Relation Between Time Spent Outdoors and Exfoliation Glaucoma or Exfoliation Glaucoma Suspect

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• PURPOSE: **To evaluate the relation between time spent outdoors at various life periods and risk of exfoliation glaucoma or exfoliation glaucoma suspect.**

• DESIGN: **Retrospective cohort study in the United States.**

• METHODS: **Participants (49 033 women in the Nurses Health Study and 20 066 men in the Health Professionals Follow-up Study) were 60+ years old, were free of glaucoma and cataract, reported eye examinations, and completed questions about time spent outdoors in direct sunlight at midday at 3 life periods: high school to age 24 years, age 25–35 years, and age 36–59 years (asked in 2006 in women and 2008 in men). Participants were followed biennially with mailed questionnaires from 1980 women/1986 men to 2010. Incident cases (223 women and 38 men) were confirmed with medical records. Cohort-specific multivariable-adjusted rate ratios from Cox proportional hazards models were estimated and pooled with meta-analysis.**

• RESULTS: **Although no association was observed with greater time spent outdoors in the ages of 25–35 or ages 36–59 years, the pooled multivariable-adjusted rate ratios for ≥11 hours per week spent outdoors in high school to age 24 years compared with ≤5 hours per week was 2.00 (95% confidence interval = 1.30, 3.08; *P* for linear trend = .001). In women, this association was stronger in those who resided in the southern geographic tier in young adulthood (*P* for interaction = .07).**

• CONCLUSIONS: **Greater time spent outdoors in young adulthood was associated with risk of exfoliation glaucoma or exfoliation glaucoma suspect, supporting an etiologic role of early exposures to climatic factors. (Am J Ophthalmol 2014;158:605–614. © 2014 by Elsevier Inc. All rights reserved.)**

EXFOLIATION SYNDROME (ES) CAN LEAD TO SERIOUS ocular disease, such as secondary glaucoma[1] and retinal vein occlusion.[2–5] It can also lead to premature cataract[6] and is frequently associated with cataract surgery complications.[7–10] The underlying pathologic mechanisms of exfoliation syndrome that lead to the characteristic extracellular deposits in the anterior segment of the eye are believed to involve disordered extracellular matrix metabolism[11];this is bolstered by the established link with common variants in the gene *LOXL1* that codes for lysyl oxidase–like 1 enzyme,[12] which catalyzes the first step in the formation of cross-links in collagens and elastin. However, *LOXL1* gene variants occur in roughly 80% of controls, indicating that many unanswered questions remain regarding the etiology of exfoliation syndrome.

One clue that may shed light on the etiology of exfoliation syndrome is the striking trend of the disease being more common with greater distance from the equator, which has been observed throughout Europe, the Middle East, Asia, and North America.[13–19] For example, in the cohorts of the Nurses Health Study and Health Professionals Follow-up Study from the United States, compared to northern tier residence (≥42 degrees north), southern tier residence (<37 degrees north), particularly in adolescence, was associated with a 75% reduced risk of exfoliation glaucoma or exfoliation glaucoma suspect.[18] In addition, Stein and associates[19] confirmed that in the United States, current residence in the southern tier was associated with the lowest risk of exfoliation syndrome; in this study, several climatic factors were explored to elucidate the latitude gradient—of these, colder temperatures in the summer and winter months as well as greater number of sunny days per year were identified as independent predictors of increased risk of exfoliation syndrome. These data might suggest that greater time spent outdoors would increase the risk. Indeed, a study from Andhra Pradesh, India, found that working in occupations involving outdoor activities[20] was associated with ES,[21] and this was confirmed in other studies from the subcontinent.[22,23] However, only 1 study has evaluated current time spent outdoors in a general population and did not identify it as a risk factor for exfoliation syndrome.[24] Thus, the data are limited, and time spent outdoors at different life stages has been little explored.

We used data from 2 cohorts of 49 033 women and 20 066 men aged 60 or more years living in the United States who were followed for at least 20 years for this analysis. They provided information on residence and time spent outdoors at 3 life periods (high school to age 24 years, age 25–35 years, and age 36–59 years), as well as other

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lifestyle and health information, so we could examine the relation between time spent outdoors and risk of exfoliation glaucoma or exfoliation glaucoma suspect.

METHODS

• **DESCRIPTION OF THE COHORT AT RISK FOR EXFOLIATION GLAUCOMA OR EXFOLIATION GLAUCOMA SUSPECT:** This was a retrospective cohort study using data from 2 health professional cohorts. The Nurses Health Study is an ongoing cohort study initiated in 1976 when 121 700 female registered nurses completed a health questionnaire; the aim was to evaluate the long-term health effects of oral contraceptives.[25,26] Established in 1986, the Health Professionals Follow-up Study is an ongoing cohort of 51 529 male health professionals (dentists, veterinarians, pharmacists, optometrists, osteopaths, and podiatrists); participants completed a similar questionnaire for the evaluation of the health effects of nutritional factors.[27] Participants from both cohorts have been followed biennially with mailed questionnaires that allowed for updating health and lifestyle information. The study period was 1980–2010 for women and 1986–2010 for men. The study and data accrual were carried out with prospective approval from the Institutional Review Boards of the Brigham & Women's Hospital and Harvard School of Public Health and are in accordance with Health Insurance Portability and Accountability Act regulations.

Participants were excluded from analysis at baseline (defined as 1980 for women and 1986 for men) for the following reasons: (1) 23 239 women who did not respond to the initial 1980 semi-quantitative food frequency questionnaire (as the relation between diet and glaucoma was a major objective of this study), (2) 5994 women and 1596 men with inadequate dietary information on the food questionnaire (for women, adequate dietary information consisted of >50 of 61 items completed, yielding 500–3500 kilocalories per day, while for men, >61 out of 131 items completed with a total caloric intake range of 800–4200 kilocalories per day was regarded as adequate), (3) 3624 women and 1927 men who reported cancers excluding non-melanoma skin cancer prior to a glaucoma diagnosis (because a cancer diagnosis could profoundly affect lifestyle), (4) 846 women and 1034 men who self-reported a diagnosis of glaucoma or glaucoma suspect at baseline, (5) 739 women and 984 men lost to follow-up shortly after baseline, (6) 5659 women and 3281 men who never reported an eye examination during follow-up, (7) 91 women and 169 men with a history of cataract extraction in either eye at baseline (because exfoliation material is difficult to detect in the pseudophakic or aphakic state), and (8) 24 945 women and 19 982 men with missing information on time spent outdoors at various life periods, which were asked about in the 2006 and 2008 questionnaires, respectively. At each 2-year risk period, we applied additional exclusions for participants who were under age 60 years and who did not report having had an eye examination in the 2 years at risk; we only included participants in a given 2-year risk period if they were at least 60 years of age or reported an eye examination. By 2010, a total of 49 033 women and 20 006 men contributed person-time. Follow-up rates through 2010 were high (>85% of the total possible person-time). Participants contributed person-time until the date of confirmation as cases of exfoliation glaucoma or exfoliation glaucoma suspect, a self-report of glaucoma, a self-report of cataract extraction, a diagnosis of cancer other than non-melanoma skin cancer, loss to follow-up, death, or the end of the study (2010), and then they were censored.

• **CASE IDENTIFICATION AND CONFIRMATION:** In all biennial questionnaires from 1986 in both cohorts, we included a question on physician-diagnosed glaucoma. For participants who self-reported such a diagnosis, we sought permission to obtain their medical information from all eye care providers. We then asked the diagnosing eye care provider of record to send all available visual field reports and to fill out a glaucoma questionnaire, which asked about the presence of exfoliation material or other secondary causes for elevated intraocular pressure, maximum untreated intraocular pressure, optic nerve features, and status of the filtration apparatus. Alternatively, eye care providers could provide copies of the complete medical records and all visual field reports related to the glaucoma diagnosis. For confirmation and classification, a glaucoma specialist (Dr Louis R. Pasquale) evaluated the questionnaire or medical record information as well as the visual field data in a standardized manner. We included in the analysis only those cases classified as having either exfoliation glaucoma or exfoliation glaucoma suspect. Specifically, exfoliation glaucoma was considered to be present if documentation showed exfoliation material with ≥2 reliable visual field tests showing reproducible visual field loss consistent with glaucoma, and exfoliation glaucoma suspect was considered to be present if documentation showed exfoliation material plus 1 of the following 3 glaucomatous signs in the same affected eye(s): (1) a history of intraocular pressure >21 mm Hg or (2) cup-to-disc ratio >0.7 or the inter-eye difference in cup-to-disc ratio ≥0.2 or (3) only 1 reliable visual field test showing glaucomatous visual field loss. Those found to have exfoliation material only without any visual field loss, intraocular pressure elevation, or abnormal cup-to-disc ratios in the affected eye(s) were not considered as cases and were censored from the analysis as of the diagnosis date. During the study period, 8032 women and 3316 men reported that they had been diagnosed with glaucoma. Among the subset of 5185 women and 1909 men in whom we were able to receive a confirmatory response from the diagnosing eye care provider, we observed the following breakdown: exfoliation glaucoma