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The Association of Refractive Error with Glaucoma in a Multiethnic Population

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Purpose: To evaluate the association between refractive error and the prevalence of glaucoma by race or ethnicity.

Design: Cross-sectional study.

Participants: Kaiser Permanente Northern California Health Plan members with refractive error measured at 35 years of age or older between 2008 and 2014 and with no history of cataract surgery, refractive surgery, or a corneal disorder.

Methods: We identified 34 040 members with glaucoma or ocular hypertension (OHTN; cases) and 403 398 members without glaucoma (controls). Glaucoma cases were classified as primary angle-closure glaucoma (PACG); 1 of the 4 forms of open-angle glaucoma: primary open-angle glaucoma (POAG), normal-tension glaucoma (NTG), pigmentary glaucoma (PIGM), and pseudoexfoliation glaucoma (PEX); or OHTN. Refractive error, expressed as spherical equivalent (SE), was coded as a continuous trait and also as categories. Logistic regression analyses were used to estimate the association between refractive error and the prevalence of glaucoma overall and in specific racial or ethnic groups.

Main Outcome Measures: The association between refractive error and glaucoma subtypes evaluated as odds ratios (ORs) with 95% confidence intervals (CIs).

Results: In controls, the mean SE was −0.59 diopters (D) (standard deviation, 2.62 D). Each 1-D reduction in SE was associated with a 22% decrease in the odds of PACG (OR, 0.78; 95% CI, 0.77−0.80) and with increases in the odds of open-angle glaucoma ranging from 1.23 (95% CI, 1.20−1.26) for PIGM, to 1.07 (95% CI, 1.03−1.11) for PEX, and to 1.05 (95% CI, 1.04−1.06) for OHTN. In addition, we observed a stronger association between myopia and POAG among non-Hispanic whites (OR, 1.12; 95% CI, 1.11−1.13) and NTG among Asians (OR, 1.17; 95% CI, 1.15−1.20) and non-Hispanic whites (OR, 1.19; 95% CI, 1.15−1.22).

Conclusions: Myopia was associated with an increased prevalence of all forms of open-angle glaucoma and OHTN, whereas hyperopia was associated with a substantially increased prevalence of PACG. Although high myopia is a strong risk factor for glaucoma subtypes, low and moderate myopia also have a significant effect on glaucoma risk. Additionally, there were moderate racial differences in the association of myopia with the risk of POAG and NTG. *Ophthalmology 2015;■:1−10 © 2015 by the American Academy of Ophthalmology.*

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Glaucoma refers to a group of ocular disorders that are associated with progressive optic neuropathy. It is the second leading cause of blindness worldwide.[1] Known risk factors include advanced age, black race, positive family history, and elevated intraocular pressure (IOP).[2−6] Several large cross-sectional studies have reported a higher prevalence of primary open-angle glaucoma (POAG), the most common form of glaucoma, among myopic individuals compared with those without myopia,[7−13] indicating that refractive error may play a role in the pathogenesis of glaucoma. Yet, the possible etiologic link between refractive error and glaucoma is poorly understood. Individuals with axial myopia may have weaker scleral support at the optic nerve, which may result in greater susceptibility of the optic nerve to glaucomatous damage.[14] In some studies, myopic eyes have been reported to have slightly higher IOP and thinner central corneal thickness (CCT) than emmetropic or hyperopic eyes.[7,15] If myopia partially mediates the risk of POAG through weaker scleral support, elevated IOP, or both, it also may predispose individuals to other forms of glaucoma.

Compared with individuals of European descent, African ancestry is associated with a higher risk of POAG developing,[4] whereas Japanese have a higher incidence and prevalence of normal-tension glaucoma (NTG).[16] In addition, some East Asian populations may be more susceptible anatomically to primary angle-closure glaucoma (PACG),[17] although reasons for this racial difference are unclear, and the role of refractive error in this difference has not been well studied. Indeed, the relationships between refractive error and the risks of glaucoma subtypes in different racial and ethnic groups are only poorly understood.

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The purpose of this study was to assess the associations between refractive error and the prevalence of glaucoma subtypes, specifically, PACG; several forms of open-angle glaucoma, including POAG, NTG, pigmentary glaucoma (PIGM), and pseudoexfoliation glaucoma (PEX); and ocular hypertension (OHTN), a condition of high IOP without signs of glaucomatous damage. The study was based on 437 438 Kaiser Permanente Medical Care Plan, Northern California Region (KPNC) members 35 years of age or older who underwent refractive error measurement during the study period from 2008 through 2014. We further examined whether the observed association of refractive error with the prevalence of glaucoma varied by race or ethnicity. Recent studies have documented an increased prevalence of myopia in younger birth cohorts worldwide, including the United States[18]; thus, it is important to understand how refractive error influences the risk of glaucoma.

Methods

Setting

Study participants were identified from the KPNC, a large nonprofit integrated healthcare delivery system with 3.5 million active members comprising approximately 30% of the population of Northern California. The KPNC membership has been shown to be representative of the general population with respect to demographic characteristics, including racial or ethnic diversity, with some underrepresentation at the extremes of income.[19] Since 1995, KPNC has recorded diagnoses, prescriptions, and procedures in a comprehensive electronic health record (EHR) system. The EHR was enhanced in 2007 to capture refractive errors, IOP, CCT, and cup-to-disc ratio (CDR) data.

Glaucoma was diagnosed by KPNC ophthalmologists through comprehensive eye examinations, which typically included measurements of visual acuity, IOP by tonometry, CCT by pachymetry, CDR by ophthalmoscopy and visual field testing, photography of the optic nerve head, and evaluation of the nerve fiber layer by optical coherence tomography. A diagnosis of glaucoma was established on the basis of optic nerve defects and corresponding visual field loss.

Study Population

Institutional Review Board approval was obtained. Eligible cases and controls were drawn from KPNC members who had refractive errors measured at 35 years of age or older between 2008 and 2014 and did not have conditions or procedures that can influence either the measurement or accuracy of refractive error. Specifically, we excluded individuals with histories of cataract surgery (in either eye), refractive surgery, keratitis, or corneal diseases (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes, 370.xx or 371.xx). We also excluded subjects who had diagnoses of borderline glaucoma (ICD-9-CM code, 365.0), preglaucoma (ICD-9-CM code, 365.00), or unspecified glaucoma (ICD-9-CM codes, 365.7 and 365.9) without a more specific diagnosis. In addition, we required controls to have 5 years or more of KPNC membership between 2008 and 2014 to ensure adequate length of observation for glaucoma. Glaucoma cases were not required to have 5 years of KPNC membership because their refractive error was measured at the time that glaucoma was recorded.

Glaucoma Cases. To investigate the association of refractive error with glaucoma subtypes, subjects with glaucoma were divided into 6 subgroups based on the most specific diagnoses recorded in the EHR. The POAG cases had 1 or more diagnoses of POAG (ICD-9-CM codes, 365.01, 365.05, 365.1, 365.10, 365.11, and 365.15) and no diagnosis of any other type of glaucoma, including secondary glaucoma. The NTG cases had at least 1 diagnosis of ICD-9-CM 365.12. The OHTN cases had an OHTN diagnosis (ICD-9-CM code, 365.04) with no diagnoses of POAG. The PEX, PIGM, and PACG cases were identified by ICD-9-CM codes 365.52, 365.13, and 365.2, respectively.

Controls. Eligible controls had no diagnosis of any type of glaucoma (ICD-9-CM code, 365.xx), no documented IOP of 22 mmHg or more in either eye, and no interocular CDR difference of 0.2 or more.

Data Collection

We categorized subjects as non-Hispanic white, black, Asian, Latino or Hispanic, or other based on self-reported race or ethnicity information recorded in the EHR.

Electronic Health Record System and Refractive Error Measures. Measurement of refractive error was a standard workflow component in most ophthalmology and optometry encounters. Intraocular pressure, CCT, and CDR usually were measured as part of the diagnostic workup for glaucoma, although IOP and CDR also were recorded commonly during routine eye examinations. Most subjects had multiple measures for both eyes, and these measures were highly correlated. For this study, we used measurements obtained from the right eye only. We selected for analysis the first documented spherical equivalent (SE) refractive error (calculated as sphere + cylinder/2), the maximum of all recorded CDR, and the median of all recorded IOP and CCT measurements.

Approximately half of the glaucoma cases were diagnosed before 2007; their SEs were recorded into the EHR after 2007, when the refractive error module in the EHR was implemented. Refractive errors generally are stable throughout adulthood. In the case of myopia, the typical onset occurs during childhood or adolescence, well before the time of onset of the glaucoma subtypes investigated in this study. Glaucoma patients usually receive IOP-lowering medications, but these treatments generally do not alter refractions, with the exception of parasympathetic miotics.[20,21] Hence, our analysis included prevalent glaucoma cases with SE measured after the glaucoma diagnosis.

Statistical Analysis

Analyses were conducted using R software version 3.1.1 (https://www.r-project.org/). After univariate analysis, we conducted multivariate logistic regression, stratifying by race or ethnicity, to evaluate the association between SE and the prevalence of each glaucoma subtype, specifically modeling SE as a continuous variable to estimate the effect of a per-diopter (D) decrease in SE, including as covariates age at the first refractive error measurement and gender. Heterogeneity across races was tested using the I^2 statistic and Cochran's Q statistic. If no significant heterogeneity was detected across racial or ethnic groups, we then combined odds ratios (ORs) across racial or ethnic groups using a fixed-effects inverse variance weighted model; otherwise, a random effects model was applied. To evaluate further how low, moderate, and high myopia, as well as degrees of hyperopia, influenced the prevalence of glaucoma subtypes, we divided SE into 6 groups, (≤ -6.00 D, -5.99 to -3.00 D, -2.99 to -1.00 D, -0.99 to 1.00 D, 1.01−3.00 D, ≥ 3.01 D) and conducted logistic regression, adjusting for age at measurement of refractive error (as continuous),

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