

The effects of gender and age

We have tested the hypotheses that the differences in the presence of dermatological conditions and their treatment between patients and controls do not depend on gender, by allowing the effect of each dermatological condition and each medication for dermatological conditions to differ for males and females. None was significant.

We have tested for the possibility of age-specific effects by allowing the effect of each dermatological condition and each medication for dermatological conditions to differ for the two age strata: less than 70 years and 70 or more years. The presence of any dermatological condition ($p=0.026$), the use of any medication for dermatological conditions ($p=0.023$), and the use of hydrocortisone for dermatological conditions ($p=0.008$) were found to differ significantly for the age strata (Table IV). No other differences depended significantly on age stratum.

Tests for homogeneity of the odds ratios

For each effect examined, the null hypothesis of homogeneity of the odds ratio was tested separately across nuclear colours, cataract locations and types of opacity. Similar tests were performed for the effects of presence of any dermatological condition and use of hydrocortisone by age group. None of the effects differed significantly by nuclear colours, cataract locations or types of opacity.

The effects of steroid use and plasma cortisol level

In a univariate analysis, use of steroid medication (systemic or topical) was significantly more prevalent ($p=0.004$) in patients compared to controls with an odds ratio of 1.73 and a 95% confidence interval of (1.18,2.54). Similarly, the level of plasma cortisol was significantly higher ($p<0.001$) in patients compared to controls with an odds ratio of 1.21 and a 95% confidence interval of (1.13,1.30) for an increase of 100 nmol/l of cortisol. (These effects have already been reported for this study population (4).)

After adjustment for use of steroid medication, all of the effects previously found significant remained significant with the exceptions of the presence of psoriasis ($p=0.056$) and the use of any medication for dermatological conditions ($p=0.080$). It is important to know that after adjustment for use of steroid medication, the use of any medication for dermatological conditions was still found to differ significantly for the age strata. Similarly, after adjustment for plasma cortisol level, all of the effects previously found significant remained signific-

Table III. *Estimated odds ratios (OR) and the corresponding 95% confidence intervals (CI) for the use of any medication for dermatological conditions and separately for the use of specific types of medication for dermatological conditions*

	Patient	Control	Total	OR	95% OR CI	*p*-value
Use of any medication for dermatological conditions						
No	904	933	1837	1		
Yes	96	67	163	1.47	(1.06, 2.03)	$p=0.020$
Total	1000	1000	2000			
Medication for dermatological conditions						
None	904	933	1837	1		
Betamethasone	19	19	38	1.01	(0.53, 1.94)	
Hydrocortisone	11	8	19	1.43	(0.57, 3.58)	
Ointment/Tar/Lotion	21	9	30	2.36	(1.08, 5.15)*	
Anti-Biotic/Fungal/Microbial	8	4	12	2.06	(0.62, 6.88)	
Other anti-inflammatory	23	16	39	1.45	(0.76, 2.74)	
Multiple	14	11	25	1.34	(0.60, 2.96)	
Total	1000	1000	2000			
For the simultaneous test of all odds ratios equal 1 $p=0.193$						

* For use of ointment/tar/lotion separately $p=0.032$.

Table IV. *Significant results are reported for the tests of the hypotheses of no effect of age stratum on the differences in the presence of dermatological conditions and their treatment, including the estimated odds ratio (OR) and its corresponding 95% confidence interval (CI)*

	OR	95% CI	OR	*p*-value
Presence of any dermatological condition				0.026*
Less than 70 Years	0.95	(0.61, 1.49)		
70 or more Years	1.78	(1.29, 2.45)		
Use of any medication for dermatological conditions				0.023*
Less than 70 Years	0.84	(0.47, 1.50)		
70 or more Years	1.89	(1.27, 2.82)		
Use of hydrocortisone for dermatological conditions				0.008**
Less than 70 Years	0.17	(0.02, 1.38)		
70 or more Years	5.00	(1.10, 22.8)		

(* is a 1 df test; ** is a 2 df test.)

ant with the single exception of the presence of psoriasis ($p=0.078$).

Multivariate analyses

Table V presents the multivariate model obtained with a step-up selection procedure, allowing effects for all of the dermatological variables (not including the use of steroid medication or plasma cortisol level).

DISCUSSION

Age-related cataract is significantly associated with dermatological abnormality, especially after 69 years of age.

Psoriasis, specifically, showed evidence of a greater prevalence among patients than among controls. Psoralen photochemotherapy (PUVA) (12) is a common therapy for psoriasis,

Table V. *The multivariate conditional logistic regression model obtained allowing effects of the presence of dermatological conditions and the use of medication for dermatological conditions*

Significant variables are listed with the *p*-value for the null hypothesis of no effect of each variable, the estimated odds ratio (OR) and its corresponding 95% confidence interval (CI).

	OR	95% CI	OR	*p*-value
Presence of any dermatological condition				0.008
Less than 70 Years	1.05	(0.66, 1.66)		
70 or more Years	1.68	(1.20, 2.32)		
Use of hydrocortisone for dermatological conditions				0.038
Less than 70 Years	0.16	(0.02, 1.38)		
70 or more Years	3.15	(0.67, 14.8)		

[No other variables were significant in the multivariate analysis.]

consisting of a combination of orally administered psoralen and long-wave ultraviolet-A radiation (UVA). This treatment is known to have potential long-term adverse effects, including cataract formation (13); however, the associated risk of cataract has been found independent of the level of exposure to PUVA (14).

The rate of dermatological abnormality found in the patients (15.7%) is similar to the rates of skin disease reported by Katoh et al. (15) in male and female age-related cataract patients (12.5% and 13.7%, respectively). These authors (15) found no significant association between cataract and skin disease; however, the lack of significant associations between cataract and any disease, any drug, or alcohol consumption may be due to the small sample size (212 patients and 212 controls) and to the lack of pair-matching.

Cataract is also significantly associated with medications for dermatological conditions, although this effect is no longer significant after adjustment for dermatological abnormality. The association of hydrocortisone use after 69 years of age

and cataract, however, remains significant even after adjustment for dermatological abnormality.

Therapeutic steroid taking was more common in the cataract group than in the controls, and patients showed a higher level of endogenous basal plasma cortisol levels than the controls, irrespective of steroid use (4). Cataract is well known to be associated with steroid use (10, 16–19). Raised circulatory glucocorticoid levels probably have a directly deleterious effect on lens metabolism, but the slight rise in basal plasma steroid may also act indirectly, for example by an association with raised blood pressure, a known risk factor (1, 20, 21). The association of hydrocortisone use after 69 years of age and cataract, however, remains significant even after adjustment for dermatological abnormality and steroid use, suggesting that even among steroid medications hydrocortisone is particularly strongly associated with cataract.

Non-participation of cataract patients and potential controls may bias the results if the non-participants differ from participants in their dermatological diseases or treatments. Nonetheless, the present study was very stringently case-controlled and used large numbers of patient-control pairs. The pair-matching on gender and age (by half-decade) has reduced the risk of bias. When a value in any patient or control was missing, the matched pair was eliminated, so that there is no difference in age between the two groups to confound our observations.

Attempts were made initially to contact 1,307 cataract patients and 2,414 potential controls, which suggests that patients were more motivated to accept the invitation to join than were controls. One factor is that several other epidemiological studies had been or were being conducted in the Edinburgh area at this time, so that some patients and controls were unwilling to agree to be disturbed again; only one practice in the whole area declined to participate, that being the reason. Among non-participants no reason could be ascertained in 141 patients and 918 potential controls because a relative or friend transmitted the refusal, or the non-participant merely left a telephone message. Of those giving reasons for not taking part, illness was cited by a much higher proportion of cataract patients than controls (86/307 compared to 52/1,414); this suggests that our survey may well have underestimated the association between ill-health and cataract.

All surveys such as the present entail the possibility that mere chance may be responsible for a particular significant difference, a proposition fundamental to all statistical analyses. The greater the number and diversity of quantifiable properties compared between groups, the greater the likelihood that one or more will differ significantly merely by chance. There are many statistical methods available to correct the p-values for the number of tests performed (22, 23); however, we have reported unadjusted p-values in order to allow the reader access to the raw test results, independent of a specific correction method. Agreement with a previous finding of a significant difference increases confidence in a conclusion, but an unexpected finding at the borderline of significance may well be attributed to chance.

Although we have focussed in this paper on associations of the presence of dermatological conditions and their treatment with cataract, potential confounders exist such as exposure to sunlight, diet, etc. (5).

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