Prevalence of Subclinical Keratoconus Among Adults Undergoing Routine, Uncomplicated Age-related Cataract Extraction

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Abstract

Purpose

To determine the prevalence of subclinical keratoconus (SKCN) among individuals undergoing routine, uncomplicated age-related cataract extraction.

Methods

At one major academic ophthalmology department in the United States, we reviewed records of patients aged 50 years and older who underwent surgery from January 2011 to April 2021. Patients who had poor-quality or unreliable tomographic data, previous corneal surgery, keratorefractive procedures, and significant vision-limiting pathology were excluded. While the diagnosis of keratoconus (KCN) was achieved clinically with highly deviated tomographic parameters, SKCN was defined by the authors using the Belin-Ambrósio enhanced ectasia index (BAD-D) > 1.7. This cut-off was selected by meta-analysis of large studies and is higher than the established recommended cut-off of 1.6 for a KCN suspect. In addition, for the eye to be considered as SKCN, at least one of three variables needed to deviate from normative values: 1) posterior elevation at thinnest point, 2) index of vertical asymmetry, and 3) index of surface variation. If one eye had manifest KCN, then the individual would be classified as KCN.

Results

Of 4894 eyes (2913 individuals), the prevalence of SKCN was 27.5% (95%CI, 26.2–28.8, 802 individuals), and prevalence of KCN was 1.6% (95% CI, 1.3–2.0, 47 individuals). Prevalence of SKCN did not increase with age and was more prevalent among females and non-white ethnicities. The mean BAD-D for the SKCN group was 2.23 (95%CI, 2.18–2.28), 1.26 (95%CI, 1.12–1.39) for the normal group ($\rho<0.001$), and 7.85 (95%CI, 6.85–8.85) for the KCN group.

Conclusion

SKCN is sufficiently prevalent such that, resources permitting, tomography ought to be part of standardized pre-operative evaluation.

Introduction

Keratoconus (KCN) is a naturally occurring and progressive bilateral corneal ectasia in which the cornea progressively thins and steepens, ultimately resulting in a cone-shaped deformity of the cornea in end-stage disease. The most recent worldwide estimate of the prevalence of KCN was reported by Hashemi and colleagues to be 0.14% based on an exhaustive meta-analysis[1], however, in some population studies, prevalence has been estimated as high as 8.9%.[2] The recent advent of corneal cross-linking to halt progression of KCN has shifted this disease into one that can not only be managed if diagnosed and treated early in the disease process, but also one with good long-term prognosis.[3 4] Thus, there has been a major impetus for earlier detection, catalyzed in part by
efforts to screen out at-risk corneas from undergoing keratorefractive procedures.[5] The earlier diagnosis has led to further understanding of subclinical keratoconus (SKCN).

SKCN lacks corneal abnormalities detected on clinical exam, significant degree of visual impairment, or large deviations from the norm on corneal tomographic parameters. Indeed, the earliest ectatic changes have been described to occur on the posterior cornea.[6] Advances in Scheimpflug tomographic imaging and the development of more robust data acquisition have made detection of SKCN easier by capturing three-dimensional data to evaluate both anterior and posterior corneal surfaces.[7–9] This knowledge-base gained from the keratorefractive and KCN literature has yet to be applied to the aging adult population with age-related cataracts. Among those age 65 years and older in the United States, the prevalence of KCN was reported at 0.0185% in 2003[10], though SKCN was not detected by corneal imaging at the time or widely diagnosed as an entity. Clinical experience from our setting suggests the prevalence of KCN and SKCN among the aging adults is substantial, though it has yet to be quantified. We propose that improved understanding of the magnitude of disease burden may drive changes in practice patterns, such as routine use of tomographic imaging in pre-operative evaluation, improved intraocular lens (IOL) selection, and better prognostication (expectation setting for post-operative visual outcomes). We therefore undertook this study to describe the basic epidemiology of SKCN in adults undergoing routine age-related cataract surgery.

Patients And Methods

This was a retrospective analysis of adults aged 50 years and older who underwent cataract extraction and IOL placement at a tertiary-referral academic eye centre in the United States, between January 2011 and April 2021. Exclusion criteria were previous corneal surgery (e.g., keratoplasty, keratorefractive surgery, pterygium surgery) and concomitant pathology limiting visual acuity potential, such as significant corneal disease, retinal pathology, severe glaucoma and other advanced optic neuropathies, and low-quality or unreliable tomographic data (e.g., due to severe ocular surface disease, previous keratorefractive surgery, or contact lens warpage). Patients with mild to moderate stage glaucoma undergoing combined cataract surgery and minimally invasive glaucoma surgery (MIGS) were included. This study was approved by the institutional review board of the University of California, Irvine (UCI, reference # HS 2020–6160).

The study aimed for sample size of 1475 individuals based on \( n = \frac{Z_{\alpha/2}^2 p(1-p)}{L^2} \), where \( Z_{\alpha/2} = 1.96 \), \( p = 0.04 \) prevalence proportion of KCN at a population level[2], and \( L^2 \) is accepted margin of error of 0.01. We justify 4.0% as the only study reporting SKCN prevalence at a population level has been Sidky and colleague's 2020 report of 4.4% prevalence[2]; given an assumed high access to healthcare in the United States such that nearly all adults who need cataract surgery would eventually undergo surgery, the 4.0% assumption for a clinic-based sample can closely approximate the underlying base population. Secondly a lower 4.0% estimation is more stringent than the 4.4%.

Clinical data

General demographics, best-corrected visual acuity pre-operatively and at post-operative month one, anterior segment exam findings from pre-operative comprehensive eye examination, clinical diagnosis of KCN, IOL type and power, and use of intra-operative aberrometry were abstracted from the medical record for each operative eye. Cataract extractions were all performed using phacoemulsification with a subset of patients undergoing femtosecond laser-assisted capsulorrhexis, nuclear fragmentation, and/or limbal relaxing incisions.
Corneal tomography

Patients underwent pre-operative tomography using a Scheimpflug camera (Pentacam HR, OCULUS Optikgeräte GmbH, Wetzlar, Germany). Artificial tear solution was used in those with evidence of dry eye syndrome (DES), and individuals with severe DES underwent further ocular surface optimization prior to final pre-operative biometric calculations and tomography. Soft contact lens and rigid gas permeable contact lens wearers were asked to avoid lens use for at least one week or one month, respectively, prior to their visit. Data from the pre-operative tomograms most proximal to surgery were used in this study. Three displays were reviewed, and data were abstracted using the Oculus' built-in export program: 1) Topometric/KC Staging for ABCD keratoconus staging, 2) Belin-Ambrósio enhanced ectasia display (BAD), and 3) Four Map displaying keratometries, total corneal refractive power, and pachymetry.

Keratoconus and subclinical keratoconus definitions

KCN was diagnosed clinically (e.g., asymmetric refraction with high astigmatism, anterior segment examination findings) and supplemented by tomographical data, including classical KISA index constituents [e.g. central keratometry > 47.2D, inferior-superior dioptic asymmetry > 1.4D, skewed radial axis > 21°, and corneal astigmatism index (SimK₁-SimK₂) > 1.5D]. The newer ABCD staging system was also used to determine severity.

There is no universally accepted diagnostic criteria of SKCN in the literature, and in general, studies have sought to establish tomographic parameters for SKCN by assessing the clinically normal fellow eye in known keratoconics. For eyes that were not already classified as KCN, we first screened these eyes with the BAD-D, then assessed if one of three other variables were outliers. Eyes meeting criteria after this two-stage process were reviewed for SKCN. We did not stipulate that the fellow eye exhibit definitive KCN; therefore, an individual could have one KCN eye and one SKCN eye, two SKCN eyes, or one SKCN and one normal. First, the BAD-D was the major criterion indicator variable using a cut-off > 1.70. This cut-off was determined by a random-effects, maximum-likelihood metanalysis to generate a pooled estimate of the mean (theta) and standard deviation (tau) of BAD-D among normal eyes. The upper limit of the 99.9% confidence interval for this metanalysis was 1.697 (Table 1). This pooled estimate was based on seven robust studies reporting mean BAD-D and SD using validated methodology described by Wan and colleagues. The ages of patients in these studies were similar, ranging mid-twenties to mid-thirties, thus when the BAD-D was computed using age-matched controls from the Pentacam normative database, the 1.7 cut-off is still valid for elderly patients since it represents 1.7 standard deviations above the mean for age-matched individual. It is important to note this 1.7 cut-off exceeds the manufacturer's suggested cut-off of 1.6. Second, if an eye met this BAD-D > 1.7 cut-off, the eye must exhibit deviation in at least one of three more variables (minor criteria) to be considered for review as SKCN; these three variables were: 1) posterior elevation at thinnest point > 16.6 µm, 2) index of vertical asymmetry (IVA) > 0.14, 3) index of surface variation (ISV) > 22. Hashemi and colleagues determined BAD-D, IVA, and ISV has the highest area under the receiver operating curve for differentiating SKCN from normal eyes, and the mean posterior elevation at thinnest point for SKCN among adults age 40 to 60 years is 15.04 (SD 1.53). With exception of front vertical coma (Z₃⁻¹), these four variables are the most comprehensively assessed in the literature, and while it would have been ideal to extract front vertical coma, the software does not yet allow automated extraction of higher order aberration datapoints. In summary, provided that the eye did not demonstrate any clinical features of KCN, attributable visual impairment, or exceedingly abnormal tomographic values in the KCN range, and no existing diagnosis of KCN in the medical record, and met the two-stage process described above, then the eye was classified as having SKCN.
Table 1
Studies used in pooled estimate of Belin-Ambrósio enhanced ectasia index (BAD-D)

<table>
<thead>
<tr>
<th>Study name</th>
<th>N</th>
<th>Age mean</th>
<th>Age control</th>
<th>Mean control</th>
<th>SD control</th>
<th>n SKCN</th>
<th>Mean SKCN</th>
<th>SD SKCN</th>
<th>n KCN</th>
<th>Mean KCN</th>
<th>SD KCN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steinberg et al 2015</td>
<td>635</td>
<td>33</td>
<td>196</td>
<td>1.3</td>
<td>1.3</td>
<td>146</td>
<td>2.4</td>
<td>1.8</td>
<td>293</td>
<td>11.2</td>
<td>7.8</td>
</tr>
<tr>
<td>Muftuoglu et al 2015</td>
<td>224</td>
<td>29</td>
<td>134</td>
<td>0.57</td>
<td>0.59</td>
<td>45</td>
<td>1.49</td>
<td>0.82</td>
<td>45</td>
<td>6.49</td>
<td>3.22</td>
</tr>
<tr>
<td>Hashemi et al 2016</td>
<td>647</td>
<td>29.6</td>
<td>200</td>
<td>0.96</td>
<td>0.8</td>
<td>63</td>
<td>3.34</td>
<td>2.9</td>
<td>384</td>
<td>9.55</td>
<td>5.35</td>
</tr>
<tr>
<td>Luz et al 2016</td>
<td>97</td>
<td>25.7</td>
<td>76</td>
<td>0.52</td>
<td>0.5</td>
<td>21</td>
<td>1.84</td>
<td>1.34</td>
<td>0.52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Awad et al 2017</td>
<td>240</td>
<td>26.6</td>
<td>144</td>
<td>1.29</td>
<td>0.6</td>
<td>48</td>
<td>1.4</td>
<td>0.5</td>
<td>48</td>
<td>6.7</td>
<td>2.5</td>
</tr>
<tr>
<td>Kataria et al 2019</td>
<td>300</td>
<td>100</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koc et al 2020</td>
<td>602</td>
<td>26</td>
<td>300</td>
<td>0.96</td>
<td>0.58</td>
<td>151</td>
<td>2.05</td>
<td>0.87</td>
<td>151</td>
<td>7.29</td>
<td>3.44</td>
</tr>
<tr>
<td>Pooled estimates</td>
<td></td>
<td>0.841</td>
<td></td>
<td>-0.015</td>
<td>1.697</td>
<td></td>
<td>1.628</td>
<td>0.449</td>
<td>12.471</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI: confidence interval

Mean and standard deviation (SD) are of the BAD-D value for controls, SKCN, and KCN.

Statistical analysis

Descriptive statistics and frequency analysis were performed on all continuous and categorical variables among demographics, clinical and surgical data, and tomographic data. Prevalence was calculated using Taylor series linearization as bootstrapping method, and the ultimate sampling unit (unit of analysis) was each eye, while the individual was used to link the two eyes. This is a widely accepted method for variance calculation in large country-level population studies (Demographic and Health Surveys, www.dhsprogram.com). Appropriate significance testing was applied for univariate associations, such as t-test for continuous parametric data, proportion test for dichotomous data, Wilcoxon rank-sum test for non-parametric, or Poisson regression for binomially distributed data. In most cases, the eyes were unit of analysis and linked to the individual's unique identifier to account for intra-subject correlation. Statistical significance was set at p < 0.05. Statistical analyses and plotting of graphs were performed with STATA 16 (StataCorp, College Station, Texas, USA), and spreadsheet-based data management performed with Microsoft Excel (Microsoft Corp, Redmond, Washington, USA).
Results

Demographics, ophthalmic and medical characteristics

There were potentially 14,495 eyes available for inclusion. After excluding eye lacking high quality, reliable tomographic data (excluded 9362 eyes) and applying the exclusion criteria expounded upon in the methods section (excluded 239 eyes), there were a total of 4894 eyes included for analysis (33.4% of available eyes) from 2913 individuals. Demographics, ocular, and medical history for each group are provided in Table 2. Comparing the normal and SKCN groups, there was no significant difference between age at time of surgery (median 72.3 years versus 72.6 years), sex distribution (56.2% female versus 58.9%), obesity distribution, or prevalence of common ocular conditions such as DES and blepharitis. However, smoking history, diabetes mellitus type 2, and primary hypertension were more prevalent among those with SKCN. Atopic diseases, such as atopic dermatitis, were slightly more prevalent among the normal group, though this was not significant.

Table 2

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Male (%)</th>
<th>Female (%)</th>
<th>Test of proportions (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50–59</td>
<td>25.5</td>
<td>24.6</td>
<td>0.723</td>
</tr>
<tr>
<td>60–69</td>
<td>23.2</td>
<td>28.6</td>
<td>0.038</td>
</tr>
<tr>
<td>70–79</td>
<td>28.6</td>
<td>28.4</td>
<td>0.813</td>
</tr>
<tr>
<td>80–89</td>
<td>27.1</td>
<td>34.2</td>
<td>0.035</td>
</tr>
<tr>
<td>≥ 90</td>
<td>19.0</td>
<td>24.4</td>
<td>0.634</td>
</tr>
</tbody>
</table>

Table 3

B. Prevalence of subclinical keratoconus (SKCN) by age and sex (N = 2913 individuals)

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>2064</td>
</tr>
<tr>
<td>SKCN</td>
<td>264 27.5% (95% CI, 26.2–28.8)</td>
</tr>
<tr>
<td>Unilateral</td>
<td>538</td>
</tr>
<tr>
<td>Bilateral</td>
<td></td>
</tr>
<tr>
<td>KCN</td>
<td>24 1.6% (95% CI, 1.3–2.0)</td>
</tr>
<tr>
<td>Unilateral</td>
<td>23</td>
</tr>
<tr>
<td>Bilateral</td>
<td></td>
</tr>
</tbody>
</table>

Prevalence of SKCN

The overall prevalence of SKCN was 27.5% (95% CI, 26.2–28.8, 802 of 2913 individuals), which is based on an individual having at least one eye with SKCN without clinically manifest KCN in the other eye. Individuals with KCN in one eye were counted toward the KCN prevalence proportion, which was 1.6% (95% CI, 1.3–2.0, 47 of 2913
individuals). The remainder had unremarkable clinical examination regarding KCN and normal tomography. Table 3A summarizes the individuals by laterality, and Table 3B represents prevalence by age categories and sex. Prevalence of SKCN did not increase with increasing age as a linear variable (ρ = 0.054, Poisson regression), but SKCN was significantly higher among a particular subgroup: females aged 60–69 (ρ = 0.038) and 80–89 years compared to their male counterparts (ρ = 0.035). Due to limitations of statistical power, comparison by race and ethnicity was required to be dichotomized as white (1948 individuals) and non-white (965 individuals), in which SKCN was more prevalent among non-whites 33.2% (95%CI, 30.8–35.5) compared to 25.3% among whites (95%CI, 23.8–26.8, ρ < 0.001, test of proportions).

Tomographic parameters

Tomographic parameters are displayed in Table 4. The mean BAD-D for the SKCN group was 2.23 (95%CI, 2.18–2.28) versus 1.26 (95%CI, 1.12–1.39) for the normal group (ρ < 0.001). The KCN group was provided as a reference, and the mean BAD-D for the KCN group was 7.85 (95%CI, 6.85–8.85). There was a significant difference among nearly all Pentacam-derived parameters except anterior corneal astigmatism, index of vertical asymmetry (IVA), average pachymetric progression index (PPI) and the related variable, BAD-Dp (deviation of the averaged pachymetric progression). The box and whisker plots of key tomographic parameters are provided in Fig. 1 comparing normal, SKCN and KCN groups. Values trended higher from normal to KCN except average Ambrósio relational thickness which trended downward from normal to KCN. Representative examples of the BAD-D displays are provided in Fig. 2 for each group.
Table 4
Tomographic parameters among normal, subclinical keratoconus (SKCN) and keratoconus (KCN)

<table>
<thead>
<tr>
<th></th>
<th>Normal (n = 3458)</th>
<th>SKCN (n = 1364)</th>
<th>KCN (n = 72)</th>
<th>Difference between normal and SKCN (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at surgery, median [interquartile range] (years)</td>
<td>72.3 [66.8, 77.6]</td>
<td>72.6 [67.1, 78.3]</td>
<td>68.6 [63.6, 74.8]</td>
<td>0.06</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>1943 (56.2)</td>
<td>803 (58.9)</td>
<td>27 (37.5)</td>
<td>0.08</td>
</tr>
<tr>
<td>Race/ethnicity, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>2424 (70.1)</td>
<td>839 (61.5)</td>
<td>48 (66.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Asian</td>
<td>401 (11.6)</td>
<td>228 (16.7)</td>
<td>3 (4.2)</td>
<td></td>
</tr>
<tr>
<td>Other race</td>
<td>308 (8.9)</td>
<td>120 (8.8)</td>
<td>12 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>157 (4.5)</td>
<td>101 (7.4)</td>
<td>4 (5.6)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>117 (3.4)</td>
<td>25 (3.4)</td>
<td>3 (4.2)</td>
<td></td>
</tr>
<tr>
<td>Multiple</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>23 (0.7)</td>
<td>45 (3.3)</td>
<td>3 (4.2)</td>
<td></td>
</tr>
<tr>
<td>Native American</td>
<td>19 (0.5)</td>
<td>6 (0.4)</td>
<td>2 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Body mass index [BMI] (kg/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight (&lt; 18.5)</td>
<td>121 (3.5)</td>
<td>47 (3.4)</td>
<td>1 (1.4)</td>
<td>0.451</td>
</tr>
<tr>
<td>Normal (18.5–24.9)</td>
<td>1438 (41.6)</td>
<td>573 (42.0)</td>
<td>25 (34.7)</td>
<td></td>
</tr>
<tr>
<td>Overweight (25–29.9)</td>
<td>1272 (36.8)</td>
<td>482 (35.3)</td>
<td>21 (29.2)</td>
<td></td>
</tr>
<tr>
<td>Obese (30–39.9)</td>
<td>569 (16.4)</td>
<td>246 (18.0)</td>
<td>25 (34.7)</td>
<td></td>
</tr>
<tr>
<td>Morbidly obese (≥ 40)</td>
<td>58 (1.7)</td>
<td>16 (1.2)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
</tbody>
</table>

Smoking status, n (%)

(N = 4894 eyes)
We determined that one in four individuals undergoing routine age-related cataract surgery at a tertiary referral centre have SKCN. We arrived at this estimate using a BAD-D threshold of > 1.7 and three additional variables of posterior elevation at thinnest point, ISV, and IVA. Our BAD-D cut-off is both higher than the threshold previously determined in the literature[15–22] and the threshold recommended by the manufacturer of > 1.6.[23] Despite this, eyes with SKCN in our cohort averaged BAD-D of 2.23 with a lower limit of the 95% confidence interval at 2.18; therefore, these SKCN eyes were deviated at least two standard deviations from the age-matched norms. Since at
least 3.7 million cataract surgeries are performed annually in United States[24], there are potentially 1.01 million with some degree of SKCN. Admittedly this is a high estimate, but the prevalence of KCN in our cohort of 1.6% is within range compared to prevalence proportions from data acquired from clinical cohorts and more modern population studies (2.3–8.9%).[2 25–30] Notably, our KCN proportion is nearly 100 fold higher compared to the United States-based Medicare claims database review prevalence of 0.0185% among adults age 65 years and older in 2003. The major difference can be attributed to data derived from medical claims in an era prior to widespread tomography-assisted diagnostics, and the authors admitted it was an underestimation as their prevalence proportion represented individuals in need of a Medicare claim, such as keratoplasty, and leaves out a larger proportion of individuals who did not need a claim-related surgery.[10] It's important to recognize SKCN is on the spectrum with KCN and may be a precursor in many instances, and our data shows a near 20 fold difference in prevalence between KCN and SKCN. The clinical significance of SKCN has yet to be determined and is part of an ongoing follow-up study. Indeed, the construct of SKCN as a clinical entity in and of itself is currently inconsistently defined, but it has become more widely recognized by the keratorefractive literature in an effort to prevent post-surgical ectasia.[31] It is important to note that SKCN should be distinguished from KCN suspect (forme fruste KCN), such that SKCN does not require a fellow eye with clinically manifest KCN.

The most recent iteration of the BAD-D regression model takes into account nine parameters evaluating corneal anterior surface, posterior surface, and pachymetry as described by Belin and Ambrósio.[23] Comparing an individual's tomographic data to age-matched normals, the BAD-D represents the standard deviation from the normal in which 1.6 or higher is considered the cut-off for a KCN suspect.[32 33] At 1.65, the false positive rate for clinically manifest KCN is already as low as 5% let alone SKCN.[34] Its validity as a screening tool as achieved widespread consensus[19–22 35–37], with area under the receiver operating characteristics curve (AUROC) for KCN ranging from 0.83–0.93.[15 19 22 33 35–37] Among SKCN and normal eyes, the BAD-D is replicable with low variations on repeat scans within a similar session.[38] There is a precedence for our method, in which the BAD-D was used solely in determining the prevalence of KCN of 1.2% in Western Australia.[39]

Other parameters have been studied and should be taken into consideration alongside the BAD-D. Luz and colleagues developed a regression model that also includes the Ambrósio relational thickness max (ARTmax), enhanced best fit sphere front (BFS front), elevation back at thinnest point and within the central 4mm zone, and max pachymetry. Awad and colleagues found ARTmax to be more sensitive and specific than the BAD-D in differentiating KCN suspect from normal. Consistent with the literature, we found highly significant differences for ARTmax, BFS front, and max pachymetry juxtaposing SKCN and normal in our cohort. Hashemi and colleagues added index of vertical asymmetry (IVA), index of surface variation (ISV) and 5th order vertical coma aberration of anterior corneal surface.[15] ISV was significantly different in our cohort but not IVA, perhaps due to our case definition allowing an eye without manifest KCN. Koc et. al. found pachymetric progression index (PPI) average and maximum to have the second highest AUROC for differentiating KCN suspect (not SKCN) from normal[22], but neither of these variables were significantly different in our cohort. This explains why the BAD-Dp variable was not significantly different between SKCN and normal in our study. Koc's study required that the contralateral eye had clinically manifest KCN, suggesting the change in corneal thickness from the thinnest point to the periphery is a hallmark of eyes likely to progress to manifest KCN, which supports the notion of KCN suspect rather than SKCN. This lack of progression aligns with our suggested framework for understanding SKCN, since the corneas of individuals aged 50 years and older are unlikely to progressively thin. Between normal and SKCN regarding PPI and BAD-Dp, there should not be a statistically significant difference. Anterior corneal astigmatism was also not
significantly different between normal and SKCN in our study, which can be attributed to the fact that posterior corneal changes are the subtle deviations of SKCN from the high anterior astigmatism in clinically manifest KCN.

As a screening index, the BAD-D was intentionally designed to screen-in suspect cases and should not be used in isolation to make a diagnosis. Researchers have been able to provide useful inflection points for the BAD-D that enable its use in diagnosis when the entire clinical context is considered. When reviewing cases with BAD-D scores sufficiently greater than BAD-D cut-offs for SKCN and KCN, we excluded cases when it was clear the patient had a poorly-controlled ocular surface disease as this usually led to high values for ISV and BAD-Df, despite within normative values for the other BAD-D indices, IVA, KI, PPI, and ART. For a similar reason, contact lens warpage comeas were excluded from analysis. Indeed, the corneal epithelium's effect on total corneal refractive power can affect the normal air-epithelial interface and lead to falsely diagnosing SKCN due to surface irregularity.[40] In cases of previous keratorefractive surgery, including radial keratotomy, photorefractive keratectomy (PRK), and laser in-situ keratomileusis (LASIK), these procedures led to extremely high ISV, IVA, BAD-Df and BAD-Dp. The assumptions of the enhanced best fit sphere cannot hold in corneas that underwent these procedures, and these patients were excluded from analysis.

After accounting for said cases that could have falsely elevated the prevalence proportion, we believe the seemingly high prevalence of 27.5% in this cohort of routine cataract surgery patients is valid. The prevalence of SKCN correlates with the increasing prevalence of KCN reported in more recent literature.[1 41] A major contributing factor is wider availability of tomography and increased early detection. As SKCN and KCN are on a spectrum, we acquired medical and other ocular history to assess for associations linked to SKCN. Atopy has long been associated with increased prevalence of KCN, and similarly SKCN, due to its potentiation of eye rubbing[42], but there was no significant difference in the prevalence of atopy between the SKCN, KCN, and normal eyes in our study. Similarly, allergic conjunctivitis was similarly prevalent among all three categories. Hashemi and colleagues’ systematic review showed allergy, asthma, eczema were associated with KCN, while diabetes mellitus type I/II were not.[1] At this age group (above 50 years), we are likely not seeing the same magnitude of impact by habit and environment since these individuals’ SKCN disease course must have stabilized. In studies that include KCN across the lifespan, these risk factors become diluted: for example in South Korea's national health survey, allergic conjunctivitis was only slightly more prevalent among those with KCN (35.5%) versus normal (31.0%) and atopy, asthma, connective tissue disorders, diabetes mellitus, and sleep apnea were no more prevalent among those with KCN than normals.[43] In regard to the latter conditions, our cohort was consistent with the Korea-based study except we showed an association with diabetes mellitus type 2 among those with SKCN. Finally, it has been documented that Asian and Arab ethnicities have a higher prevalence of KCN[44]; our cohort showed a higher prevalence of SKCN and KCN among non-whites which is consistent with what is known about KCN. Further granularity is needed, and this level of risk stratification requires prospective cohort studies.

Prospective studies will shed light on the clinical impact and guide more specific recommendations for clinical practice. At this moment, we can extrapolate from cases of mild KCN eyes, in which 80% of phacoemulsification cataract extractions eventually refracted within + 1.0 dioptre of aimed refractive target, with an average of 0.52 dioptre more hyperopic than predicted by a combination of third and fourth generation IOL formulas.[45] Based on these outcomes in mild KCN, we hypothesize that individuals with SKCN would likely have low deviations from refractive targets had the eye been considered a normal eye. Understanding results of toric IOLs, determining magnitude of refractive deviation from aimed target, and best-corrected visual acuity are several key questions to determining clinical significance of SKCN.
Our study is limited by its retrospective design, acquiring data from a single tertiary referral centre that tends to attract a patient population with ocular disease of higher acuity than that in the average population of the United States. Two mitigating factors include consistent pattern of practice in pre-operative evaluation by four cataract surgeons and acquisition of Pentacam scans by a core cadre of experienced technicians. Dynamic Scheimpflug analysis has become a powerful tool owing to its appreciation of the biomechanical properties of the cornea and necessarily improves accuracy of the diagnostic yield[21 46]; however, an applanation device coupled to a Scheimpflug camera, such as a Corvis ST (Oculus GmbH, Wetzlar, Germany), was not available and has not been routinely applied in the setting of cataract surgery preoperative evaluation, even for known manifest KCN. Anterior segment optical coherence tomography is another modality that, while not implemented in our cohort, may have a role in increasing sensitivity in SKCN case detection in future clinical practice.[47] Nevertheless, our study has a large sample size powered to answer the primary question of prevalence, and is the only known study among the cataract-age population.

In conclusion, we have demonstrated that approximately one in four routine cataract surgery patients may have some degree of SKCN. This study highlights the importance of acquiring tomography as routine practice in pre-operative evaluation of cataract surgery if resources allow. Besides general optimization of astigmatism management, uncovering SKCN may affect IOL selection in patients who may otherwise be good candidates for enhanced depth of focus, multifocal, or other advanced technology IOLs. At a minimum, if a patient without identifiable contributing factors has a BAD-D 1.7 or above, the clinician can use this information to better modulate patient expectations.

**Declarations**

**Author contributions**

Design of the study (TMT, AM, SG); conduct of the study (TMT, SG); collection and management of data (TMT); analysis and interpretation of data and preparation of manuscript (TMT, AM, PC, MW, SG).

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**Competing interests**

The authors have no relevant financial or non-financial interests to disclose

**Ethical approval**

All procedures performed were during course of routine clinical care as this a retrospective study. Data collection and deidentification involving human participants adhered to ethical standards of the institutional review board and the Declaration of Helsinki and its ethical principles.

**References**


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**Figures**

![Figure 1](image-url)

**Figure 1**

Example Belin/Ambrósio displays of normal, subclinical keratoconus (SKCN) and keratoconus (KCN)

**A.** Normal: BAD-D

**B.** SKCN: BAD-D 2.72, back elevation thinnest point 26 μm (highly deviated), index of vertical asymmetry 0.33 (highly deviated), keratoconus index 1.09 (highly deviated)

**C.** KCN: BAD-D 5.44, back elevation thinnest point 53 μm (highly deviated), pachymetric progression index average 1.52 (highly deviated), Ambrósio relational thickness max 184 (highly deviated)
Figure 2

Box plots of tomographic parameters

KCN: keratoconus, SKCN: subclinical keratoconus

A. Belin/Ambrósio final index with manufacturer's suggested cut-off of 1.6 for keratoconus suspect and 2.6 for definitive keratoconus demarcated.

B. Keratoconus index

C. Average pachymetric progression index

D. Average Ambrósio relational thickness

E. Index of surface variation

F. Index of vertical asymmetry (no significant difference between normal and SKCN)

G. Index of height asymmetry

H. Index of height decentration