



Original Research Article

Comparison of dry eyes tests among Smokers and Non-smokers: Does smoking predispose to dry eye?

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ABSTRACT

Introduction: Smoking tobacco is a risk factor for ocular disorders including dry eyes. This study correlates dry eye tests among smokers and non-smokers, type of smoking and smoking load.

Materials and Methods: Dry eye tests were conducted on 80 smokers and 80 age matched non-smokers after ethical approval and written informed consent.

Results: Smoker and non-smoker groups were comparable (Mean age: 48.98 and 49.03 years). All were males. Majority of smokers belonged to the lower socioeconomic status and had outdoor professions. Abnormalities in dry eye scores (DEQ-5), corneal sensitivity, Schirmer's 1 and 2, Tear film break up time (TBUT) and corneal staining were significantly more among smokers ($p < 0.05$). The mean values of dry eye score (9.75; 3.42), Schirmer's 1 (18.95; 21.51mm), Schirmer's 2 (19.16; 21.38 mm) and TBUT (8.47; 12.26) were significantly more affected in smokers ($p < 0.05$). Abnormalities in tear meniscus height, corneal sensation, Schirmer's 1 and 2, and TBUT were significantly more in higher pack years ($> 40,000$) than in lower (20,000 to 40,000) ($p < 0.05$). Dry eye score and corneal staining did not correlate with smoke load. Abnormalities in tear meniscus height, corneal sensation, Schirmer's 2 and TBUT were significantly more among cigarette smokers (< 0.05). Regression analysis showed a significantly increased propensity for abnormal test results with higher smoking load (Pack-years $> 40,000$; $R^2 = 0.529$). Severe corneal staining showed goblet cell loss and squamous metaplasia, however this sample size was too small for statistical inference.

Conclusion: Dry eye test abnormalities correlate significantly with smoking, higher smoking load and type of smoking.

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1. Introduction

Tobacco smoking remains a common recreation in India despite legal bans in public places, and anti-tobacco programs. India has about 108 million tobacco smokers (2015)¹ with a fast increase in the trend among females.² Smoking is a risk factor for lung cancer, cardiovascular morbidity and does not spare the eyes. Smoking is a risk factor for dry eye and is known to smoking affects tear secretion, osmolarity and stability, lipid layer dysfunction and causes ocular irritation.³⁻⁸ However, a systematic review between 2000 to 2016 reported a

debatable association.⁹

We designed this study to compare dry eye tests among smokers and age and sex -matched controls; and to compare the dry eye tests with smoking load and the type of smoking: cigarette and bidi.

2. Materials and Methods

The authors carried out a cross-sectional observational case-control study between December 2015 and August 2017 in a medical college hospital in South India. The study was conducted respecting the principles of the Declaration of Helsinki (2013) and the ICMR's National Ethical Guidelines for Biomedical and Health Research involving Human Participants (2017). We recruited participants

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only after the ethical approval from the institutional ethics committee. Every participant signed a written informed consent form in the local language, before enrolment in the study. Privacy of participants and confidentiality of data was and continues to be maintained. After the study, participants were counselled about the ill effects of smoking with a message that it was never too late to quit smoking, irrespective of whether they had dry eyes or not.

Participants were recruited by purposive, convenience sampling from clients visiting the out-patient departments and were divided into two groups depending on whether they smoked or not. The study group consisted of 80 male smokers aged 20-65 years with at least 20,000 pack-years or more of smoking. The control group consisted of 80 age and gender-matched non-smokers. We excluded "light" smokers with less than 20,000 pack-year load, on the presumption that even passively exposed persons reporting as "non-smokers" would be counted as "light" smokers. Participants with diabetes, atopic dermatitis, connective tissue disorders, eyelid abnormalities, conjunctival and corneal degenerations or dystrophies were excluded. Additionally, we excluded people with contact lens, use of topical ophthalmic medications in the past one year and those with past ocular surgeries.

Anonymized details of type and amount of smoking and socioeconomic status were noted. We performed detailed dry eye evaluation on the right eye of every participant using standard assessment methods. These included the Dry Eye Questionnaire-5 (DEQ-5) score for dry eye symptoms, tear meniscus height (millimeters), Schirmer's 1 & 2 test (millimeters), corneal sensitivity test (subjective grading), tear film break-up time (TBUT) (seconds), corneal staining, and conjunctival impression cytology.¹⁰ We measured the tear meniscus height using a slit-lamp beam. Schirmer's I test was performed in a dimly lit room non-AC with the fan switched off using a standard sterile Schirmer's strip (Graduated Tear Strips, Contacare Ophthalmics and Diagnostics, Vadodara, India) and the amount of wetting was measured after 5 minutes. We assessed corneal sensitivity by observing the fastness of the blink when a sterile wisp of cotton was brought into contact with the centre of the cornea from the temporal side. Tear film break-up time (TBUT) was measured as the time between the last blink and the appearance of the first random dark spot in the tear film stained with a drop of fluorescein instilled into the eye using a sterile fluorescein strip (Fluostrip, 1 mg fluorescein sodium, IP) and observed in slit lamp using cobalt blue filter in diffuse illumination. We instilled a drop of fluorescein into the eye as described for TBUT and then graded the corneal staining in terms of area (A 1 to 3) and density (D 1 to 3) of staining. The severity of corneal staining was described as the product of the two scores.¹¹ Schirmer's 2 test was done similar to Schirmer's 1 test after instilling a single drop of sterile Proparacaine HCl,

0.5% (measured in millimetres). Conjunctival impression cytology (CIC) was performed in those with corneal staining score of A1D2 or more under topical anaesthesia with single drop of sterile Proparacaine HCl, 0.5% using two filter strips of 13 x 6.5 mm in size, applied onto the superotemporal bulbar conjunctiva without exerting pressure. The strips were fixed in 96% ethanol, specimens were stained with PAS, H&E. We assessed goblet cell density & squamous metaplasia by Nelson's grading.

The following results were considered abnormal: DEQ-5 score ≥ 6 , tear meniscus height < 1 mm, TBUT < 10 seconds, corneal sensation -1 or -2 (late or no blinking), Schirmer's 1 & 2 < 10 mm/5min and any positive fluorescein staining. CIC was studied qualitatively. Assuming the data to be normally distributed, descriptive statistics and Chi-square test were performed for the data emanating from tear meniscus height, TBUT, corneal sensation and Schirmer's 1 and 2. The data was subjected to regression analysis to assess the association of the dependent variable (smoking load) with the independent variable (dry eye test results). Statistical analysis was done using SSPS software (version 22) A *p-value* < 0.05 was considered significant.

3. Results

3.1. Demographic characteristics

Only male participants were included in the study; the authors found it difficult to recruit females reporting smoking habit in this geographical region. Most participants belonged to the fourth and fifth decades of life; the mean age in the two groups was statistically comparable (Smokers: 48.98 ± 8.47 years and Non-smokers: 49.03 ± 8.38 years; $t=0.038$, $p=0.970$). The socioeconomic distribution of smokers and non-smokers showed statistically significant difference ($t=2.867$, $p=0.005$) with maximum (50%) smokers belonging to the lower socioeconomic groups and majority (67.5%) non-smokers belonging to the middle socioeconomic groups as per Modified Kuppuswamy's socio-economic status 2016. Majority of the smokers (91.48%) and non-smokers (75.75%) were outdoor workers.

3.2. Smoking characteristics

Nearly two-thirds smoked bidis and one-third, cigarettes. The mean age of the bidi and cigarette smokers was 52.7 years and 41.7 years and the age distribution of the bidi and cigarette smokers showed statistically significant difference ($t=-4.750$; $p=0.000$) with bidi smokers belonging to the older age groups. The mean years of smoking was 34.85 years ± 19.87 and did not statistically differ among bidi and cigarette smokers ($p > 0.05$).

3.3. Dry eye tests

The most common test found to be abnormal was DEQ-5 score (48.75%) followed by TBUT, Schirmer's 2 and 1, tear film height, corneal staining and corneal sensation in that order among both smokers and non-smokers (Table 1).

Abnormal dry eye test frequencies in smokers and non-smokers (Table 1): Abnormal DEQ -5 scores, reduced corneal sensation, abnormal TBUT, Schirmer's tests and abnormal corneal staining; were more common among smokers than non-smokers and the difference was statistically significant. Tear meniscus height was not significantly different between smokers and non-smokers.

Mean dry eye test values among smokers and non-smokers: (Table 2): The smoker's group was found to have statistically significant higher abnormal mean values of the following dry eye tests when compared to the non-smoker's: DEQ-5 score, Schirmer's 1 and 2, TBUT and tear meniscus height. Multiple regression analysis ($R = 0.872$; $R^2 = 0.760$; $p = 0.000$) and ANOVA test ($p = 0.000$) of these dry eye test variables among smokers and non-smokers revealed statistical significance.

Smoking load and dry eye (Table 3 Figure 1): Although the frequency of occurrence of most abnormal dry eye test results (TBUT, Schirmer's tests, corneal sensation and tear meniscus height) was found to increase with increase in the smoke load, the average mean values of these tests did not reveal a statistically significant difference with increasing smoke load. Only DEQ-5 score and corneal staining appeared to demonstrate a statistically significant increase with increase in smoke load. Linear regression analysis (Figure 1) revealed a significant correlation between the occurrence of abnormal dry eye tests and smoking load ($R^2 = 0.529$).

Type of smoking and dry eye (Table 4): Cigarette smokers were found to have abnormal dry eye tests more frequently than bidi smokers and the difference was statistically significant for TBUT, Schirmer's 2 test, corneal sensation and tear meniscus height, but were not statistically significant for DEQ-5 score, Schirmer's 1 test and corneal staining.

Conjunctival impression cytology: Cytology was performed in 5 of the 9 eyes with grades $> A1D2$ corneal staining and these showed loss of goblet cells and higher Nelson's grades of squamous metaplasia (3 had grade 2 squamous metaplasia and 2 had grade 1 metaplasia), but these results could not be statistically tested due to small numbers.

4. Discussion

This is a hospital based case-control study comparing dry eye tests among 80 smokers and 80 age and gender- matched non-smokers.

4.1. General characteristics

The authors found it difficult to enrol female smokers, although studies reveal that there is an increase in the prevalence of smoking among females.² Females may be under-reporting smoking possibly due to the perceived social stigma associated with smoking as a habit. Majority of the smokers belonged to the 5th and 6th decades of life and this finding was similar to a systematic study on smoking trend in India.¹ Majority of the smokers belonged to lower socio-economic status and studies show that socio-economic status is known to have a varying influence on smoking trends in India.¹² Also, the majority smoked bidis probably reflecting the cost factor. Most had outdoor professions.

4.2. Dry eye symptoms

In our study, the mean DEQ-5 score was significantly higher among smokers than non-smokers. This is similar to the study by Altinors (Table 5) indicating that smoking may be a risk factor for dry eye symptoms. Since abnormal DEQ-5 scoring is not specific to smoking related dry eye, the symptoms may also be attributable to other associations of dry eye like out-door occupations, AC environments, age or systemic conditions.

4.3. Dry eye tests

Tear film Break Up Time (TBUT): The abnormal TBUT value was more common and the mean TBUT value was lower among smokers than non-smokers and this difference was statistically significant indicating that smokers have a higher risk of abnormal TBUT. This finding is comparable with other studies (Table 5). Our study showed that TBUT shortened significantly with increased smoking load as is also observed by Yoon indicating a clear association.¹³ Studies indicate that tobacco smoke damages the lipid layer of the tear film and causes evaporation of the tear film leading to early tear film break up.^{6,14-17} However, the present study has not studied Meibomian gland function among the study groups. Further, TBUT was found to be abnormal in all those with positive corneal staining possibly indicating that TBUT may be a precursor of corneal epithelial defect in smokers. However, it will require a longitudinal study to establish this hypothesis. On the contrary, the study by Thomas et.al did not find a change in TBUT with the amount of smoking; which may be the result of other confounding factors like occupational exposure and indoor air pollution.¹⁵

Schirmer's tests: Abnormal Schirmer's tests 1 and 2 were more common and the mean Schirmer's test 1 and 2 values were significantly lower among smokers when compared to non-smokers. These findings were similar to other studies as shown in the Table 5 indicating that smoking is a risk factor for decreased reflex tear production.^{14,15}

Reduction in the Schirmer's 2 test value indicates reduction in the basal secretion of the aqueous component of the tears by the accessory lacrimal glands. Studies suggest that smoking can damage the ocular surface as evidenced by decreased goblet cell density and squamous metaplasia.^{4,14} Further, 62.5% of smokers with abnormal Schirmer's 1 value, had reduced corneal sensation indicating an association as also supported by other studies.¹⁴

Altinors and Matsumoto did not find a significant difference in Schirmer's 1 test among smokers and non-smokers; and Thomas et al did not find significant change in Schirmer's 2 test among smokers and non-smokers or with smoking load.^{6,15,16} Differences in the observation may be due to discrepancies in the smoking load and environmental confounding factors.

Tear meniscus height: Abnormal tear meniscus height was not found to be significantly different among smokers and non-smokers in our study. However, we found that tear meniscus height was negatively correlated to the amount of smoking. This indicates that tear meniscus height is affected in higher smoke loads and might indicate chronic effects of smoking.

Corneal sensation and staining: We found that reduced corneal sensation significantly more common among smokers than non-smokers and is comparable with other studies (Table 5). It was observed that decrease in corneal sensation increased with increasing smoke load. Studies state that reduced corneal sensation causes damage the ocular surface by reducing basal tear secretion and goblet cell secretion.¹⁸ We also observed that corneal staining which is indicative of corneal epithelial damage, was significantly more among smokers than non-smokers. There is evidence that smoking causes toxic damage to the conjunctival goblet cells or increases the tear film osmolarity leading to corneal epithelial damage.^{3,4} However, Yoon did not find significant difference in corneal staining among smokers and non-smokers which the author attributes to the increased reflex tear secretion among smokers in their study.¹⁴ Contrary to Yoon's study, we found reflex tear secretion (estimated by Schirmer's 1 test) to be significantly decreased among smokers. Whether smoking affects the corneal epithelium and tear secretion independent of each other or as a collective inter-dependent system needs further studies. Yoon's explanation that smokers demonstrate an increased reflex tear formation and this protects the corneal epithelium from damage, also needs further enquiry¹⁴.

Regression analysis in the present study showed significant linear correlation between the occurrence of abnormal dry eye tests and smoking load, indicating that these parameters are 52.9% more likely to be abnormal in those smoking more than 40,000 pack years when compared those smoking less than 40,000 pack years. This indicates that with increasing smoke load, there is an increasing

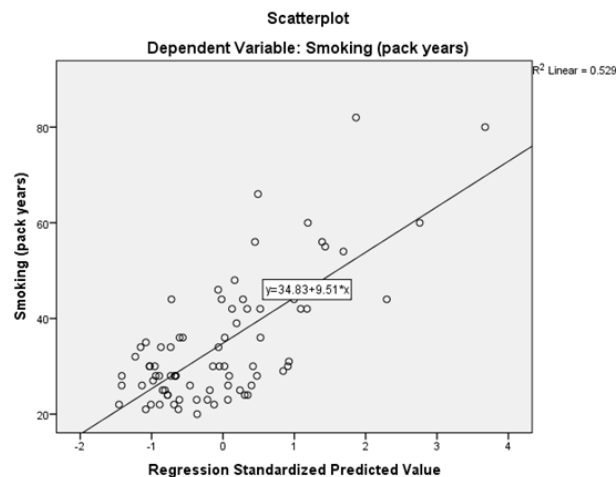


Fig. 1: Regression analysis of various dry eye indicators with the amount of smoking

risk of dry eye manifestations, although it is also known that smoke load does not correlate linearly with the toxin exposure.¹⁹ Of the nine smokers who had positive corneal staining, six were younger than 40 years of whom 3 were heavy smokers (>60, 000 pack years) indicating that age and smoking load may collectively influence the severity of dry eyes, rather than individually. Seven out of the nine subjects who had corneal staining had a smoking load of more than 40,000 pack years and eyes with corneal staining showed loss of goblet cells and squamous metaplasia, similar to other studies.^{4,14} However, in a study by Yoon, there was no association between staining and increasing amount of smoking and could point out to other confounding environmental factors.¹⁴

4.4. Dry eye tests and type of smoking

The abnormal dry eye tests (reduced TBUT, Schirmer's 2 test, tear meniscus height & corneal sensations) appeared to be significantly more common among cigarette than bidi smokers. However, Malson J et al. found higher nicotine concentration in bidis than cigarettes and postulated that ocular surface damage may be caused by other toxins as cigarette smoke is known to have numerous toxins other than nicotine.²⁰ In our study, the number of bidi smokers and cigarette smokers are unequal and not age-matched. Also, serum or tear nicotine levels have not been tested. Other factors may be responsible for these differences.

Limitations of the study: This study did not include female participants and therefore the results of the study are not generalizable to the population. The methodology comprised only clinical evaluation and the abnormal tests were not correlated with biochemical assays of tear film and levels of smoke induced toxins in the blood or tear film. Conjunctival impression cytology was reserved only

Table 1: Comparison of frequencies of abnormal dry eye tests among smokers and non-smokers

	Smokers (n=80)	Non-smokers (n=80)	Total (n=160)	Chi square test
	No. (%)	No. (%)	No. (%)	<i>p value</i>
Dry Eye Questionnaire-5 score (>6)	68 (85)	10 (12.5)	78(48.75)	<0.05
Tear Meniscus Height (<1.0)	15(18.75)	0	15(9.37)	0.092
Corneal sensation (-1 &-2)	10(12.5)	0	1(0.62)	<0.05
Schirmer's 1 (<10mm/5m)	16(20)	5(6.25)	21(13.12)	<0.05
Schirmer's 2 (<10mm/5m)	19(23.75)	8(10)	27(16.87)	<0.05
Tear-film Break Up Time (<10 sec)	42(52.5)	10(12.5)	52(32.5)	<0.05
Positive corneal staining	9(11.25)	0	9(5.62)	<0.05

Table 2: Comparison of mean dry eye test values among smokers and non-smokers

	Smokers (n=80)	Non-smokers (n=80)	P value
Mean Dry Eye Questionnaire-5 score	9.75 ± 4.47	3.42 ± 4.23	<0.05
Mean Schirmer's 1 (mm/5m)	18.95 ± 6.41	21.51 ± 6.13	<0.05
Mean Schirmer's 2 (mm/5m)	19.16 ± 6.31	21.38 ± 7.23	<0.05
Mean Tear-film Break Up Time (Seconds)	8.47 ± 2.66	12.26 ± 2.61	<0.05

Table 3: Comparison of frequencies of abnormal dry eye tests with the smoking load

	Pack years (20,000 to 40,000) (n= 56)	Pack years (>40,000)(n=24)	Total (n=80)	Chi square
	No. (%)	No. (%)	No. (%)	<i>P value</i>
Dry Eye Questionnaire-5 score (>6)	44(78.57)	24(100)	68(85)	>0.05
Tear Meniscus Height (<1.0)	5(8.92)	10(41.66)	15(18.75)	<0.05
Corneal sensation (-1 &-2)	3(5.3)	7(29.16)	10(12.5)	<0.05
Schirmer's 1 (<10mm/5m)	4(7.14)	12(50)	16(20)	<0.05
Schirmer's 2 (<10mm/5m)	6(10.71)	13(54.16)	19(23.75)	<0.05
Tear-film Break Up Time (<10 sec)	24(42.85)	18(75)	42(52.5)	<0.05
Positive Corneal staining	3(5.35)	6(25)	9(11.25)	>0.05

Table 4: Comparison of frequencies of abnormal dry eye tests among bidi and cigarette smokers

	Bidi Smokers (n=52)	Cigarette smokers (n=28)	Total (n=80)	P value
	No. (%)	No. (%)	No. (%)	
Dry Eye Questionnaire-5 score (>6)	41(78.84)	27(96.4)	68(85)	>0.05
Tear Meniscus Height (<1 mm)	3(5.76)	12(42.85)	15(18.75)	<0.05
Corneal sensation (Grade-1 & -2)	2(3.48)	8(28.57)	10(12.5)	<0.05
Schirmer's 1 (<10mm/5m)	7(13.46)	9(32.14)	16(20)	>0.05
Schirmer's 2 (<10mm/5m)	6(11.5)	13(46.4)	19(23.75)	<0.05
Tear-film Break Up Time (<10 sec)	17(32.7)	25(89.28)	42(52.5)	<0.05
Positive corneal staining	5(9.6)	4(14.28)	9(11.25)	>0.05

for cases with moderate to severe degrees of corneal staining and therefore could not be statistically conclusive of its association with smoking. The cross-sectional nature of the study design could not establish the chronology of the occurrence of abnormal dry eye tests with increase in smoke load. Also, the effect of other confounding factors cannot be ruled out: like age, outdoor professions, and some of the conditions like Meibomian gland dysfunction cannot be ruled out only with clinical examination.

Further studies are necessary to understand whether younger ocular surface is more prone to damage when compared to older ocular surface and also whether the rapidity of achievement of high smoke load is crucial in the causation of severity of ocular surface disorders.

Table 5: p values comparison of dry eye tests in smokers and non-smokers across other studies

	Present study	Altinors (2006) ⁶	Yoon (2005) ¹⁴	Thomas (2012) ¹⁵	Matsumoto (2008) ¹⁶
Abnormal Dry Eye Questionnaire-5 score	<0.05	<0.05	0.973	-	-
Reduced Tear-film Break Up Time	<0.05	-	<0.01	0.0001	-
Lipid layer abnormality	-	<0.05	-	-	<0.0001
Abnormal corneal sensation	<0.05	<0.05	0.042	0.0001	-
Abnormal corneal staining	<0.05	<0.05	0.758	<0.0001	<0.0001
Reduced tear meniscus height	<0.05	-	-	-	-
Abnormal Schirmer's 1 test	<0.05	>0.05	<0.01	-	>0.05
Abnormal Schirmer's 2 test	<0.05	-	-	0.22	-

5. Conclusion

In this age and gender-matched case-control study, dry eye tests were found to be significantly affected among smokers when compared to non-smokers. The most common abnormal test was a high DEQ-5 score, followed by TBUT, Schirmer's 2, Schirmer's 1, tear meniscus height, corneal sensation and corneal staining. The mean values of DEQ-5 scores, TBUT, Schirmer's 1 and 2 were significantly more affected in smokers when compared to non-smokers. Increased smoking load and cigarette smoking increased the risk of abnormal dry eye tests. Smoking is therefore an important risk factor for abnormal dry eyes.

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7. Conflict of Interest

None.

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