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Research Article

ASSOCIATION BETWEEN SMOKING AND VARIOUS VOCAL CORD PATHOLOGIES: A CASE CONTROL STUDY

Nirupama V[1]*, Pradeep Gundu[2], Dwarakamai K[3]

[1]Associate Professor, Otorhinolaryngology, Kamineni Institute of Medical Sciences, Narketpally, Telangana, India.
[2]Associate Professor, Otorhinolaryngology, Kamineni Academy of Medical Sciences and Research Centre, Hyderabad, Telangana, India.
[3]Assistant Professor, Otorhinolaryngology, Kamineni Academy of Medical Sciences and Research Centre, Hyderabad, Telangana, India.

Corresponding Author*: Dr. Nirupama V, Associate Professor, Otorhinolaryngology, Kamineni Institute of Medical Sciences, Narketpally, Telangana, India.

Email ID: nirupamareddy.v@gmail.com

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ABSTRACT

Background: Smoking is an established cause of laryngeal cancer, but its link with the wider range of benign and premalignant vocal cord pathologies is less clearly defined in rural India.

Methods: An age and gender matched case control study was conducted at a rural tertiary care hospital in Telangana from June 2024 to May 2025. It included 100 patients with laryngoscopically confirmed vocal cord pathology, each matched 1:1 to a control with normal vocal cords. Smoking status and pack-years were recorded on a structured pro forma. McNemar tests, matched odds ratios with 95% confidence intervals and paired t tests were used.

Results: Cases and controls were comparable in residence and occupation. Ever smoking was present in 64% of cases and 34% of controls, matched odds ratio 3.50, 95% CI 1.84 to 6.65, $p<0.001$. Current smoking had higher odds, 5.67, $p<0.001$, and, compared with never smokers, the odds rose with pack-years, reaching 20.00 at 20 or more, $p<0.001$. Smoking was strongly associated with Reinke's edema, 12.00, $p=0.003$, and premalignant and malignant lesions, 7.50, $p=0.002$, but not with polyps, 2.75, $p=0.12$, or nodules, 0.80, $p=1.00$. Reflux was also associated in unadjusted analysis, $p=0.006$, while the associations with alcohol use, $p=0.042$, and dust exposure, $p=0.040$, were borderline.

Conclusion: Smoking is strongly and dose dependently associated with vocal cord pathologies, especially Reinke's edema and premalignant and malignant lesions.

KEYWORDS: Smoking, Vocal Cord, Reinke's Edema, Hoarseness, Matched Case Control Study.

Introduction

Hoarseness is among the commonest reasons for referral to an otolaryngologist and reflects structural or functional change in the vocal folds. Its causes range from self limiting laryngitis and phonotraumatic lesions such as polyps and nodules to Reinke's edema, keratosis and laryngeal carcinoma, so laryngoscopy is advised when dysphonia persists beyond four weeks[1,2]. Distinguishing these pathologies matters because their management and prognosis differ sharply.

Tobacco remains a leading driver of this burden. The Global Burden of Disease Study 2019 attributed 7.69 million deaths and 200 million disability adjusted life years to smoking worldwide. It was the leading risk factor for death among males, accounting for 20.2% of male deaths[3]. Population based laryngoscopic data from Korea place the prevalence of benign vocal fold lesions between 7% and 12%, with smoking history more frequent among affected persons[4]. In India, a tertiary series of 1033 patients with dysphonia found 70% were male, mean delay to presentation was 24

months, malignancy was present in 18% and tobacco use in 35.24%[5]. Laryngeal cancer contributes roughly 3% to 6% of all cancers in Indian men, with five year survival near 28%[6]. In a rural hospital in Karnataka, smoking was the commonest habit, present in 54.29% of patients with hoarseness[7].

Cigarette smoke harms the vocal folds through chemical and thermal irritation, smoker's cough and increased keratinisation of the delicate epithelium[5]. Carcinogens such as polycyclic aromatic hydrocarbons bind directly to DNA and drive malignant change[7].

Most Indian reports are descriptive hospital series that count smokers among patients without a comparison group[5,7]. Controlled data comparing individual pathologies with unaffected controls are scarce. Age and sex strongly influence both smoking and vocal pathology, so a matched design is well suited to this question.

Present study conducted an age and gender matched case control study to estimate the association between smoking and vocal cord pathologies, to examine dose response, and to compare the association across individual pathologies.

Materials and Methods

Study Design

Hospital based, individually matched case control study, with one control per case matched on gender and age within 5 years.

Study Place and Period

Department of Otorhinolaryngology of a rural tertiary care hospital in Telangana, from June 2024 to May 2025. Institutional Ethics Committee approval and written informed consent were obtained.

Sample Size

For 1:1 matched pairs, the number of discordant pairs required was

$$m = [\ Z\alpha/2 / 2 + Z\beta \times \sqrt{[\ P \times [\ 1 - P\ ]\ ]}\ ]^2 / [\ P - 0.5\ ]^2,$$ where $P = OR / [\ 1 + OR\ ]$

and the total number of pairs was

$$N = m / [\ p0 \times q1 + p1 \times q0\ ]$$

Assuming p0 = 0.25, the expected proportion of smokers among male predominant ENT outpatient controls [8] , a minimum detectable odds ratio of 2.5, a two sided α of 0.05, Zα/2 = 1.96, and 80% power, Zβ = 0.84, gave P = 0.7143 and p1 = 0.4545. Then m = 40.3, rounded up to 41 discordant pairs, and N = 41 / 0.4773 = 85.9, so 86 pairs were required. Allowing for 10% incomplete records, 86 / 0.90 = 95.6, so 96 pairs were needed and 100 pairs were enrolled. This formula assumes that exposure is independent within pairs, so that the expected proportion of discordant pairs is p0q1 + p1q0 = 0.477. Because matching on age and sex can lower this proportion, the assumption was checked against the study data: 54 of the 100 pairs were discordant for ever smoking, more than the 41 required, which gives an achieved power of 89% to detect an odds ratio of 2.5 with the exact McNemar test.

Inclusion Criteria

- Cases: age 18 years or above with a new diagnosis of vocal cord pathology confirmed by laryngoscopy, with histopathology where indicated
- Controls: ENT outpatients with non laryngeal complaints, normal vocal cords and no voice complaints, of the same gender and within 5 years of the age of the matched case
- Willingness to give written informed consent

Exclusion Criteria

- Vocal cord palsy, laryngeal trauma or neurological voice disorders
- Previous laryngeal surgery, radiotherapy or neck surgery
- Laryngeal tuberculosis or recurrent respiratory papillomatosis
- Acute laryngitis at presentation
- Inability to give a reliable smoking history

Data Assessment Procedure

A trained primary investigator administered a structured pro forma covering age, sex, residence, occupation, smoking, smokeless tobacco, alcohol, reflux symptoms, vocal overuse and occupational dust or chemical exposure. Never smokers had smoked fewer than 100 cigarettes or bidis in their lifetime. Current smokers smoked within the preceding six months. Former smokers had quit six months or more earlier. Pack-years were cigarettes or bidis per day divided by 20, multiplied by years smoked, with one bidi counted as one cigarette. Reflux was defined as heartburn or regurgitation at least weekly.

Methodology

Every participant underwent ENT examination and rigid 70 degree or flexible laryngoscopy with video recording, and stroboscopy where available. Cases were classified as vocal polyp, vocal nodule, Reinke's edema, or premalignant and malignant lesions, the last comprising leukoplakia and early glottic carcinoma confirmed by biopsy. Each case was matched to a concurrently recruited control at enrolment.

Statistical Analysis

Exposure differences were tested by McNemar chi-square test without continuity correction, or by the exact binomial (exact McNemar) test when discordant pairs were fewer than 25. Age was compared by paired t test. For smoking status, each category was compared with participants not in that category. For the dose response analysis, never smokers were the reference category, and each pack-year category was compared with them using only the pairs in which one member was in that category and the other was a never smoker; pairs in which both members smoked were

not informative for these comparisons. Where a discordant cell was small, exact conditional 95% confidence intervals, from the Clopper-Pearson interval for b / (b + c), are also given. All tests were two sided, with $p<0.05$ considered significant. Exact p values are reported, and values below 0.001 are shown as $p<0.001$.

Results

All 100 matched pairs completed the study. The cases comprised 30 vocal polyps, 22 vocal nodules, 20 cases of Reinke's edema, 16 of leukoplakia and 12 of early glottic carcinoma.

Table 1 depicts the demographic profile of the 100 matched pairs. The mean paired age difference was 0.4 years, t = 1.38, p=0.17, and 78 pairs were male, confirming successful matching. Residence had 18 case only and 12 control only discordant pairs, p=0.27, and occupation 17 against 9, p=0.12, so the groups were comparable. A paired t test was used for age and the McNemar test for categorical variables.

Table 2 explains the association between smoking status and vocal cord pathology. Ever smoking was present in 64 cases and 34 controls, with 42 pairs having only the case exposed and 12 only the control, matched odds ratio 3.50, 95% CI 1.84 to 6.65, $\chi^2 = 16.67$, $p<0.001$. The remaining 46 pairs were concordant, 22 both exposed and 24 neither exposed. Current smoking carried higher odds, 5.67, $p<0.001$, whereas former smoking showed no association, p=0.84. The McNemar chi-square test was used, with the exact form for former smoking since discordant pairs were below 25.

Table 1: Demographic characteristics of matched cases and controls

Characteristic	Cases, n=100	Controls, n=100	Test	p value
Age, years, mean ± SD	46.8 ± 11.9	46.4 ± 11.8	Paired t = 1.38	0.17
Male sex	78	78	Matching variable	1.00
Female sex	22	22		
Rural residence	68	62	McNemar $\chi^2 = 1.20$	0.27
Urban residence	32	38		
Manual occupation	55	47	McNemar $\chi^2 = 2.46$	0.12
Non manual occupation	45	53		

Table 2: Smoking status and risk of vocal cord pathology

Exposure	Cases	Controls	Case only pairs	Control only pairs	Matched odds ratio, 95% CI	p value
Ever smoker	64	34	42	12	3.50, 1.84 to 6.65	<0.001
Current smoker	48	20	34	6	5.67, 2.38 to 13.50	<0.001
Former smoker	16	14	13	11	1.18, 0.53 to 2.64	0.84

Table 3: Dose response by pack-years, each category compared with never smokers

Pack-years	Cases	Controls	Case only pairs	Control only pairs	Matched odds ratio, 95% CI	p value
Never smoker	36	66	0	0	1	1.00
Below 10	14	18	8	7	1.14, 0.41 to 3.15	1.00
10 to 19.9	24	11	14	4	3.50, 1.15 to 10.63	0.031
20 or above	26	5	20	1	20.00, 2.68 to 149.02	<0.001

Table 4: Ever smoking by type of vocal cord pathology

Pathology	Pairs	Smokers, cases and controls	Case only pairs	Control only pairs	Matched odds ratio, 95% CI	p value
Vocal polyp	30	17 and 10	11	4	2.75, 0.88 to 8.64	0.12
Vocal nodule	22	7 and 8	4	5	0.80, 0.21 to 2.98	1.00
Reinke's edema	20	18 and 7	12	1	12.00, 1.56 to 92.30	0.003
Premalignant and malignant	28	22 and 9	15	2	7.50, 1.72 to 32.80	0.002
Benign lesions combined	72	42 and 25	27	10	2.70, 1.31 to 5.58	0.005
All pathologies	100	64 and 34	42	12	3.50, 1.84 to 6.65	0.001

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Table 5: Other risk factors, unadjusted

Factor	Cases	Controls	Case only pairs	Control only pairs	Matched odds ratio, 95% CI	p value
Alcohol use	46	33	27	14	1.93, 1.01 to 3.68	0.042
Reflux symptoms	38	21	28	11	2.55, 1.27 to 5.11	0.006
Vocal overuse	52	40	28	16	1.75, 0.95 to 3.23	0.07
Smokeless tobacco use	24	18	17	11	1.55, 0.72 to 3.30	0.26
Occupational dust or chemical exposure	34	22	23	11	2.09, 1.02 to 4.29	0.040

Table 3 depicts the dose response between cumulative smoking and pathology within matched pairs. Never smokers formed the baseline group, with an odds ratio of 1.00 by definition, and 24 pairs had both members as never smokers. The odds ratio rose from 1.14 below 10 pack-years, p=1.00, to 3.50 at 10 to 19.9 pack-years and 20.00 at 20 or more, both p<0.05. The very wide interval at the highest level reflects only one control only pair. The exact McNemar test was used because all discordant counts were below 25.

Table 4 explains the association of smoking with each pathology. Smoking was strongest in Reinke's edema, where 18 of 20 cases were smokers, odds ratio 12.00, and in premalignant and malignant lesions, where 22 of 28 were smokers, odds ratio 7.50, both p<0.05. Polyps, 2.75, p=0.12, and nodules, 0.80, p=1.00, showed no significant association. Benign lesions combined had an odds ratio of 2.70, p<0.005. The exact McNemar test was used for single pathologies and the chi-square form for the combined rows.

Table 5 depicts other risk factors compared within matched pairs. Reflux symptoms, 2.55, alcohol use, 1.93, and dust or chemical exposure, 2.09, were significantly associated, p=0.006, p=0.042 and p=0.040. Vocal overuse, p=0.07, and smokeless tobacco use, p=0.26, were not. The McNemar chi-square test was used for all factors.

Discussion

This matched study shows a strong, dose dependent association between smoking and vocal cord pathologies that varies by lesion type. Ever smokers had 3.50 times the odds of pathology and current smokers 5.67 times, with the odds reaching 20.00 at 20 or more pack-years. We compared these findings with six recent studies.

Kravos and colleagues compared 53 men with Reinke's edema with 45 controls in Slovenia. Smoking, including former smoking, was present in 90.57% of cases and 20% of controls, p<0.05, and it was the only variable to remain significant in multivariable analysis[9]. Their case proportion matches our 90.0%, 18 of 20. Their crude odds ratio from the published counts is about 38, above our 12.00, because their control prevalence was lower than our 35% among Reinke's edema controls.

An Iranian case control study of 23 patients with Reinke's edema and 50 sinusitis controls found smoking significantly associated with the disease, p<0.05, with mean ages of 54 and 42 years and opium use in 90% of cases against 4% of controls[10]. That age gap is the confounding our matching removes.

In the large Indian tertiary series of 1033 hoarseness patients, smoking was significantly associated with laryngeal malignancy, premalignant lesions and scars, all p<0.05[5]. Our odds ratio of 7.50 for premalignant and malignant lesions supports this. A rural Karnataka series of 70 patients reported smoking in 54.29% and a significant link between smoking and laryngeal malignancy, p<0.05[7]. Our smoking proportion among cases, 64%, was higher, which may reflect case mix, since malignancy made up 38.6% of their series against 12% of ours.

We found no association with nodules, odds ratio 0.80, p=1.00. This agrees with a Korean national survey of 258 persons with vocal nodules, a prevalence of 1.31%, which found no association with smoking[11]. Nodules are chiefly phonotraumatic, so voice use is the likelier driver. Our polyp estimate, 2.75, p=0.12, was raised but not significant, probably because only 15 pairs were discordant. A Korean nationwide study of 10,170 participants found smoking history significantly more common in persons with benign vocal fold lesions[4]. Our combined benign lesion odds ratio of 2.70, p=0.005, is in the same direction, carried mainly by Reinke's edema.

Biologically, smoking drives oxidative stress and endothelial dysfunction, which raise hyaluronic acid synthesis and vascular leakage into Reinke's space, a plausible reason for the strongest association in Reinke's edema[9]. Chemical and thermal irritation with chronic cough promotes keratinisation, consistent with our premalignant findings[5]. Reflux was also associated in unadjusted analysis, and alcohol and dust exposure only marginally, whereas in Kravos and colleagues smoking alone survived multivariable adjustment[9].

Conclusion

Smoking is strongly and dose dependently associated with vocal cord pathologies, most markedly with Reinke's edema and premalignant and malignant lesions. Patients with

hoarseness should be asked about smoking and advised to quit, and heavy smokers with persistent hoarseness warrant early laryngoscopy.

Limitations

This was a single centre study with hospital based controls, so selection bias is possible. Smoking was self reported without biochemical verification. Matching prevents estimating the effect of age and sex, other risk factors were not adjusted for, and subgroup sizes were small with wide confidence intervals. Cigarettes and bidis were not analysed separately, and temporality cannot be established.

Conflict of Interest

None

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