Selected Sun-Sensitizing Medications and Incident Cataract

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Objective: To examine the relationship between the use of sun-sensitizing medications and cumulative incidence of age-related cataract.

Methods: Sun exposure was estimated from residential history of adults in the Midwestern community of Beaver Dam, Wisconsin, which permitted calculation of Wisconsin sun-years at the baseline examination. Medication history was reported at each examination. Cataract presence was determined by standardized lens photographs that were taken at each examination and graded according to standard protocols.

Results: No significant effects were noted of Wisconsin sun-year exposure or use of sun-sensitizing medications on the cumulative incidence of any type of age-related cataract when controlling for age and sex. However, an interaction term combining Wisconsin sun-years and use of any sun-sensitizing medication was significant (P = .04) such that risk of cortical cataract is significantly higher for the joint risk group. Further controlling for the presence of diabetes mellitus, history of heavy drinking, and hat or sunglasses use did not alter the relationships.

Conclusions: Data suggest that the use of sun-sensitizing medications interacts with sun exposure to influence the risk of cortical cataract, a common age-related cataract. If confirmed, this finding may have important implications for medication use.


Several risk factors, aside from age, have been identified for common types of cataracts that vary by type of cataract. For example, cigarette smoking has commonly been found to be related to nuclear cataract,1-3 diabetes mellitus to cortical and posterior subcapsular cataracts,6,7 and hypertension (or use of thiazide diuretics) to posterior subcapsular cataract.8 Ritter et al9 reported that heavy drinking was associated with all 3 types of cataract. Sunlight and UV-B exposures have been found to be associated with cortical cataract.10,11 Several systemic medications are reported as being sun sensitizing. The description of signs and symptoms attributable to sun sensitization by a medication include the development of itching or rash in areas of the skin exposed to the sun. Because cortical cataract has been previously associated with sunlight or UV-B exposure and because of the common ectodermal derivation of the lens and skin, we sought to examine the possible modifying effect of sun-sensitizing medication on the association of incident cortical cataract with estimated UV-B exposure.

METHODS

POPULATION

Methods used to identify and describe the population have been reported in previous publications.12-16 In brief, a private census of the population of Beaver Dam, Wisconsin, was performed from September 15, 1987, to May 4, 1988, to identify all residents in the city or township of Beaver Dam who were aged 43 to 84 years. Of 5924 eligible individuals, 4926 participated in the baseline examination between March 1, 1988, and September 14, 1990. Ninety-nine percent of the population were of white race/ethnicity. Of these, 3684 (81.1%) participated in the 5-year follow-up examination from 1993 to 1995. Of 3324 surviving participants in the baseline and second examination, 2764 (82.9%) participated in the 10-year follow-up examination. Of 2480 surviving participants who were examined at the baseline, 5-year, and 10-year follow-up examinations, 2119 (85.4%) participated in the 15-year follow-up examination. Comparisons be-
between participants and nonparticipants at the time of the baseline, 5-, 10-, and 15-year follow-up examinations have been published elsewhere.15-16

EXAMINATION, INTERVIEW, AND GRADING PROTOCOLS

The same protocols with few additions or deletions were used at each examination phase. A standardized interview was administered. These were approved by the institutional human subjects committee of the University of Wisconsin–Madison, and conform to the tenets of the Declaration of Helsinki. Participants were asked about residential history, including time spent in the tropics and southern United States. The residential history was used to construct a measure of the average annual ambient UV-B exposure for each individual using an adaptation of the technique in the Maryland Watermen Study.11,17 Each year spent in another region was weighted by the ratio of the total ambient UV-B light present in that area to the level for 1 year in Wisconsin (Wisconsin sun-year [WISY]).11 One WISY is equivalent to the total ambient UV-B irradiance of a horizontal surface in Wisconsin over 1 year. The cumulative ambient UV-B exposure was computed and divided by age to obtain the average annual ambient UV-B exposure for an individual. Because most participants had spent most of their lives in Wisconsin, this variable was categorized into 2 groups (<1.01 vs ≥1.01 WISYs).10 We assume that a person’s exposure is constant over time, so we use WISYs computed from baseline data in the time-varying models.

During the medical interview, the examiner reviewed the medications that the participants had been asked to bring to the examination. Every prescription and over-the-counter medication was used. If the participant neglected to bring the medications, the examiner called him or her at home after the interview to obtain the information. Medications were later linked to a local database containing lists of the active ingredients. Participants were also asked whether there had been a time in their lives when they had drunk 4 or more alcoholic beverages per day on a regular basis.

Photographs of the lens were taken after pharmacologic dilatation. Slitlamp photographs were obtained to grade the degree of nuclear sclerosis. Retrolamination photographs were taken to grade the presence and severity of cortical and posterior subcapsular cataracts. The protocols for photography and for the grading procedures were based on detailed codified rules.15 Graders were masked as to subject identity.

DEFINITIONS

Scores for cortical and posterior subcapsular cataracts were based on the estimated amount of “area” involved after superimposition of the film on a grading grid. Cortical opacities involving more than a weighted average of 5% of the total lens were considered cortical cataract. Posterior subcapsular opacities involving a weighted average of more than 3% of any of 9 individual grid segments were considered posterior subcapsular cataract.18 Scores for nuclear sclerosis were based on comparisons with standard photographs, which resulted in a 5-step scale of severity based on opacity of the nucleus. Severities exceeding a standard of 3 were considered nuclear cataract.

Diabetes was defined as a history of diabetes mellitus treated with insulin, oral hypoglycemic agents, or diet. If there was no medical history of diabetes or use of hypoglycemic medications, then diabetes was considered present by a random blood glucose level exceeding 200 mg/dL and a glycated hemoglobin level exceeding 2 SDs above the mean for a given age-sex group (>9.5% for men and >9.6% for women aged 43–54 years, >9.4% for men and >10.0% for women aged 55–64 years, >9.6% for both men and women aged 65–74 years, and >9.5% for men and >9.6% for women ≥75 years) (to convert glucose level to millimoles per liter, multiply by 0.0555; to convert hemoglobin level to a proportion of 1.0, multiply by 0.01).14 Heavy drinking was defined as a history of ever having had a period in life when the individual drank 4 or more drinks per day on a regular basis.

Photosensitizing medications considered in this study are hydrochlorothiazide, furosemide, glyburide, amitriptyline hydrochloride, paroxetine hydrochloride, sertraline hydrochloride, tetracycline hydrochloride, sulfamethoxazole, trimethoprim sulfate, ciprofloxacin hydrochloride, amiodarone hydrochloride, and naproxen sodium.20 In time-varying models, drug use at the beginning of each interval is used.

STATISTICAL ANALYSIS

Analyses were based on cataract incidence when it was the first eye to develop that lesion. Individuals contributed data for every interval that photographs for both eyes were gradable and when gradable photographs were also available for all previous examinations. Those who had cataract surgery in 1 eye were not considered for analysis because it was impossible to know whether the phakic eye was the first to develop a given lesion. Cumulative incidence was calculated accounting for the competing events of death and cataract surgery. Discrete linear logistic regression models were used to determine whether medication (and any interaction terms) added significantly to explaining incident cataract. Medication use was obtained at each examination, and time-varying models updating medication use at each examination were included in the analyses. Because all relevant information for updating WISY data was unavailable at later examinations, we assumed the same relative exposure for each examination in the time-varying models. Statistical analyses were performed using commercially available software (SAS, version 9.1; SAS Inc, Cary, North Carolina).

RESULTS

There were 4926 participants at the baseline examination. The percentage of participants using sun-sensitizing medications as a group increased across 15 years, although the percentages using individual medications varied (Table 1). Of the sun-sensitizing medications documented at that examination, preparations containing hydrochlorothiazide were the most commonly used and ciprofloxacin the least commonly used.

Of 4068 participants seen at baseline and at least 1 follow-up examination or who had died after the baseline examination and could contribute some information for incidence, 156 had cataract surgery in at least 1 eye at baseline. An additional 214 had no gradable photographs at baseline and/or the first follow-up visit and were excluded from the analysis. Among the remaining 3698 persons, the number of participants varied by type of cataract analyzed. Individuals with a specific lens opacity at baseline or missing information for the specific lesion were excluded from analysis for that opacity but were included for the other opacities. An additional 531 participants were excluded because of prevalent cortical cataract at baseline, and 169 participants were excluded.
because of missing information in at least 1 eye for that lesion at later visits. Parallel exclusions were made when analyzing the other cataract types.

A total of 2998 participants contributed data for the 15-year cumulative incidence of cortical cataract. Those excluded from analyses were older, female, more likely to have had cardiovascular disease, and more likely to have diabetes at the baseline examination. They were slightly more likely to have been taking sun-sensitizing medications.

Cumulative incidence of each cataract type by WISYs and by use of any sun-sensitizing medication is given in Table 2. Cumulative incidence was higher for those with high WISYs and for those taking sun-sensitizing medications, but the differences were not statistically significant. However, in multivariate models adjusting for age and sex, an interaction term combining WISYs and use of sun-sensitizing medications was significant for risk of cortical cataract. No difference was noted in the estimated odds whether or not the presence of diabetes (or a history of heavy drinking) was included in the models. When stratified by WISYs, the association of use of sun-sensitizing medications with cumulative incidence of cortical cataract was significant among those with high WISYs (Figure). No other associations were significant. Use of hats with brims or use of sunglasses

Table 1. Use of Sun-Sensitizing Medications at Each Examination Before the 15-Year Follow-up

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Baseline (n=4926)</th>
<th>Follow-up Examinations, y&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5 (n=3722)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiodarone hydrochloride</td>
<td>4 (0.1)</td>
<td>6 (0.2)</td>
</tr>
<tr>
<td>Amitriptyline hydrochloride</td>
<td>76 (1.5)</td>
<td>78 (2.1)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>4 (0.1)</td>
<td>4 (0.1)</td>
</tr>
<tr>
<td>Furosemide</td>
<td>198 (4.0)</td>
<td>185 (5.0)</td>
</tr>
<tr>
<td>Glyburide</td>
<td>80 (1.6)</td>
<td>112 (3.0)</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>809 (16.4)</td>
<td>479 (12.9)</td>
</tr>
<tr>
<td>Naproxen</td>
<td>67 (1.4)</td>
<td>70 (1.9)</td>
</tr>
<tr>
<td>Paroxetine or sertraline hydrochloride</td>
<td>0</td>
<td>21 (0.6)</td>
</tr>
<tr>
<td>Tetracycline hydrochloride</td>
<td>29 (0.6)</td>
<td>26 (0.7)</td>
</tr>
<tr>
<td>Sulfamethoxazole</td>
<td>25 (0.5)</td>
<td>22 (0.6)</td>
</tr>
<tr>
<td>Any sun-sensitizing medication</td>
<td>1188 (24.1)</td>
<td>879 (23.6)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reported subsample sizes include everyone examined irrespective of participation in previous examinations.

Table 2. Incidence of Cataract Type With Use of Any Sun-Sensitizing Medication

<table>
<thead>
<tr>
<th>Cataract Type</th>
<th>No. at Risk (% Incidence)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Interaction P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low WISYs</td>
<td>High WISYs</td>
</tr>
<tr>
<td>Cortical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1784 (21.7)</td>
<td>587 (23.1)</td>
</tr>
<tr>
<td>Yes</td>
<td>469 (24.6)</td>
<td>149 (31.8)</td>
</tr>
<tr>
<td>Nuclear</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1745 (27.2)</td>
<td>596 (33.2)</td>
</tr>
<tr>
<td>Yes</td>
<td>464 (32.6)</td>
<td>140 (36.8)</td>
</tr>
<tr>
<td>Posterior subcapsular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1972 (7.7)</td>
<td>652 (9.5)</td>
</tr>
<tr>
<td>Yes</td>
<td>562 (9.1)</td>
<td>174 (10.2)</td>
</tr>
</tbody>
</table>

Abbreviation: WISYs, Wisconsin sun-years.

<sup>a</sup>Cumulative incidence accounting for competing risk of death and cataract surgery.

<sup>b</sup>For interaction term combining WISYs and use of any sun-sensitizing medication adjusted for age and sex.

<sup>c</sup>For interaction term combining WISYs and use of any sun-sensitizing medication adjusted for age, sex, presence of diabetes mellitus, and history of heavy drinking.

Figure. Hazard ratio (95% confidence interval) for incidence of specific cataract types among users of any sun-sensitizing medication by Wisconsin sun-years (WISYs).
for at least half the time spent outside did not affect this relationship (data not shown). However, we had this information for only about half of our study population and could not assess the effect of this association on the entire population.

Similar analyses were performed for each individual medication. Among medications for which we had adequate numbers, the odds ratios were in the same direction as for the entire category of sun-sensitizing medications (data not shown). Time-varying models incorporating medication use at each examination after baseline failed to demonstrate significance for sun exposure, medication use, or the interaction term (data not shown).

COMMENT

We found evidence of an interaction between UV-B exposure and use of sun-sensitizing medications on 15-year cumulative incidence of cortical cataract in the Beaver Dam Eye Study cohort. The medications (active ingredients) represent a broad range of chemical compounds, and the specific mechanism for the interaction is unclear. The effect seems to be specific to cortical cataract, the cataract type that has been found in some cross-sectional investigations to be associated with UV-B exposure. A previous article reported such an effect among men in a cross-sectional analysis of the baseline data. The present analyses may indicate that the effect of sunlight exposure may be modified by use of sun-sensitizing medications.

This study has several limitations. We measured UV-B exposure by accounting for the average ambient UV-B light in Wisconsin. Because the range of sunlight exposure was not great, we dichotomized this to less than 1.01 vs 1.01 or higher WISYs. Therefore, we cannot assess whether there might be an effect across the range of UV-B exposure. Also, because our measure was based on residential history, it is a measure of potential exposure and not a direct estimate of ocular or lens exposure. Use of sunglasses and brimmed hats may alter direct UV-B exposure on the lens, but adjustment for this did not change the associations.

In addition, although we have data on medication use as reported at each examination, we do not know the dose or duration of use. Therefore, our measure of medication exposure is dichotomous and only accounts for current use or nonuse of any medication at that one time point.

We included sun-sensitizing medications on a current list compiled by the Department of Administration, Bureau of State Risk Management, and the Wisconsin State Employees Union. We used this source because there was no codified listing available from the Centers for Disease Control and Prevention, the Food and Drug Administration, the drug database at Slone Epidemiology Center (Boston University, Boston, Massachusetts), or other local or national sources. We have not included all medications that have been reported to be associated with sun sensitivity in a compendium such as the Physicians’ Desk Reference. We have no way to assess the possibility that entries in that publication were coincidental findings or that the sun sensitivity report was made in error or if it was appropriate. Also, sun sensitivity is not always clearly defined.

Our results need to be evaluated in other populations, especially in view of the increasing frequency of sun-sensitizing medications (Table 1). If our findings are confirmed, it would be important to examine whether the effect is greater in those with higher levels of ambient sunlight (UV-B) exposure and if dose or duration of medication use is also important. Because cortical cataract is a common lens opacity in adults, present in about 16% of the Beaver Dam Eye Study population at the baseline examination, our study findings may be relevant to public health.

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