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## ORIGINAL ARTICLE

# Conjunctival Epithelial Flap in Continuous Contact Lens Wear

Andrew D. Graham*, Tan N. Truong†, and Meng C. Lin‡

**ABSTRACT**

***Purpose.*** Composed of sheets of cells detached from the underlying conjunctiva, conjunctival epithelial flap (CEF) is a recently reported phenomenon associated with contact lens wear with potential consequences for ocular health. Although CEF is generally asymptomatic, it is not known to what extent it might increase the longer-term risk of discomfort, inflammatory response, or infection. In this study, we use survival analysis methods to obtain unbiased estimates of the probability of developing CEF, the mean survival time free of CEF, and the effects of age, gender, ethnicity, and contact lens type.

***Methods.*** Two hundred four subjects were recruited for a continuous wear (CW) study of silicone hydrogel (SiH) and gas permeable (GP) contact lenses. Subjects were examined by optometrists throughout contact lens adaptation and CW periods. Statistical methods included the Kaplan-Meier nonparametric estimator of the survival function and the Cox proportional hazards model for estimating the relative effects of covariates.

***Results.*** Of the 204 subjects, 72 (35%) developed CEF. In 64% of cases, CEFs were observed bilaterally. The majority of cases (90.3%) presented with CEF in the superior conjunctiva. Mean survival time free of CEF was longer for GP lenses (94.3 days) than for SiH lenses (76.5 days), and the probability of developing CEF was significantly greater for SiH lenses (p = 0.002). Although there was some evidence that women and non-Asians remain free of CEF longer, the effects of age, gender, and ethnicity were not statistically significant.

***Conclusions.*** There was a significantly increased risk of CEF in subjects wearing SiH lenses, compared with GP lenses. Subjects wearing SiH lenses remained free of CEF for a shorter time on average. Further study is needed to determine whether the increased incidence of CEF in CW with SiH lenses poses an increased risk of adverse ocular response or infection.
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Key Words: conjunctiva, contact lens, continuous wear, silicone hydrogel, gas permeable, conjunctival epithelial flap, survival analysis

Conjunctival epithelial flap (CEF) is a recently reported phenomenon first observed in silicone hydrogel (SiH) contact lens wear.[1] It is believed that the interaction of the lens edge with the ocular surface, particularly in continuous wear (CW) with higher modulus SiH lenses, causes the superficial layers of conjunctival cells to delaminate. On awakening, blinking and subsequent lens movement plow the detached sheets of cells into loose folds or flaps that can be observed under magnification by slit lamp with fluorescein, cobalt blue illumination and a yellow filter (Figs. 1 and 2). In the original study by Løfstrøm and Kruse,[1] 16 subjects who had worn either lotrafilcon A or balafilcon A contact lenses for a minimum of 6 months in CW were examined. Of the 32 eyes, 11 (34%) were found to have CEF in the superior, inferior, or both quadrants. No CEF was observed in the nasal or temporal quadrants. The authors also noted that the majority of CEF was observed in subjects wearing the lotrafilcon A lenses, and that this lens has a chisel-shaped edge design, compared with the rounded edge design of the balafilcon A lens.

The cellular composition of CEF observed in CW appears to depend on the duration of lens wear. Impression cytology after 1 week of CW showed that CEF is composed primarily of vital epithelial and goblet cells.[2] However, this is reported from only two cases of CEF, and it is not clear that the technique is sufficiently localized to have sampled only the CEF and not the surrounding, intact conjunctiva as well. We have found that CEF

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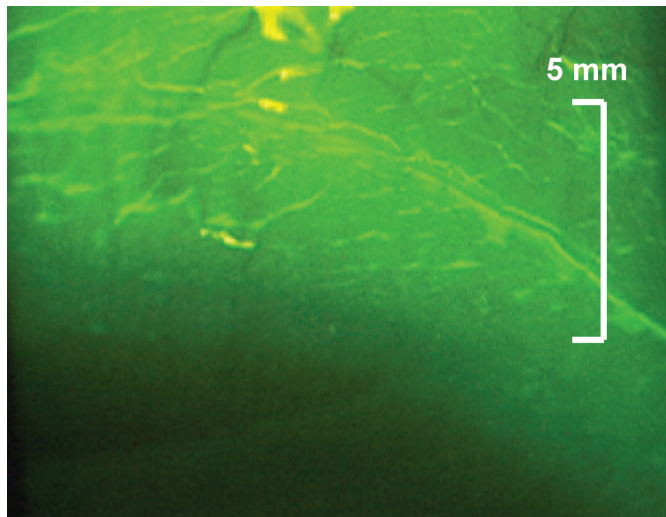
**FIGURE 1.**

Conjunctival epithelial flap after 30-day continuous wear of silicone hydrogel contact lenses can be viewed under magnification using fluorescein with cobalt blue illumination and yellow filter (12× magnification).
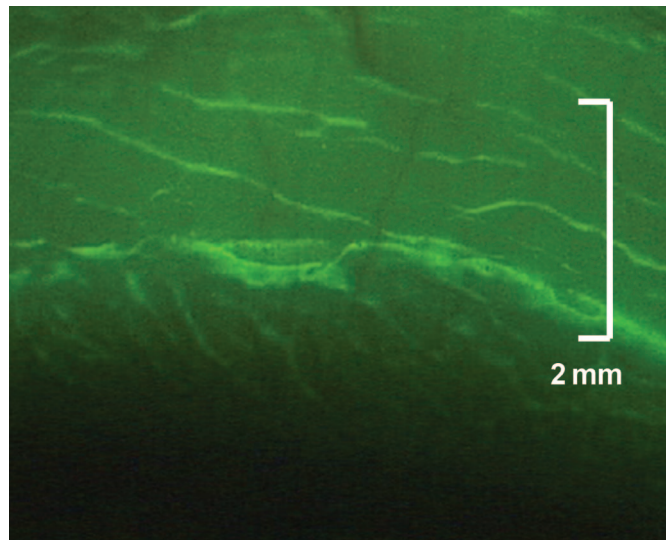


**FIGURE 3.**

Conjunctival epithelial flap observed after 1 day of gas permeable continuous wear (32× magnification). To the right of the image is an arcuate indentation close to the limbus and to the left-center is a small flap.
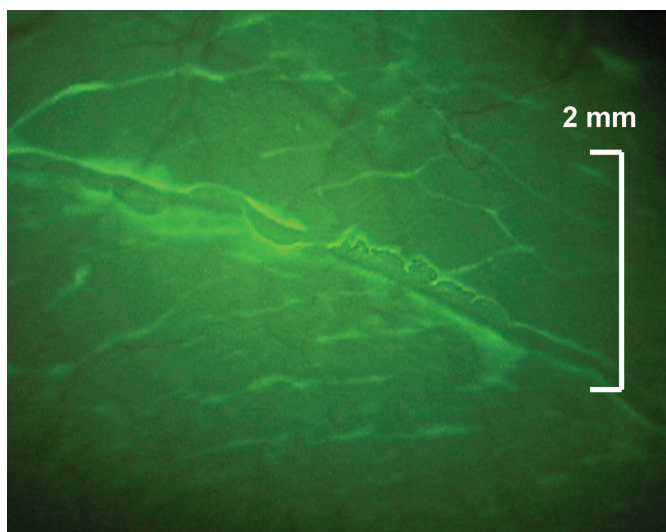


**FIGURE 2.**

The same conjunctival epithelial flap as in Fig. 1, but under 32× magnification. Note that parts of the flap are folded over superiorly, whereas other parts are folded over inferiorly.
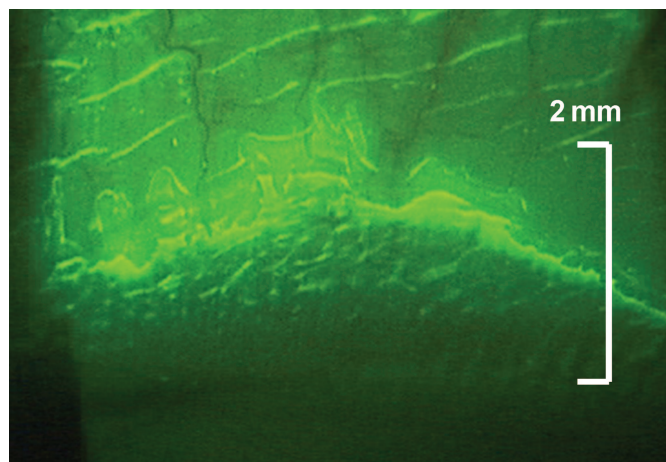


**FIGURE 4.**

Conjunctival epithelial flap in the same subject as in Fig. 3, but after 1 week of gas permeable continuous wear (32× magnification). The flap is larger and far more extensive than after 1 day of continuous wear.

observed after 1 week of CW does not stain with rose bengal, but will stain brightly after 30 days of CW.[3] This may indicate that after prolonged exposure the cells of the CEF become devitalized or it may be that there is an insufficient protective layer of mucin covering the flap.

CEF has also been reported in day-wear (DW) with SiH contact lenses. Researchers in our laboratory (Lin et al.[3]) examined 390 eyes over 1 month of DW with three different SiH lenses and one conventional hydrogel lens. Lotrafilcon B had the highest occurrence rate of CEF (6%), followed by comfilcon A (2%) and galyfilcon A (1%), with no cases of CEF occurring in DW with the conventional hydrogel omafilcon A. In that study, the authors observed CEF ranging in size from 0.1 to 0.5 mm, which is considerably smaller than the CEF of up to 9 mm reported in CW.[4,5] CEF was observed exclusively in the superior and inferior quad-

rants, approximately 0.5 to 1 mm from the lens edge near the margin of vertical lens travel,[3] further supporting the hypothesis that the contact lens edge plays an important role in the etiology of CEF.

We have observed CEF in gas permeable (GP) lens wearers (Figs. 3 and 4), and occasionally in noncontact lens wearers (Figs. 5 and 6), which has not been previously reported. CEF in these cases tends to occur near the limbus in the superior conjunctiva, rather than further into the bulbar conjunctiva near the limit of lens travel as is the case with CEF observed secondary to SiH contact lens wear. In contact lens wearers, CEF is thought to develop through interaction between the lens edge and conjunctival surface and is likely to be affected by lens modulus, ocular surface curvature, and lens fitting characteristics. It is not known precisely how conjunctival flaps form spontaneously in noncontact lens wearers; however, there are suggestions from clinical, cytological,
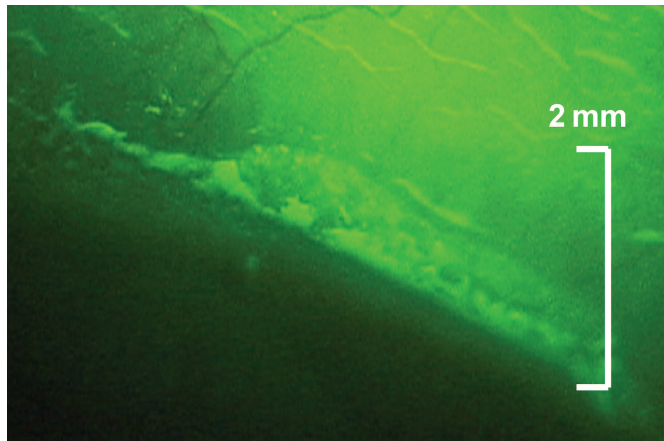
**FIGURE 5.**

Conjunctival epithelial flap observed in a noncontact lens wearer. The flap occurs closer to the limbus than is the case with SiH contact lens-induced CEF.
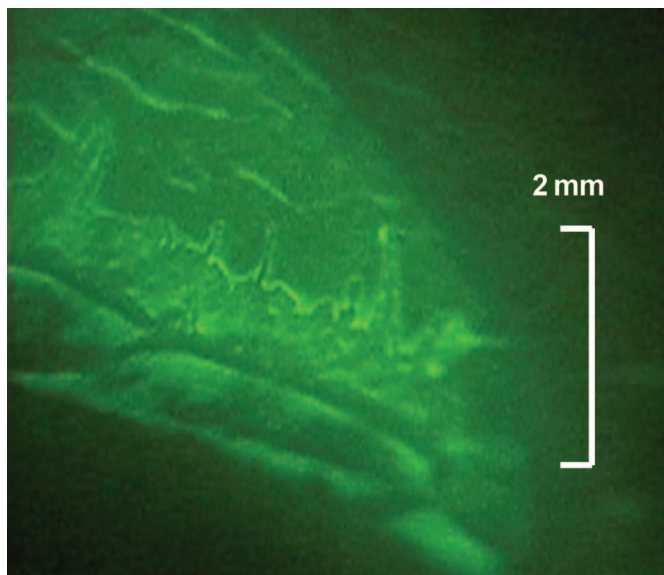


**FIGURE 6.**

The same conjunctival epithelial flap as in Fig. 5, but after manipulating the upper eye lid. It can be seen that the flap is a loose, flexible fold of conjunctival tissue.

and electron microscopic studies of the ocular surface. Pfister[6] showed that the superior conjunctival tissues undergo significant expansion and contraction with lid movement, and that there is substantial variability across the conjunctiva in both the tightness of intercellular junctions and in the distribution of the small, microfilamentous protrusions known as filopodia, which connect adjacent cells and are important for cellular migration and wound healing. Conjunctival folds or pleats have been observed in noncontact lens wearers exposed to stressful environments, such as surgical operating rooms, which have sealed windows and ventilation systems, strong air turnover, and contain airborne anesthetics and bio-aerosols known to affect the tear film.[7] Conjunctival folding is also observed in patients with ocular surface abnormalities, such as conjunctivochalasis[8] or dry eye disease.[9,10] Although these observations do not explain the occurrence of CEF in noncontact lens wearers, they do demonstrate that the bulbar conjunctival tissues are spatially nonuniform, flexible, and subject to deformation.

There are few other studies of CEF in the literature to date. Lakkis et al.[11] report an incidence proportion of 27% at 9 months of CW with SiH lenses. As with other researchers, they observed CEF in the superior and inferior conjunctiva only. Santodomingo-Rubido et al.[12] report the incidence of CEF over 18 months of SiH lens wear to be 3.8% for DW, which is in agreement with other studies. However, they report an incidence of 7.5% for CW, which is considerably lower than other researchers have found. These differences among published incidence rates are likely due to differences in study protocols, lens materials and edge designs, or bias in statistical calculations (discussed further below).

Although most subjects who develop CEF are asymptomatic, the presence of flaps of delaminated conjunctival cells is of potential clinical concern. It is not presently known whether such a disruption of the conjunctiva could pose a longer-term risk for discomfort leading to discontinuation of contact lens wear, for inflammatory events because of cellular debris being sloughed from the ocular surface and trapped under the contact lens or for infection because of microorganisms accumulating within the loose folds of disrupted conjunctival tissue. Given the potential for adverse events, clinicians considering prescribing contact lenses for CW face a disadvantage in that several basic facts about CEF are not currently understood. The majority of incidence rates of CEF reported in the literature are unreliable because of small sample sizes, lack of detail about the experimental techniques or study protocols, biased statistical estimators, or a combination of these factors. The incidence rates of CEF for some lens types, such as GP lenses, have not been estimated. It is not known how the probability of developing a CEF changes over time during lens wear, or how long wearers of certain types of contact lens can expect to remain free of CEF. Potential differences in the development of CEF between age groups, genders, and ethnicities have not been investigated. In this study, we propose to address these questions directly, using the statistical methodology of survival analysis.

Our goals in the present study are three-fold: (1) to use survival analysis methods to obtain unbiased estimates of the probability of developing CEF and the mean survival time free of CEF in contact lens wear; (2) to determine whether the probability of developing CEF or mean survival time differs between SiH and GP contact lenses; and (3) to determine whether development of CEF is related to the age, gender, or ethnicity of the contact lens wearer.

## METHODS
### Subjects

Subjects were recruited for a study of CW with SiH and GP contact lenses, conducted at the University of California, Berkeley, School of Optometry's Clinical Research Center. A total of 204 subjects completed the study, with 137 subjects wearing SiH lenses and 67 subjects wearing GP lenses. Initially, 133 subjects were randomly allocated to the GP (n = 67) and SiH (n = 66) lens groups. For the analysis, we also included data from 71 additional subjects recruited for a previous study of SiH CW. These additional subjects were required to meet identical entrance criteria, wore exactly the same type and brand of SiH lenses, followed the same study protocol, and were fit according to the same standard clinical procedures.

**TABLE 1.**

Demographic composition of the SiH and GP lens groups

| Demographic | N | % of subjects in silicone hydrogels | % of subjects in gas permeables | $\chi^2$ p-value |
|---|---|---|---|---|
| Age (yr) | | | | |
| ≤21 | 120 | 66 | 34 | |
| >21 | 84 | 69 | 31 | 0.630 |
| Gender | | | | |
| Female | 110 | 67 | 33 | |
| Male | 94 | 67 | 33 | 0.970 |
| Ethnicity | | | | |
| Asian | 108 | 67 | 33 | |
| Non-Asian | 96 | 68 | 32 | 0.874 |

It is important to note that the GP and SiH groups did not differ significantly in ocular parameters that could potentially affect lens performance (e.g., movement), and thus, the risk of CEF because of the addition of nonrandomized subjects to the SiH group. Corneal curvature in the vertical meridian did not differ significantly between the GP and SiH groups (p = 0.288), nor did curvature in the horizontal meridian (p = 0.117). Refractive sphere (p = 0.825) and cylinder (p = 0.640) also did not differ significantly.

All potential subjects were in good ocular health and had no history of contact lens wear for at least 12 months before the study. Subjects ranged in age from 18 to 38 years, with a mean age of 21.9 years. Approximately 54% of subjects were women and 46% were men, with 53% of subjects being of Asian ethnicity and 47% being non-Asian. The Asian group included subjects of Chinese, Japanese, Korean, and Vietnamese descent. The age, gender, and ethnic makeup of the two lens groups was similar (Table 1) and was typical for the study population of the university campus and surrounding community from which we recruited. All subjects were oriented as to the goals, risks, and benefits of the study and signed statements of informed consent. This study adhered to the tenets of the Declaration of Helsinki and was approved by institutional review board.

## Study Protocol

An initial screening served to determine whether potential subjects met the entrance criteria, which included being between the ages of 18 and 39 years, having no history of contact lens wear for at least 12 months before the study, having refractive error of at least −1.00 DS with <0.75 D of astigmatism and <2.00 D of anisometropia, being free of ocular disease or systemic disease with ocular manifestations, and not taking medications that could affect the tear film or ocular surface. All subjects were free of CEF on entrance to the study, before commencing contact lens wear. Subjects meeting the initial entrance criteria were then given comprehensive eye examinations by qualified optometrists, which included visual acuity, keratometry and refraction, tonometry, a dilated fundus examination, and assessment of the ocular surface using both white light and fluorescein under cobalt blue light with a yellow filter.

Subjects meeting all entrance criteria and who elected to participate in the study were then fit with either lotrafilcon A SiH contact lenses (Focus Night and Day, CIBA VISION, Duluth, GA), or tisilfocon A GP contact lenses (Menicon Z, Menicon, Nagoya, Japan). After contact lens dispensing and training, subjects were scheduled for progress checks after 1 week of DW, after 1 night of overnight wear, and after 1 week of CW. On successful completion of the adaptation period, subjects were instructed to wear their lenses on a CW basis for the next 30 days. Actual lens wearing times and number of follow-up visits differed substantially among subjects for several reasons. Most subjects had never worn contact lenses and required more than the minimum number of visits to successfully adapt to CW. In our largely student-based study population, scheduling problems because of coursework, examinations, and vacations were frequent. Some subjects experienced discomfort or redness that required an unscheduled visit for assessment. In some cases, lenses were lost and had to be dispensed again. In a few cases, subjects discontinued lens wear for a period of time until symptoms (n.b., unrelated to CEF) resolved. For subjects who lost lenses or otherwise temporarily discontinued lens wear, only the actual time in lens wear was included in the analysis.

## Statistical Methods

Many of the incidence rates for CEF found in the literature suffer from a significant bias because frequently not all subjects in a study contribute the same time at risk for development of CEF. Subjects who exit a study at various times before onset of CEF (e.g., they may elect not to continue, be disqualified for not adhering to study protocol, or be lost to follow-up) provide what are known as *censored* observations. In the present study, for example, some subjects developed CEF after a certain amount of wearing time, some subjects completed the study period without having developed CEF, and other subjects did not complete the study for reasons unrelated to CEF as noted previously. In addition, subjects required varying amounts of time to complete the DW and CW adaptation periods, so that not all subjects had exactly the same amount of wearing time, and thus not the same amount of time at risk for development of CEF. In such cases, the typical estimator of the incidence (i.e., number of subjects with an adverse event/total number of subjects) is biased, because it does not take censoring into account. The majority of incidences reported in the literature are calculated in this way. In addition to failing to account for censoring, these simple proportions are not true incidence *rates*, except in that the duration of the study is implicitly assumed—and rarely stated—to be the relevant time period over which the incidence rate is defined.

A class of statistical techniques known collectively as *survival analysis* provides the means for obtaining unbiased estimates of the incidence in the presence of censoring. We used the Kaplan-Meier nonparametric estimator of the survival function, which gives the probability of surviving at least to a specified time without development of CEF, and from which we estimated the mean survival times. With this method, we assume that survival and censoring times are independent, and that the survival probability is constant within each time interval in which CEF was observed. Cox proportional hazards models allowed us to estimate the effects on survival of the covariates age, gender, ethnicity (i.e., Asian vs. non-Asian) and contact lens type (i.e., SiH vs. GP). These models

provided estimates of the hazard function, which gives the instantaneous risk of developing CEF at a certain time point, given survival free of CEF up to that point. The Cox proportional hazards approach takes censoring into account, and assumes that the hazard rates at two levels of a covariate (e.g., female vs. male) are related by a multiplicative constant. Schoenfeld residual plots and $\chi^2$ tests were used to check proportionality assumptions. The standard assumption of survival analysis that censored and uncensored subjects did not differ in key variables was verified by $\chi^2$ test.

## RESULTS

Overall, 72 (35%) of the 204 subjects developed CEF, which is in agreement with other reports that did not take censoring into account. Using the Kaplan-Meier estimator of the survival function to account for actual person-time at risk, we find that the overall 30-day incidence rate is approximately 16.8%, and increases to approximately 40.3% at 60 days. Of the 72 subjects with CEF, 46 (64%) exhibited CEF bilaterally. Approximately 39% of subjects who developed CEF presented with the condition in more than one conjunctival quadrant. The majority of subjects with CEF (90.3%) developed the condition in the superior conjunctiva, and 37.5% developed CEF in the inferior conjunctiva. Nearly half of all cases in the SiH group (45.3%) presented with CEF in the inferior quadrant, in contrast to the relatively few inferior CEF cases (15.8%) occurring in the GP group. There were relatively few cases of CEF in the temporal region, and none in the nasal region

(Table 2). The few cases of CEF in the temporal quadrant were all arcuate, starting in the superior quadrant and extending temporally. Of 11 such cases of superiotemporal CEF, 10 occurred in SiH lens wearers.

Of the 72 CEF events, 53 (73.6%) occurred in the SiH lens group, compared with 19 (26.4%) in the GP lens group. This corresponds to 38.7% of the 137 SiH wearers developing CEF, compared with 28.4% of the 67 GP wearers. The mean number of days that GP subjects remained free of CEF was 94.3 days, somewhat longer than the mean of 76.5 days for SiH subjects (Table 3). The probability of developing CEF with SiH lenses was significantly greater than for GP lenses (p = 0.003), with the estimated relative risk of CEF being approximately 2.3-fold higher for SiH lenses (Table 4). Fig. 7 shows the Kaplan-Meier survival curves and approximate 95% confidence bounds for the two lens types. The probability of remaining free of CEF is only slightly greater for the GP lens wearers during the initial DW phase but diverges rapidly during the CW phase (Table 5).

The mean number of days in contact lens wear free of CEF for subjects older than 21 years of age was 85.4, compared with 82.2 days for those subjects younger than 21 years of age (Table 3). The Kaplan-Meier survival curves show that the probabilities of developing CEF over time in contact lens wear were similar for older and younger subjects. Multivariable Cox proportional hazards models show that, when taking into account the effects of lens type, gender, and ethnicity, age is not a significant factor in the development of CEF, whether considering age as a binary (p = 0.290) or continuous (p = 0.310) covariate.

The number of cases of CEF among women (30.9%) was somewhat less than among men (40.4%). Women remained free of CEF for 91.1 days of lens wear on average, compared with 73.9 days for men (Table 3). This difference was not significant, and Cox proportional hazards models show that after taking lens type and the other covariates into account, the probability of developing CEF was not significantly greater for men (p = 0.130). In addition, the Kaplan-Meier survival curves for CEF onset over time in contact lens wear are very similar for women and men.

Although Asian subjects remained free of CEF on average for a significantly shorter time than did non-Asian subjects (Table 3),

**TABLE 2.**
Cases of CEF observed in the four conjunctival quadrants

| Conjunctival quadrant | No. subjects w/CEF in this quadrant | | % of CEF cases w/CEF in this quadrant | |
|---|---|---|---|---|
| | GP | SiH | GP | SiH |
| Superior | 17 | 48 | 89.5 | 90.6 |
| Inferior | 3 | 24 | 15.8 | 45.3 |
| Temporal | 1 | 10 | 5.3 | 18.9 |
| Nasal | 0 | 0 | 0 | 0 |

**TABLE 3.**
Mean wearing time free of CEF derived from Kaplan-Meier estimates of the survival function

| Covariate | N | No. subjects w/CEF | Mean wearing time free of CEF (d) | 95% confidence interval |
|---|---|---|---|---|
| Lens type | | | | |
| Silicone hydrogel | 137 | 53 | 76.5 | 61.1–91.9 |
| Gas permeable | 67 | 19 | 94.3 | 80.5–108.1 |
| Age (yr) | | | | |
| ≤21 | 120 | 39 | 82.2 | 69.9–94.5 |
| >21 | 84 | 33 | 85.4 | 68.0–102.8 |
| Gender | | | | |
| Female | 110 | 34 | 91.1 | 72.5–109.7 |
| Male | 94 | 38 | 73.9 | 60.5–87.3 |
| Ethnicity | | | | |
| Asian | 108 | 39 | 65.4 | 58.6–72.2 |
| Non-Asian | 96 | 33 | 94.4 | 77.2–111.6 |

**TABLE 4.**

Hazard ratios for CEF derived from Cox proportional hazards models

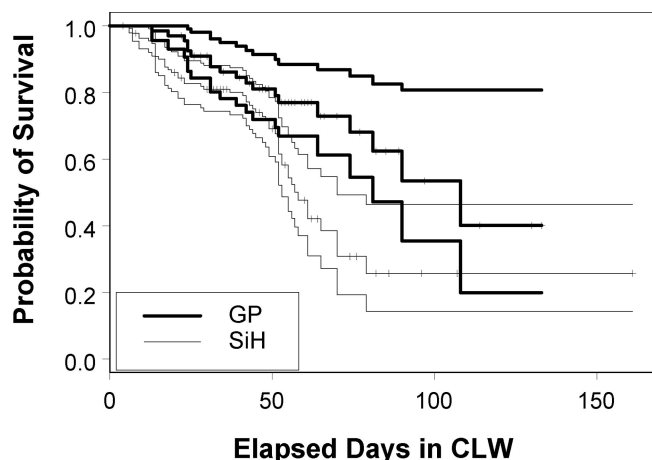| Covariate | Hazard ratio | Wald test p-value |
|---|---|---|
| SiH vs. GP | 2.267 | 0.003 |
| >21 yr vs. ≤21 yr | 1.144 | 0.580 |
| Male vs. female | 1.441 | 0.130 |
| Asian vs. Non-Asian | 1.152 | 0.570 |



**FIGURE 7.**

Kaplan-Meier survival curves show that the probability of developing a conjunctival epithelial flap is greater for silicone hydrogel lens wearers, particularly in continuous wear.

**TABLE 5.**

Estimated incidence rates for SiH and GP lenses over time in CW

| Weeks in lens wear | Incidence (%) of CEF w/gas permeable lenses | Incidence (%) of CEF w/silicone hydrogel lenses |
|---|---|---|
| 1 | 0 | 2.2 |
| 3 | 3.0 | 15.6 |
| 5 | 13.8 | 19.0 |
| 7 | 18.9 | 30.9 |
| 9 | 23.1 | 57.9 |

this difference may not be clinically relevant because of a bias due to censoring. The mean days free of CEF for Asians was 65.4 days, compared with 94.4 days for non-Asians; however, this difference was driven primarily by a small group of non-Asian subjects, free of CEF, who had much longer periods of contact lens wear than did any of the Asian subjects. Indeed, the Kaplan-Meier survival curves for the two ethnic groups are virtually coincident up to approximately 90 days of wear. Cox proportional hazards models show that after taking lens type and the other covariates into account, the probability of developing CEF is not significantly greater for Asian subjects (p = 0.570).

For the final multivariable Cox proportional hazards model containing all the covariates, we examined plots of Schoenfeld residuals over time for each covariate and χ² tests of their slopes.[13] The assumption of proportional hazards was supported by the relatively flat residual plots, and the lack of significant χ² statistics for lens type (p = 0.970), age (p = 0.290), gender (p = 0.076), and ethnicity (p = 0.465). In addition, it was verified that censored and uncensored subjects were not significantly different in allocation to lens type (p = 0.147) nor did they differ in age (p = 0.318), gender (p = 0.156), or ethnicity (p = 0.796).

## DISCUSSION

We observed a 38.7% overall rate of occurrence of CEF in 30-day CW among the SiH lens wearers, without taking censoring of observations into account, which agrees with previous reports.[1–5] The size of the flaps we observed, the distance from the lens edge near the margin of lens travel, and the predominance of CEF in the superior and, to some extent, the inferior conjunctiva are all consistent with the hypothesis that contact lens edge design plays a role in the formation of CEF and are consistent with previous reports. We also observed some cases of CEF in the temporal quadrant, which were arcuate and extended from the superior to the temporal conjunctiva. Of 11 such cases of superiotemporal CEF, 10 occurred in the SiH lens group. That we observed more than half of CEF cases occurring bilaterally is also in agreement with previous studies.

This study is the first to report on CEF in GP contact lens CW and the first to compare SiH and GP contact lenses directly in terms of CEF development. We found a higher rate of occurrence of CEF, and that CEF onsets sooner with SiH CW. Taking censoring of observations into account, we found that the probability of developing CEF is significantly greater over time in contact lens CW with SiH lenses, being especially greater after a week or more of CW. There are several factors that are likely to contribute to the reduced incidence of CEF with GP lenses compared with SiH lenses. Although GP lenses exhibit greater movement than soft lenses, GP lenses are of smaller diameter and rarely travel beyond the limbus except in the superior quadrant for a lid attachment fit, and thus have less impact on the conjunctival surface cells than do soft lenses. The three cases of CEF in GP wearers that were found in the inferior quadrants were reviewed and it was found that in these subjects the lens had decentered inferiorly. Similarly, temporal lens decentration was found in the one case of temporal CEF in a GP subject. We hypothesize that CEF in GP wearers is induced by deep indentation of the lens edge into the bulbar conjunctiva, leaving a loose flap of tissue hanging over a concavity excavated by the edge of the high modulus GP lens. In contrast, the more flexible SiH lenses tend to be fit with a better alignment of the lens edge along the ocular surface, and we hypothesize that in this case, CEF is caused by shearing of the surface layers of cells with lens movement and blinking. SiH lenses have a larger diameter and less movement, and particularly with a nonrounded edge design may impact the conjunctival surface to a greater degree. This is made more likely by the thinner cushioning postlens tear film behind the lens.[14–16] Many of these factors are also present in conventional hydrogel lenses; however, the higher modulus of the silicone-based lenses may exacerbate the impact of the interaction among contact lens, lids, and ocular surface during CW.

This study is also the first to examine whether age, gender, or ethnicity might be risk factors for CEF. We found very little difference in either the probability of CEF or mean time to onset in

younger as opposed to older subjects, whether in a stratified or continuous analysis, whether lens type is taken into account or not. However, it should be noted that the age distributions in our two study groups are representative of the study population from which we recruited and not necessarily of the contact lens-wearing population in general. We did not recruit subjects older than 39 years of age, and the pool of potential subjects from the university campus and surrounding community resulted in a preponderance of subjects younger than 25 years of age. Although we found no evidence that age is a factor in either the probability or timing of CEF onset, further study is needed to determine whether this result is generalizable across the age range of the contact lens wearing population at large.

There is some evidence that male contact lens wearers develop CEF sooner, on average, than women, and the survival curve is consistently lower for men throughout the lens wear period. However, the difference in probability of CEF between women and men is relatively small and not statistically significant.

We also found that Asians developed CEF sooner, on average, than non-Asians, although this may be more an artifact of our dataset than a real population difference, especially because the survival curves of Asians and non-Asians are virtually coincident throughout 90 days of lens wear.

Although from a patient perspective CEF is not generally associated with symptoms and resolves with cessation of lens wear, there is cause for concern among clinicians that a marked disruption of the conjunctival surface—particularly with contact lens CW for extended periods of time— could significantly increase the risk of inflammation or infection or have other long-term effects not yet documented. The relatively small CEF observed after 7 days of CW does not stain with rose bengal and typically resolves within 24 to 72 h after cessation of lens wear; however, after 30 days of CW the CEF is much larger, takes much longer to resolve— up to several weeks[5]—and does stain with rose bengal. This suggests that the mechanical interaction among the lens, lid, and ocular surface progressively disrupts the conjunctival tissue, possibly resulting in an eventual sloughing of these cells. Cellular debris and biochemical components trapped under a lens could cause an inflammatory reaction[17–20] or a decrease in epithelial barrier function,[17,21] especially in the case of SiH lenses, which are known to have relatively poor tear exchange compared to GP lenses.[22,23] The presence of vital dye staining of the CEF after long periods of CW could indicate insufficient mucin protection. Because mucin-producing goblet cells are found to be present in the CEF, and goblet cell density has been shown to decrease with prolonged contact lens wear,[24] there is concern that the normal balance of tear film components could be locally disrupted, eventually leading to tear film instability and associated dry eye symptoms.[25,26] In larger CEF, fluorescein is seen to pool at the margin of the flap. It is possible that environmental contaminants and microorganisms could become trapped and accumulate within the loose folds of delaminated conjunctival tissue, thereby increasing the risk of serious infection.[20] It is, therefore, necessary for clinicians to understand how CEF develops, what factors impact the onset and resolution of CEF, and what the potential long-term effects of disrupting the conjunctival tissue may be.

This study shows that CEF formation occurs with both SiH and GP lenses, although the incidence rates and exact mechanisms differ. The etiology of CEF must be explained in terms of the interactions among the conjunctiva, lids, and contact lens, with consideration of the available base curves, lens modulus, edge design, fitting characteristics, and on-eye performance given patient ocular surface curvatures.[27,28] Research in this direction is ongoing, and further study is needed to determine the long-term effects of CEF, so that clinicians will have the information they need to assess the risks and benefits associated with prescribing contact lenses for CW.

## ACKNOWLEDGMENTS

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