Research Article
E-ISSN : 3048-1368

Volume 07, Issue No. 03. 2024
P-ISSN : 3048-1376

The International Journal of Medical Science and Health Research



The Analysis Study of Association of Cigarette Smoking and Dry Eye Disease : A Comprehensive Systematic Review

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Article History :
Received date : 2024/09/16
Revised date : 2024/10/04
Accepted date : 2024/11/02
Published date : 2024/12/20

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E-ISSN :
ISSN 3048-1368
9 773048 136000

P-ISSN :
ISSN 3048-1376
9 773048 137007

ABSTRACT

Background: Dry eye disease prevalence is significantly influenced by smoking, with cigarette smoke contributing to over seven million deaths annually. Despite the widespread use of electronic cigarettes, public awareness remains limited, and debates persist regarding their safety and long-term health implications, highlighting the urgent need for improved health measures. **Methods:** This systematic review complied with the PRISMA 2020 requirements, concentrating solely on full-text papers published in English from 2014 to 2024. Editorials and review articles lacking a DOI were omitted to guarantee the use of high-quality sources. A comprehensive literature review was performed using esteemed databases such as ScienceDirect, PubMed, and SagePub to locate pertinent studies. **Result:** An initial database search identified more than 60 publications relevant to the topic. Following a meticulous three-stage screening process, eight studies were ultimately selected based on predefined inclusion criteria and deemed appropriate for in-depth analysis. These studies underwent a thorough critical appraisal to ensure their quality and relevance, providing a solid foundation for a comprehensive investigation into the association between cigarette smoking and dry eye disease. **Conclusion:** DED, a common ophthalmology condition, is often underdiagnosed due to its nonspecific symptoms and variability in diagnostic approaches. Cigarette smoke causes lipid peroxidation, tear film instability, and ocular surface damage, impairing epithelial differentiation.

Keywords: dry eye disease, cigarette smoke, electronic cigarette, ocular damage

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INTRODUCTION

Tobacco consumption remains one of the leading causes of morbidity and mortality worldwide, with cigarette smoke containing a myriad of toxic substances, including heavy metals and other harmful elements.[1] Smoking is closely associated with severe health conditions such as cancer, heart disease, and strokes, contributing to significant global health burdens.[2,3] In 2019, the global prevalence of smoking among adults was estimated at 19.2%, with notable regional variations. For instance, the World Health Organization (WHO) reported smoking rates of 15.1% in the United Kingdom, 19.9% in the United States, and 14.9% in Australia, while the rate soared to 35% in Greece, a major tobacco-producing country.[1] Alarmingly, tobacco use accounts for more than seven million deaths annually, with over six million resulting from direct consumption and approximately 890,000 deaths attributed to exposure to second-hand smoke. In Europe alone, smoking causes around 700,000 deaths per year and incurs an economic cost exceeding 100 billion euros.[4]

Beyond its well-known systemic health impacts, smoking has been implicated in various ocular pathologies.[5,6] Among these, dry eye disease (DED) has emerged as a significant concern, affecting millions of individuals worldwide.[7] DED is characterized by discomfort, visual disturbance, and potential damage to the ocular surface, often resulting in a diminished quality of life. Despite the clear evidence linking smoking to ocular diseases, public awareness of these associations remains limited [8,10–12].[5,8,9] The toxic components of cigarette smoke can compromise tear film stability and induce inflammatory responses, exacerbating the prevalence and severity of DED. This underscores the need for greater education and targeted interventions to mitigate smoking's impact on eye health.

Over the past decade, electronic nicotine delivery systems (ENDS), including electronic cigarettes (ECs), have gained

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popularity as alternatives to conventional cigarettes. Promoted as potentially safer options, ECs have garnered the attention of global health authorities, including the WHO, which addressed their usage in its 2019 global tobacco report. However, data on global EC prevalence remain limited, with only 39 of 195 surveyed countries providing statistics. Reported EC use is 5.5% in the United Kingdom, 3.2% in Australia, and 1.9% in Greece.[1] ECs function by delivering nicotine via heated vapor rather than tobacco combustion, eliminating many harmful byproducts of traditional smoking.[10] Despite these perceived advantages, debates persist regarding their safety and long-term health implications. This review examines the effects of both conventional cigarette smoking and EC use, with a particular focus on their roles in the development and exacerbation of dry eye disease.

METHODS

Protocol

This study was carefully designed and conducted in strict accordance with the PRISMA 2020 guidelines, ensuring methodological rigor and high research quality. By adhering to these comprehensive standards, the review process was transparent, reproducible, and scientifically robust. Critical steps, such as thorough literature searches, precise data extraction, and systematic synthesis of findings, were meticulously executed to minimize bias and maximize reliability. This rigorous approach not only enhances the credibility of the study but also establishes a strong foundation for advancing evidence-based research in the field.

Criteria for Eligibility

This study aims to evaluate the association between cigarette smoking and dry eye disease through a systematic review and synthesis of data from diverse studies. By identifying patterns and emerging trends in the existing literature, the research seeks to inform the development of more effective diagnostic tools and therapeutic strategies, ultimately improving clinical management and patient outcomes. The overarching goal is to

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contribute to a deeper understanding of the relationship between smoking and dry eye disease, laying the groundwork for evidence-based advancements in patient care.a

To ensure analytical rigor, the study applied stringent inclusion and exclusion criteria. Only peer-reviewed studies published in English between 2014 and 2024 were included, with each study's authenticity confirmed through DOI validation. Non-research materials such as reviews, editorials, and duplicate entries were excluded to maintain a focused and high-quality dataset. This meticulous selection process ensures that the findings are based on reliable and relevant sources, enhancing the validity and robustness of the analysis.

The research adopts a systematic and methodologically sound approach to guarantee that its conclusions are supported by credible, high-quality data. By evaluating the association between cigarette smoking and dry eye disease, the study aims to contribute valuable insights that can improve patient care and health outcomes for individuals affected by this challenging condition.

Search Strategy

A meticulously crafted search strategy was implemented to identify relevant studies for this systematic review. Key terms such as "cigarette smoking," "association," and "dry eye disease" were strategically employed to ensure the capture of a broad spectrum of pertinent literature. The search spanned three major academic databases—PubMed, SagePub, and ScienceDirect—facilitating a comprehensive and inclusive exploration of the topic. This rigorous approach allowed for the identification and selection of high-quality and diverse sources, providing a robust foundation for synthesizing findings and enhancing the reliability and validity of the review.

Data retrieval

The authors employed a meticulous preliminary screening process to evaluate each article systematically. Titles and abstracts were carefully reviewed to assess their relevance, and only studies that aligned with the research objectives

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and met predetermined inclusion criteria were selected for in-depth analysis. This structured approach ensured the identification of consistent and meaningful patterns across the literature, focusing exclusively on studies directly pertinent to the research question.

To ensure consistency and enhance the comparability of findings, only full-text articles published in English were included. A rigorous screening process verified that all selected studies adhered to the established inclusion criteria and addressed the study's objectives. Articles failing to meet these standards were excluded, resulting in a refined dataset characterized by high quality, focus, and alignment with the research goals.

The evaluation process further involved a detailed assessment of key elements such as study titles, authorship, publication dates, research locations, and methodologies. By rigorously examining these factors, the authors ensured the inclusion of only the most credible and relevant studies. This systematic and methodologically robust approach reinforced the reliability and rigor of the review, providing a strong foundation for drawing credible, evidence-based conclusions.

Quality Assessment and Data Synthesis

The authors employed a meticulous initial screening process, systematically reviewing the titles and abstracts of each article to identify studies relevant for further analysis. Only those that met the predefined relevance criteria progressed to a comprehensive and detailed evaluation. This rigorous approach prioritized the inclusion of high-quality, contextually significant studies, ensuring a focused and thorough examination of the existing literature. By refining the selection process, the authors ensured that the included studies were directly aligned with the research objectives, thereby enhancing the relevance, methodological rigor, and reliability of the systematic review.

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Table 1. Search Strategy

Database	Search Strategy	*Hits*
Pubmed	*("cigarette smoking" AND "association" AND "dry eye disease")*	2
Science Direct	*("cigarette smoking" AND "association" AND "dry eye disease")*	62
Sagepub	*("cigarette smoking" AND "association" AND "dry eye disease")*	4

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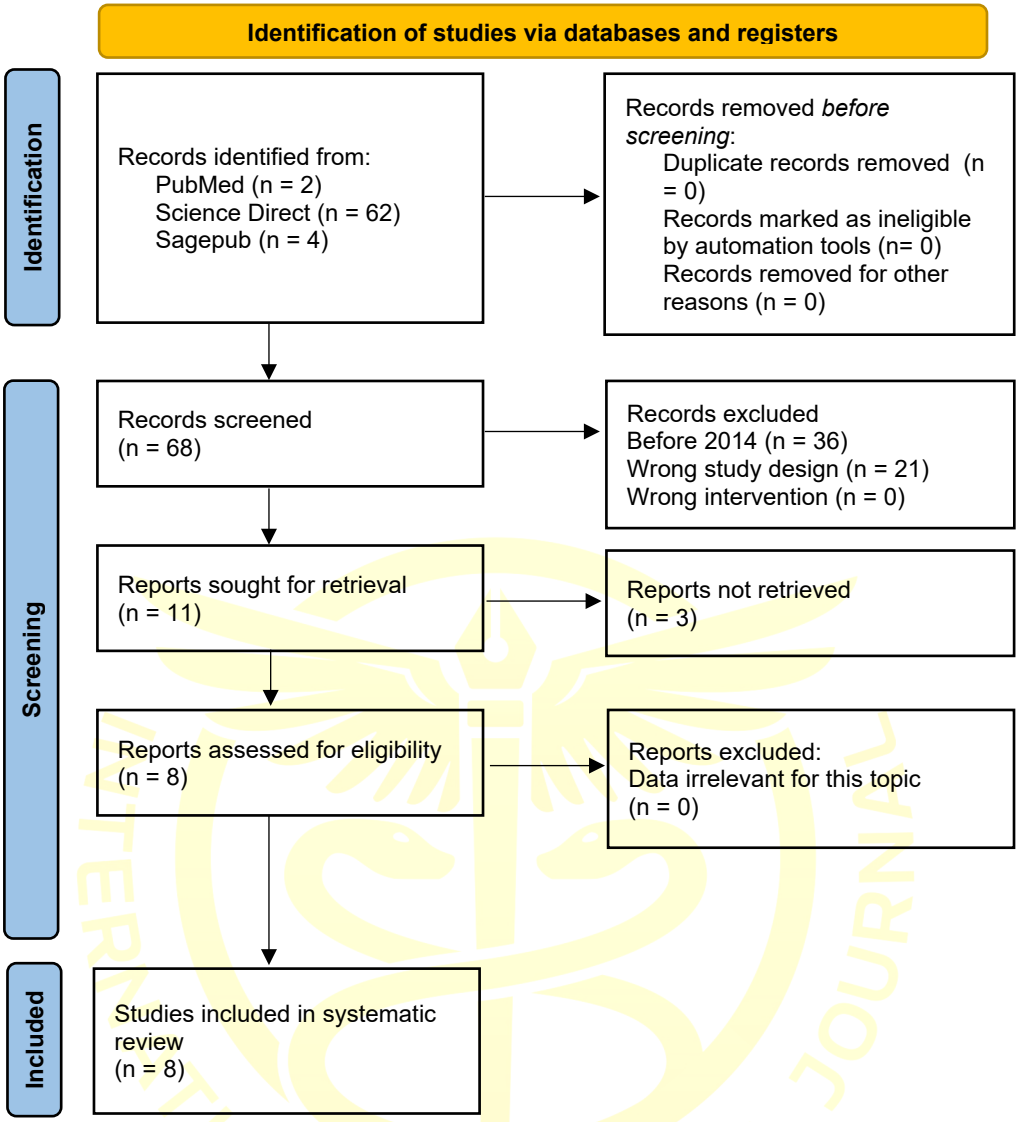


Figure 1. Article search flow chart

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Table 2. Critical appraisal of Study

Parameters	(Rong et al., 2014)	(Md Isa et al., 2019)	(Pritasari et al., 2019)	(Chakraborty & Mal, 2020)	(Makrynioti et al., 2020)	(Tariq et al., 2022)	(Kulkarni & Banait, 2023)	(Bandara et al., 2024)
1. Bias related to temporal precedence								
Is it clear in the study what is the "cause" and what is the "effect" (ie, there is no confusion about which variable comes first)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Bias related to selection and allocation								
Was there a control group?	No	No	No	No	No	No	No	No
3. Bias related to confounding factors								
Were participants included in any comparisons similar?	Yes	Yes	Yes	Yes	No	Yes	No	Yes
4. Bias related to administration of intervention/exposure								
Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Yes.	No.	No.	No.	No.	Yes.	No.	Yes.
5. Bias related to assessment, detection, and measurement of the outcome								
Were there multiple measurements of the outcome, both pre and post the intervention/exposure?	No	No	No	No	No	No	No	No
Were the outcomes of participants included in any comparisons measured in the same way?	No	No	No	No	No	No	No	No
Were outcomes measured in a reliable way?	Yes	Yes	Yes	Yes	No	Yes	No	Yes
6. Bias related to participant retention								
Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	No	No	No	No	No	No	No	No
7. Statistical conclusion validity								
Was appropriate statistical analysis used?	Yes	Yes	Yes	Yes	No	Yes	No	Yes

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RESULT

The investigation began with a systematic search of reputable academic databases, including ScienceDirect, PubMed, and SagePub, to identify studies relevant to the review. A rigorous three-stage screening process was meticulously applied to filter and select the most pertinent studies, ultimately resulting in the inclusion of eight papers that met the predefined inclusion criteria. These selected studies underwent comprehensive analysis, with key themes and findings carefully extracted for detailed examination. To ensure clarity and enhance the presentation of results, the findings are summarized in Table 3, offering a concise and organized overview of the analyzed data.

Table 3. The literature included in this study

Author	Origin	Method	Sample	Result
Rong et al.[11] (2014)	China	Systematic Review	24 studies	Smoking has a protective effect on pterygium risk, with a combined OR of 0.82. Current smokers have a consistent effect, while ex-smokers have a higher risk. UV exposure and sex do not significantly impact the effect of smoking. Sensitivity analysis confirms the protective effect.
Md Isa et al.[12] (2019)	Malaysia	Cross Sectional	42 participants	Vapers experience moderate-to-severe eye dryness, with significant reductions in tear breakup time, fluorescein breakup time, and tear meniscus height. However, the Schirmer test shows higher results in vapers compared to nonsmokers. Increased vaping voltage worsens dry eye symptoms and tear instability, with higher results observed as voltage increases.

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Pritasari et al.[13] (2019)	Indonesia	Cross Sectional	60 participants	The study reveals that cigarette smoke can damage the tear film's fat layer, leading to dry eye syndrome. The results show that smokers have a higher risk of developing dry eye syndrome (80.6%) compared to non-smokers (25.0%), with a 3.222 times higher chance of developing the condition compared to non-smokers.
Chakraborty & Mal[14] (2020)	India	Cross Sectional	205 participants	Cigarette smoking negatively impacts the health of the ocular surface, with a significant decline in mean TBUT and OSDI scores from Group A to C, while aqueous tear secretion remains unaffected, despite a significant proportion of smokers.
Makrynioti et al.[15] (2020)	Greece	Review	-	Cigarette smoking, a widespread addiction, is linked to various ocular pathologies and systemic conditions like cancer, heart attack, and stroke. Electronic cigarettes (ECs) have emerged as alternatives, but their association with dry eye disease, contact lens wear, cataract, age-related macular degeneration, glaucoma, and Graves' ophthalmopathy remains unclear.
Tariq et al.[16] (2022)	Pakistan	Systematic Review	22 studies	A systematic review of 22 studies found no significant relationship between current and former smokers for the risk of DED. The results remained consistent

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				across various subgroups, indicating that current or former smoking may not be involved in the risk of DED. Further studies are recommended to understand the interaction mechanism.
Kulkarni & Banait[17] (2023)	India	Review	-	Smoking, a widespread habit, significantly impacts health across various care settings, including ocular health. Smokers face a heightened risk of age-related macular degeneration (AMD) and cataracts due to oxidative stress and inflammation. Raising awareness about ocular risks is crucial for promoting eye health and implementing comprehensive anti-smoking initiatives and cessation programs.
Bandara et al.[18] (2024)	Canada	Systematic Review	18 studies	This review of 18 studies found significant risks associated with electronic cigarettes, including non-intended and intended ocular surface exposures. It suggests the need for risk communication tools and future long-term studies to better understand the long-term effects of vaping.

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DISCUSSION

Dry eye disease (DED), defined as "a disorder of the tear film due to tear deficiency or excessive tear evaporation, which causes damage to the inter-palpebral ocular surface and is associated with symptoms of ocular discomfort".[19] Clinically, DED is one of the most commonly encountered conditions in ophthalmology practice. Despite its prevalence, DED is often underdiagnosed or overlooked due to its nonspecific symptoms and the variability in diagnostic approaches.[20] The absence of a universal diagnostic standard further complicates its identification, with some studies relying solely on subjective symptomatology and others integrating both symptoms and objective clinical signs. This variability underscores the importance of symptom-based assessments, which were prioritized in the current study to provide a comprehensive understanding of DED.[19,20]

Cigarette smoke is a potent environmental irritant, containing a complex mixture of harmful substances, including free radicals, aldehydes, and other pro-oxidants. Each puff exposes the ocular surface to over 14 free radical species, with greater concentrations during the tar phase. These radicals induce lipid peroxidation of the pre-corneal tear film's lipid layer, resulting in accelerated tear film instability and evaporation.[21] Altinors et al. identified this lipid peroxidation process as a central mechanism of tear film damage in smokers.[22] Matsumoto et al. further validated these findings using lipid layer interferometry, which demonstrated a significant increase in tear evaporation rates and delayed lipid layer spreading in chronic smokers. These biochemical disruptions highlight the direct adverse effects of cigarette smoke on tear film integrity, particularly its lipid layer.[23]

In addition to disrupting the tear film, cigarette smoke inflicts cellular and structural damage on the ocular surface. The free radicals and toxins in cigarette smoke induce chronic inflammation, impairing epithelial differentiation and leading

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to squamous metaplasia of the conjunctiva.[24] Moreover, cigarette smoke reduces goblet cell density, alters tear protein composition, and decreases conjunctival sensitivity, further compromising ocular surface homeostasis. Brush cytology studies reveal an increased presence of neutrophil infiltration in smokers, reinforcing the role of inflammation in ocular surface damage.[23] This inflammation also upregulates proteolytic enzymes, such as plasmin and matrix metalloproteases, which exacerbate epithelial damage and disrupt the ocular surface's structural integrity. Together, these findings emphasize the multifaceted impact of cigarette smoke on the ocular surface.[23-26]

The current study's findings align with previous research, revealing a significant relationship between cigarette smoking and the severity of DED symptoms. The progressive increase in Ocular Surface Disease Index (OSDI) scores with higher smoking intensity indicates a dose-dependent effect, with 79.6% of participants in the heavy-smoking group experiencing severe symptoms. This is consistent with Matsumoto et al., who reported similar symptom prevalence in smokers.[23] Additionally, Tear Break-Up Time (TBUT) values showed a marked reduction in smokers, correlating with the number of cigarettes consumed.[27]

Interestingly, Schirmer's test values remained largely unaffected across smoking groups, echoing the findings of previous researchers.[22,23] This suggests that cigarette smoke primarily affects the lipid layer of the tear film and the cellular structure of the ocular surface rather than aqueous tear production from the lacrimal glands.[22,23,27] These findings highlight the importance of focusing on lipid layer stability and ocular surface health when assessing smoking-related DED. Future research should explore the long-term effects of smoking cessation on tear film and ocular surface recovery, as well as investigate targeted therapeutic interventions to mitigate the damage caused by smoking. The integration of advanced diagnostic tools, such as interferometry and proteomic analysis, could also provide deeper

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insights into the mechanisms of smoke-induced ocular damage.

CONCLUSION

Dry eye disease (DED) is a common condition in ophthalmology, often underdiagnosed due to its nonspecific symptoms and variability in diagnostic approaches. Cigarette smoke, a potent environmental irritant, induces lipid peroxidation, accelerated tear film instability, and evaporation, leading to damage to the lipid layer of the tear film. Smoking also inflicts cellular and structural damage on the ocular surface, impairing epithelial differentiation and compromising ocular surface homeostasis. Future research should focus on lipid layer stability and ocular surface health when assessing DED.

DISCLOSURE STATEMENT

- Disclosure Statement : The authors have no conflicts of Interest to declare
- Funding Sources : None
- Acknowledgements : -
- Author Contribution : All authors discussed and contributed the final content for journal submission and publication

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