Longitudinal Study of the Normal Eyes in Unilateral Keratoconus Patients

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Purpose: To determine the rate at which clinically normal eyes in unilateral keratoconus (KC) patients progress to KC and to identify the risk factors that might predict the development of KC in a longitudinal study.

Design: Prospective observational study.

Participants: We recruited 778 patients with KC and 252 normal controls in Los Angeles, California. One hundred sixteen of 778 patients (14.9%) were diagnosed with clinically unilateral KC at baseline.

Methods: Both eyes of these unilateral KC patients were examined at baseline, and 85 patients were followed up with clinical evaluation and videokeratography for a period ranging from 6 months to 8 years.

Main Outcome Measures: Progression to clinical KC from previously normal fellow eyes. Quantitative and qualitative videokeratography variables, contact lens wear, and demographic variables were analyzed as potential predictive factors for this progression.

Results: During the follow-up period, 30 of 85 (35.3%) clinically normal fellow eyes had KC develop, and 25 of these 30 (83.3%) had KC develop within the first 6 years after the initial KC diagnosis. By use of the time period from the patients' first diagnosis of unilateral KC to the end of the follow-up period (range, 6 months–41 years), the median time (estimated from the survival analysis) to the development of KC was 16.7 years (95% confidence interval, 11.34, 28.91). Fellow eyes with higher inferior-superior dioptric asymmetry value (I-S) or KC percentage index (logKISA) values had higher risk for KC developing (I-S, risk ratio [RR] = 1.348, P = 0.022; log(KISA), RR = 4.245, P = 0.003). Asymmetric patterns also showed an increased risk for KC developing (P = 0.03), especially the asymmetric bowtie with skewed radial axes (AB/SRAX) pattern.

Conclusions: Approximately 50% of clinically normal fellow eyes will progress to KC within 16 years. The greatest risk is during the first 6 years of the onset. Quantitative indices (I-S and KISA values) and qualitative patterns (AB/SRAX) might predict this progression. *Ophthalmology 2004;111:440–446 © 2004 by the American Academy of Ophthalmology.*

Keratoconus (KC) is a clinical term used to describe a condition in which the cornea assumes a conical shape as a result of noninflammatory thinning and protrusion. The estimated prevalence of KC is approximately 50 to 230/100 000 in the general population.[1] The age of onset is typically during puberty, and the disorder is progressive until the third to fourth decade of life, when it usually arrests. It is a major cause of cornea transplantation in developed countries. Its underlying biochemical processes and its cause remain poorly understood.[1]

Keratoconus is a progressive disorder ultimately affecting both eyes (bilateral KC), although only 1 eye may be affected initially (unilateral KC). The reported frequency of unilateral KC among all KC patients varies, depending on the methods used for diagnosis. The estimated prevalence of unilateral KC ranges from 14.3% to 41% in several early studies.[2–4] In recent studies, the reported frequencies of unilateral KC by use of computerized videokeratography techniques range from only 0.5% to 4%.[5–8]

Unilateral KC can be studied to provide insight into the pathogenesis of the disease. Because KC can exist in the absence of slit-lamp findings, clinically normal fellow eyes might be useful for detecting subclinical changes and progression of the disease. In some instances, unpredictable results and patient dissatisfaction have been attributed to the existence of undiagnosed early KC in refractive surgery patients.[9,10] Detecting early KC and its predictive factors in the clinically normal fellow eyes might also be important in screening for refractive surgery.[11]

Computer-assisted videophotokeratoscopes represent a sensitive means for detecting subtle changes of topography on the corneal surface and allow for detailed qualitative and quantitative analysis of corneal shape.[12–14] In recent years, several quantitative indices that assign numeric values to certain topographic patterns have been developed to reduce

complicated videokeratographs into more manageable quantitative indices.[13,15–17]

The purpose of this study was to determine the rate at which clinically normal eyes in unilateral KC patients develop KC and to identify the risk factors that might predict the development of KC in a longitudinal study.

Materials and Methods

Subjects

We prospectively recruited 778 patients with clinically diagnosed KC and 252 normal patients as controls as a part of a longitudinal videokeratography and genetic study at the Cedars-Sinai Medical Center, Los Angeles, California. Institutional Review Board/Ethics Committee approval was obtained.

The diagnosis of KC was made on the basis of clinical examination. Any patient who had 1 or more of the following clinical signs with no other pathology was classified as having KC: obvious corneal stromal thinning, Vogt's striae, or a Fleischer ring detected by a slit-lamp examination; obvious scissoring of the red reflex; or the Charleaux oil droplet sign identified by retinoscopy.

Normal controls, with no known clinical evidence or family history of KC, were recruited from spouses or acquaintances of KC patients, as well as employees of Cedars-Sinai Medical Center.

All patients and controls underwent clinical and videokeratography evaluation. The clinical examinations included slit-lamp biomicroscopy, retinoscopy, and fundus evaluation. The slit-lamp biomicroscope was used to examine for stromal corneal thinning, Vogt's striae, or a Fleischer ring. Retinoscopy was performed with a fully dilated pupil (20 minutes after 2.5% phenylephrine and 1% cyclopentolate drops had been instilled in the eye) to determine the presence or absence of retroillumination signs of KC, such as the oil droplet sign and scissoring. Videokeratography evaluation was also performed on each eye.

Of 778 patients, 116 patients (14.9%) who were clinically normal in 1 eye were considered unilateral. Eighty-five unilateral patients were followed longitudinally from 1993 to February 2002, with a minimum of 2 visits. Most patients were examined annually with both clinical and videokeratography evaluation.

Videokeratograph Measurements

Videokeratography was performed on both eyes of each subject with the Topographic Modeling System (TMS-1; software version 1.61, Computed Anatomy, Inc., New York, NY) at baseline and each time during the follow-up visit. At least 4 pictures were taken of each eye to ensure the reproducibility of video images. The best videokeratograph of the 4 was selected on the basis of the quality of the keratoscope photos by visual inspection.

Each videokeratograph from each eye was put into 1 of 10 categories as judged subjectively by 3 observers, who agreed on the same pattern in 90% of videokeratographs studied.[18] This classification scheme has previously been reported in detail.[18]The other 10% of videokeratographs were assigned according to a pattern agreed to by at least 2 of the 3 observers. The categories were as follows: round, oval, irregular, inferior steepening (IS), superior steepening (SS), symmetric bowtie (SB), and asymmetric bowtie (AB) with SS, AB with IS, SB with skewed radial axes (SRAX), and AB with SRAX (AB/SRAX).[18] Because of the moderate sample size, we grouped the 10 categories analyzed into 3 groups of patterns: group 1, symmetric patterns including round, oval, and SB; group 2, all asymmetric patterns except AB/SRAX; and group 3, only the AB/SRAX pattern, which is extremely rare in normal individuals.[18]

Quantitative indices of average central keratometry reading (CK), inferior-superior dioptric asymmetry value (I-S), and KC percentage index (KISA) on each eye were generated from the TMS-1.

Central K (CK) was calculated by averaging the dioptric power points on rings 2, 3, and 4 of the videokeratographs generated by the TMS-1.

Inferior-superior dioptric asymmetry value, the amount of steepening of the inferior cornea compared with that of the superior cornea, was calculated by subtracting the superior value from the inferior value. The inferior value was calculated by averaging 5 data points along the inferior cornea 3 mm from the center of the cornea at 30° intervals (that is, 210, 240, 270, 300, and 330°). The superior value was derived from averaging 5 points on the superior cornea, also 3 mm from the center of the cornea, at 30, 60, 90, 120, and 150.

The KC percentage index was derived from 4 indices, including the CK value; the I-S value; and the AST index, which quantifies the degree of the regular corneal astigmatism (SimK1–SimK2), as well as the SRAX index, an expression of irregular astigmatism occurring in KC. The algorithm for calculating the KISA index was initially derived as follows:

$$KISA = (K) \times (I\text{-}S) \times (AST) \times (SRAX) \times 100/300$$

All the preceding indices have previously been described in detail in the peer-reviewed literature.[13,14,17]

Statistical Methods

All data, including demographic information, clinical examination, and videokeratographic measures, were entered into a relational database. Statistical analyses were performed with SAS 8.0 (Statistical Analysis Software, Cary, NC).[19] For quantitative traits, the comparisons between 2 groups were tested by Student's t test when variables had a normal distribution or by nonparametric Wilcoxon rank test when traits deviated from normal distribution. Logarithm transformation was used for KISA to obtain normal distribution for the statistical analysis. We used the chi-square test to compare proportions of qualitative traits between groups. Pearson correlation between variables was calculated, and the t test was used to determine whether the null hypothesis ($H_0 = 0$) can be rejected, that is, whether the observed correlations were significantly different from 0.

The estimation of number of years for KC developing was calculated with survival analysis. Survival analysis is a statistical method for studying the occurrence and timing of events. In our study, the "event" was defined as the occurrence of KC in the fellow eye during the follow-up period, and the "time of the event" represented the length of time from the first diagnosis of KC to the time when the fellow eye developed KC. For the subjects who did not have KC develop or whom we did not follow-up during this period, we used the "time of the censoring," the length of time from the first diagnosis of KC to the latest date of follow-up, as the timing variable. The Kaplan-Meier estimator, the most widely used method for estimating survival functions and the most suitable one for smaller data sets in the survival analysis, was calculated in our study. On the basis of the Kaplan-Meier estimator, the estimated median time, which is usually the preferred measure of central tendency for censored survival data,[20] for KC developing was reported in the results. We also compared the difference of survival functions between groups by use of the nonparametric method.

Multivariate analysis was performed with the Cox proportional hazards model. The "event" variable was the same as the survival analysis, and the "time" variable was defined as the period from the baseline to the end of the end point. All quantitative and

Table 1. Videokeratography Indices of the Clinically Normal Fellow Eyes and Normal Controls at the Baseline

| Variables | Fellow-Eye Group | | Normal Controls* | | P Value[†] |
	N	Mean ± Standard Deviation	N	Mean ± Standard Deviation	
CK	116	44.26 ± 1.78	252	43.97 ± 1.44	0.1305
I-S	116	1.56 ± 1.15	252	0.42 ± 0.51	<0.0001
Log(KISA)	116	1.57 ± 0.53	252	1.27 ± 0.42	<0.0001

CK = average central keratometry reading; I-S = inferior-superior dioptric asymmetry value; KISA = keratoconus percentage index.
*In control group, the maximum value of each index from 2 eyes for each individual was used.
[†]Student's t test.

qualitative variables at baseline were entered into the Cox model as independent variables (i.e., age onset, duration of being unilateral KC at the baseline, gender, race, contact lens wear, CK, I-S, and KISA values in fellow eye, as well as the KC eye). Because CK, I-S, and KISA might have a collateral relationship, we tested each index separately under each of the 3 models. The likelihood ratio test was used to fit models in the Cox regression.

Results

Comparison between Normal Fellow Eyes of KC Patients and Normal Controls

The mean age at baseline in the unilateral KC patient group was lower than that in normal controls (34.28±12.24 vs. 38.81±12.18; $P<0.001$). There were more males in the unilateral KC patient group (62.9%) than in the controls (40.5%; $P<0.0001$). No significant difference in race was found between the 2 groups.

The clinically normal fellow eyes had higher I-S and logKISA values compared with normal controls at baseline (Table 1).

Estimated Median Time for the Fellow Eyes Developing KC

Among 85 patients with at least 2 visits, the years of follow-up ranged from 0.56 to 8.78 (median, 3.40). During this time, 30 of 85

(35.3%) fellow eyes had progressed to KC. Taking into account the period when these patients were first diagnosed with unilateral KC to the end of the follow-up period, the total period for analysis ranged from 0.56 to 41 years. The median time from the first unilateral KC diagnosis to become bilateral KC was 16.69 (95% confidence interval, 11.34, 28.91) years. Figure 1 shows the survival curve of the normal fellow eyes from the initial unilateral KC diagnosis to bilateral KC. The term "survival" was defined as the time during which the normal eyes remained normal. It seemed that the curve dropped quickly during the first 6 years (25 of 30 fellow eyes developed clinical KC). In other words, among patients who had bilateral KC develop during the follow-up, most of them had KC develop within the first 6 years after the first diagnosis. The longest time from the first diagnosis to the development of bilateral KC was 28.91 years. However, 1 KC patient still remained unilateral after 40 years from the date when the diagnosis of KC was first made.

Predictive Factors

To identify factors that might predict the development of KC in fellow eyes, we evaluated baseline variables, including age at baseline, age at onset of unilateral KC, duration of fellow eyes, gender, race, contact lens wear, CK, I-S, and logKISA values in the normal eye and the KC eye.

Univariate analysis showed that higher baseline I-S and logKISA values in normal eyes were associated with the develop-
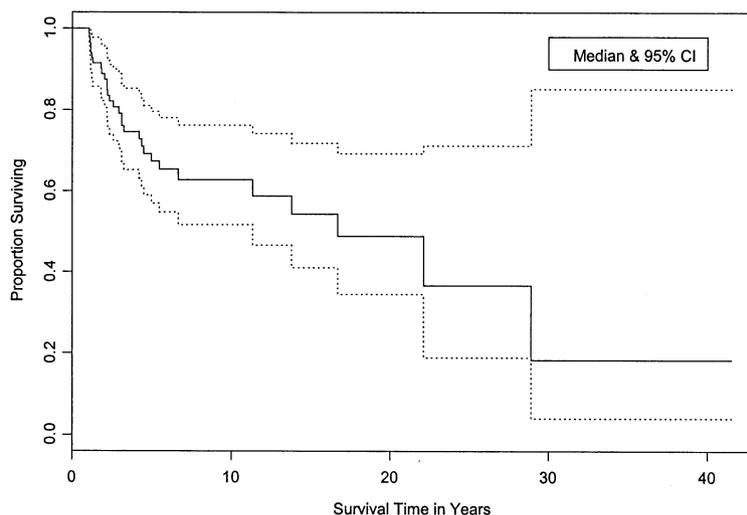

Figure 1. Survival* curve of all fellow eyes from initial unilateral keratoconus (KC) diagnosis to the development of bilateral KC. Top line, Upper 95% confidence intervals of the survival curve; middle line, survival curve of estimated developing time and proportions; bottom line, lower 95% confidence intervals of the survival curve. *Defined as the period during which the normal eyes remained normal.

Table 2. Multivariate Analysis Using Cox Regression

Model*	Variables Associated with the Development of Bilateral Keratoconus	Risk Ratio†	95% Confidence Interval	P
Model two	I-S in fellow eye	1.348	1.043, 1.742	0.022
Model three	LogKISA in fellow eye	4.245	1.626, 11.083	0.003

I-S = inferior-superior asymmetry value; KISA = keratoconus percentage index.
*A total of three models was tested. In model one, which included average central keratometry reading in fellow eye and other variables, none of variables was significantly associated with the development of bilateral keratoconus.
†Relative risk means that for each 1-unit increase in inferior-superior dioptric asymmetry value or log keratoconus percentage index, there is a comparable increased risk for developing keratoconus.

ment of KC. Among 30 fellow eyes that developed KC during the follow-up period, mean ± standard deviation for I-S value was 2.04±1.56 and for logKISA was 1.88±0.43. These values were significantly greater (I-S, $P<0.05$; KISA, $P<0.001$) than those observed in the group who did not develop KC (n = 55) during a similar period of follow-up (I-S, 1.36±0.97; logKISA, 1.47±0.47). In multivariable analysis controlling other covariates, I-S and logKISA in the normal eye at the baseline were still significantly associated with the development of KC (Table 2).

For 46 of 85 unilateral KC patients, KC was first diagnosed before the study entry when the baseline information was obtained. The time from the first KC diagnosis to the study entry varied among the patients (ranging from 1–38 years). Because baseline I-S and logKISA were associated with the development of KC in fellow eyes, it was important to evaluate whether such an association was confounded by the length of time between the first KC diagnosis and the baseline examination. Therefore, we tested the correlation of the length of time with I-S and logKISA values individually and did not observe any significant correlation (both $P>0.5$).

To illustrate the relationship between I-S, log KISA, and the

development of KC in fellow eyes in a different way, we compared the estimated time of developing clinical KC between the groups stratified by I-S and logKISA (cut point for I-S = 1.4 and for logKISA = 2). These cut points were chosen on the basis of the normal/abnormal definition for I-S and KISA described previously for these quantitative values.[17] The estimated median time for developing KC was much shorter in the group with high values of I-S (5.48 vs. 22.11, $P = 0.018$) or logKISA (4.36 vs. 22.11, $P = 0.017$). Figures 2 and 3 show the survival curves for progression to KC for each subgroup divided by I-S and logKISA values, respectively.

Relationship of Videokeratography Patterns and Development of KC

At the time of entry, there were 17 (20.0%) fellow eyes with symmetric patterns, 42 (49.4%) with asymmetric patterns (excluding AB/SRAX), and 26 (30.6%) with AB/SRAX pattern. The total proportion of asymmetric patterns including AB/SRAX was 80.0% for all fellow eyes. More than one half (15 of 26, 57.7%) of fellow eyes with AB/SRAX patterns developed KC, whereas only 28.6% (12 of 42) with asymmetric patterns (excluding AB/SRAX) and 17.6% (3 of 17) with symmetric patterns developed KC during the follow-up period ($P = 0.012$) (Table 3). The estimated time for developing bilateral KC decreased gradually according to groups by patterns during the follow-up period ($P = 0.03$) (Table 4).

Discussion

In this longitudinal study, we have provided new information regarding: (1) the incidence and duration of the progression of clinically normal fellow eyes to development of KC; (2) the predictive factors for developing KC in the normal eye; and (3) the distribution of qualitative and quantitative factors in normal eyes of KC patients.

As previously discussed, KC is most commonly bilateral, and the prevalence and incidence of unilateral KC varies, depending on the methods used for diagnosis. By use of
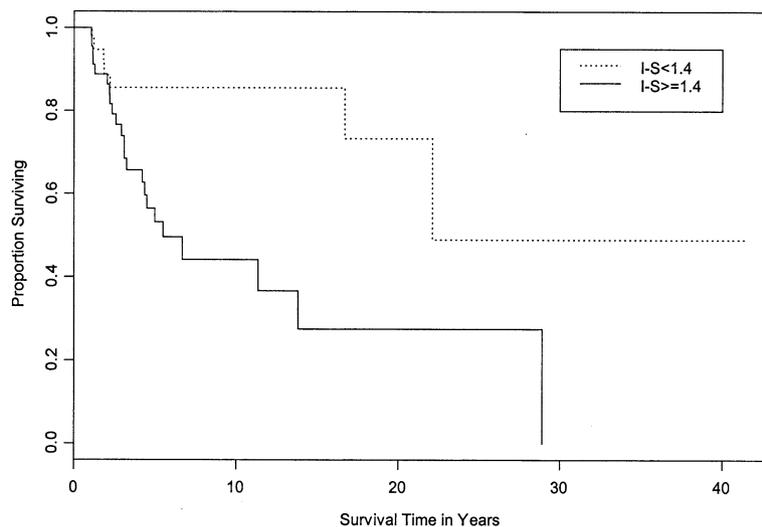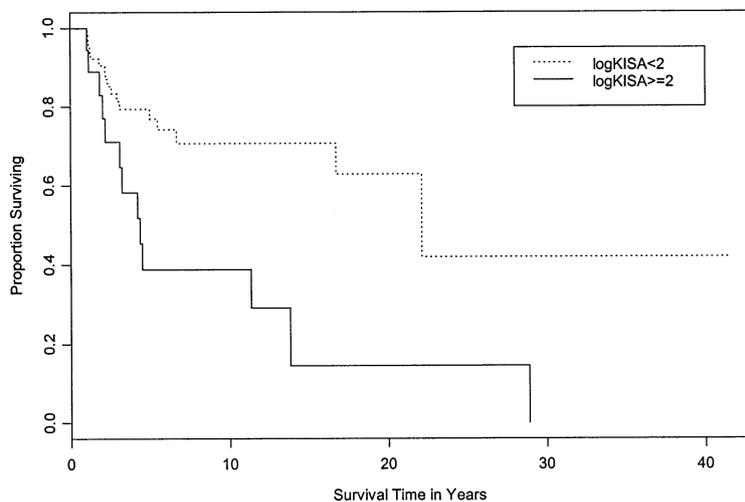

Figure 2. Survival* curve of fellow eyes from initial unilateral keratoconus (KC) diagnosis to the development of bilateral KC stratified by inferior-superior (I-S) dioptric asymmetry values. Top line, The survival curve of the fellow eyes with I-S<1.4; bottom line, the survival curve of the fellow eyes with I-S≥1.4. *Defined as the period during which the normal eyes remained normal.

Figure 3. Survival curve of fellow eyes from initial unilateral keratoconus (KC) diagnosis to the development of bilateral KC stratified by keratoconus percentage (logKISA) values. Top line, The survival* curve of the fellow eyes with logKISA<2; bottom line, the survival curve of the fellow eyes with logKISA≥2. *Defined as the period during which the normal eyes remained normal.

clinical methods only, we found 116 cases of unilateral KC in 778 patients (14.9%). This rate was similar to that reported by Krachmer et al[3] and higher than the studies in which the unilateral KC was diagnosed with the aid of computer-assisted videokeratoscopy.[5-8] The latter method can detect subclinical KC and might result in a decreased prevalence of clinically unilateral KC. Our study showed that more than one third of clinically normal eyes progress to KC during the follow-up period. The estimated median time for developing KC was 16.69 years from the time the disease was first diagnosed. This information might be useful to clinicians interested in disease progression and in screening for keratorefractive surgery. Holland et al[7] believed that most patients eventually would have bilateral disease develop if the patients were observed for a sufficient period of time. In our study, of those who had bilateral KC develop during the follow-up period, most had a lag time (from the initial unilateral diagnosis to the development of bilateral KC) of less than 6 years, and only 2 had bilateral KC develop more than 20 years after the initial unilateral diagnosis. Of those who remained unilateral at the end of this study, many (53%) have not to date been followed up for a long enough time (less than 6 years). Four patients remained unilateral for longer than 20 years after the initial

diagnosis of unilateral KC (1 of them has been unilateral for more than 40 years). These resistant fellow eyes not only influence the estimates of survival analysis but also pose new questions (i.e., What influences the fellow eye to remain clinically normal over such a long period?).

The use of quantitative videokeratography–derived indices potentially represents a more reproducible way of quantifying KC and its early phenotypes.[17] Some studies suggest that topographic features might be useful in detecting KC before the development of the clinical findings.[5,6,21-23] Several quantitative indices such as KPI, KCI%, CK, I-S, and KISA have been used.[14-17,22] Rabinowitz et al[22] developed 3 indices (CK, I-S, and R vs. L) and distinguished eyes with KC from normal eyes in a small preliminary study (28 family members of 5 patients with KC). Their results supported that these 3 indices might be the descriptor of the earliest stages of KC. They also developed a new index, KISA%, in a later study.[17] After comparing KISA% with KCI%, KPI, K, and I-S, they found the sensitivity of KISA% was the highest for detecting KC (99.6%). This high sensitivity was also confirmed by a recent Polish study.[24] However, the sensitivity and accuracy of quantitative indices for studying subclinical changes and early KC

Table 3. The Distribution of Baseline Patterns between the Groups That Developed and Did Not Develop Bilateral Keratoconus

Videokeratography Patterns	Fellow Eyes That Did Not Develop Bilateral Keratoconus		Fellow Eyes That Developed Bilateral Keratoconus		Total	
	N	(%)	N	(%)	N	(%)
Symmetric patterns	14	25.4	3	10.0	17	20.0
Asymmetric patterns without AB/SRAX	30	54.6	12	40.0	42	49.4
AB/SRAX	11	20.0	15	50.0	26	30.6
Total	55	100.0	30	100.0	85	100.0

AB = asymmetric bowtie; SRAX = skewed radial axes.
Chi-square test for the distribution of patterns between 2 fellow eye groups: P = 0.012.

Table 4. Estimated Median Time by Survival Analysis for Developing Bilateral Keratoconus by Pattern Groups

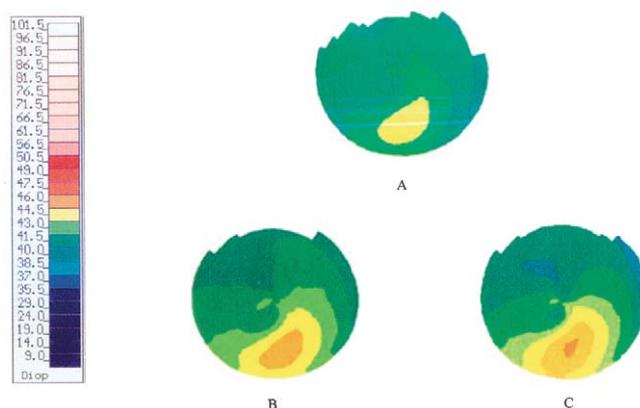| Videokeratography Patterns	Number at Entry	Number of New Bilateral Keratoconus	Proportion of Developed (%)	Median time for Developing (yrs)
Symmetric patterns	17	3	17.6	—*
Asymmetric patterns without AB/SRAX	42	12	28.6	16.69
AB/SRAX	26	15	57.7	4.98

*We cannot estimate the median, because the number of patients who developed keratoconus in this group was too small.

Figure 4. Example of the videokeratographs showing progression of keratoconus (KC) "suspect" in a clinically normal fellow eye to KC over time. (Note all maps are in the same "absolute scale" for comparison. **A,** Clinically normal fellow eye: "keratoconus suspect" (July 1996): inferior-superior dioptric asymmetry (I-S) value = 2.14, keratoconus percentage index (KISA) value = 77.14%. **B,** "Early" KC (keratoconus diagnosed by retinoscopy only, otherwise clinically normal, 1 year later) (November 1997): I-S value = 3.24, KISA = 122.93%. **C,** KC (detectable by slit-lamp evaluation, 3 years later; March 1999): I-S value = 4.5, KISA value = 204.00%.

still needed to be confirmed by longitudinal studies and serial topographic analysis.

Our study provides useful information about the value of 3 quantitative indices: CK, I-S, and KISA. We found that the fellow eyes have higher values of I-S and KISA indices than those of normal eyes. However, the CK value did not show any difference between the 2 groups. This was consistent with Rabinowitz et al's study,[6] in which 4 of 8 fellow eyes had an I-S value of more than 1.4, and none of these patients had a CK value higher than the normal controls. Longitudinal data in our study also show that higher I-S and KISA values are associated with progression to bilateral KC. Although KISA was calculated proportionally by CK and I-S, after taking out the I-S value from the calculation, we also obtained the significant association between KISA and KC development using multivariate analysis ($P = 0.01$). It seems that the effect of KISA for KC progression is independent of I-S. We have not as yet conclusively described all quantitative indices that truly represent early KC. However, our study suggests that 2 indices, the I-S and KISA values, are valuable adjuncts for identifying the early stages of KC and for recognizing and predicting patients at risk for progression to KC in screening for refractive surgery (Fig 4).

Beside the quantitative indices, videokeratographic patterns also showed different distributions in clinically normal fellow eyes than in normal control eyes. A high proportion (80.0%) of asymmetric patterns was found in the clinically normal fellow eyes compared with only 40.1% in normal eyes in the Bogan et al study[25] and 32.6% in the Rabinowitz et al study.[18] The AB/SRAX pattern (present in only 0.5% of normal eyes reported by Rabinowitz et al[18]) was much more common in fellow eyes and predicted a greater risk of KC developing than other patterns. Our results confirmed that the AB/SRAX pattern could be used to distinguish preclinical KC from normal eyes and potentially predict the development of clinical KC.

The limitations of our study should be noted. It is important to recognize the comparability between those patients who remained in the study and those who were lost to follow-up. Although the distribution of CK and I-S did not show any difference, the mean value of logKISA in normal eye was lower in the patients lost to follow-up than in those with follow-up (1.35 vs. 1.62, $P = 0.02$). Therefore, the 85 eyes with follow-up might have KC develop faster than

those lost to follow-up. The period of follow-up was still not long enough for many patients. The relatively small sample size also warrants caution. Furthermore, it is noteworthy that the results were obtained only on the basis of 1 data set; they need to be confirmed by other studies.

In summary, the data presented in this article suggest that refractive surgeons and geneticists might, with a reasonable degree of confidence, predict that clinically normal eyes with high I-S values or asymmetric bowtie (AB/SRAX) patterns might progress to KC.

Longitudinal studies regarding quantitative indices and videokeratography patterns as predictors for the development of KC that use a longer period of time for follow-up are currently in progress. These studies will be necessary to confirm the preliminary findings of this study.

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