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Eyelid sebaceous gland carcinoma: a protocol for a systematic review and meta-analysis of clinicopathological studies of prevalence

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ABSTRACT

Introduction Sebaceous gland carcinoma (SGC) of the eyelid is an aggressive tumour with the ability to metastasise and an increased morbidity. Controversies regarding the epidemiology of this malignant eyelid tumour is widespread in the scientific literature. Western reports repeatedly describes eyelid SGC as a rare occurring tumour in general, accounting for 1%–3% of all eyelid tumours, however studies from Asia have uncovered a higher frequency of eyelid SGC including 54% of all eyelid tumours in Japan, and 43%–56% in India. We wish to retrieve observational data of eyelid SGC prevalence in proportion to total eyelid tumours, from pathological studies published worldwide to resolve this controversy.

Methods and analysis We will search Ovid Medline, EMBASE, Cochrane Central Register of Controlled Trials, Scopus and Google Scholar to identify published reports on eyelid SGC prevalence proportions, aiming to clarify the incidence of the tumour. We will include observational clinicopathological studies reporting prevalence with confirmed histopathology. No limitations on publication date or language will be applied. Data from the individual studies and study quality will be extracted by two individual reviewers. Study quality will be assessed using the JBI Critical Appraisal Instrument for Studies Reporting Prevalence Data. Raw proportions will be transformed and pooled using a random effects model for meta-analysis. And subgroup analysis according to geography will be performed. If data are deemed unsuitable for a meta-analysis, a narrative synthesis will be presented. We will judge the certainty of evidence and present whether this has an overall effect on the results. The results may shed light on a long-standing academic disparity of the scientific literature.

Ethics and dissemination This systematic review does not require ethical approval. The results of this proposed review will be the subject to a publication in an international peer-reviewed journal within the ophthalmic or pathological specialty.

PROSPERO registration number CRD42023487141.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The quality of this study and protocol has been adjusted to align with studies based on observational data.
⇒ The retrieved data will be stratified according to geography to investigate on worldwide differences in reports.
⇒ A clear and reproducible electronic search strategy has been designed for each of the included databases including additional search strategies for existing grey literature.
⇒ Possible publications only indexed in Asia-specific databases may limit this study; however, due to a lack of search expertise within these, we chose to omit such.
⇒ We will assess the quality of the included studies using a recognised tool designed for use in prevalence studies.

INTRODUCTION

Malignant eyelid neoplasms are among the most common non-melanoma cancers of the skin. They are pathologically classified according to the histological tissue from which they derive. Sebaceous gland carcinomas (SGC) originate from the sebaceous glands in the skin, and on the eyelids, they stem from the Meibomian and Zeis glands associated with the eyelashes. In contrast to basal cell carcinoma of the eyelids, eyelid SGC displays an aggressive local behaviour,[1] with metastasis to the local lymph nodes reported in one study to be 21%.[2] The same study ultimately reported the need for orbital exenteration in 14% and a mortality of 6% due to the growth of the tumour.

Controversies regarding the epidemiology of this malignant eyelid tumour is widespread in the scientific literature. Pathological observational studies in Western countries report eyelid SGC to account for <1%–3% of all malignant eyelid neoplasms.[3–5] As a result, the scientific and academic literature repeatedly describes eyelid SGC as a rare occurring tumour.[2 6] However, recent observational studies from Asia on pathological specimens

have uncovered a much higher frequency of eyelid SGC in this part of the world. These include 8% in Taiwan,[7] 30% in the Phillipines[8] and 54% in Japan.[9] Recent studies from India also report observations of 43%–56%[10 11] and are among the highest in the world. Based on these findings and the large populations of these countries, we identified the need for a systematic review and analysis of the published literature worldwide on observations on eyelid SGC prevalence. We hypothesise that eyelid SGC is more prevalent on a worldwide scale than the previous academic consensus and common phrasing in the literature suggests. The aim of this proposed systematic review is to retrieve and asses reports from pathological studies on observational data of eyelid SGC prevalence in proportion to total eyelid tumours published worldwide. Additionally, we aim to report the geographical variances of these reports.

METHODS AND ANALYSIS

This protocol for a systematic review and meta-analysis has been approved and registered by PROSPERO with the registration number CRD42023487141.

This protocol was reported using the guidelines of the Meta-analysis of Observational Studies in Epidemiology[12 13] and in addition was elaborated using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Protocols[14 15] where applicable, as the PRISMA statements are focused on the reviewing of interventional studies and not observational studies.[13 14] Any methodological changes will be published in the final systematic review. We will follow the recommendations of the JBI Manual for Systematic Reviews of Prevalence and Incidence.[16]

Eligibility criteria

We will consider the following study designs and Condition, Context and Population for observational studies criteria for inclusion.

Study designs

We will include observational studies on eyelid neoplasms, encompassing case-control studies, cohort studies and cross-sectional studies. Both prospective and retroperspective studies will be included. No language barriers will be applied.

Condition

Eyelid SGC with a confirmed histopathological diagnosis.

Context

Eyelid neoplasms with a confirmed histopathological diagnosis after surgical removal. Studies on all ocular neoplasms will be included if eyelid SGC can be determined as a prevalence proportion of the estimated total cases.

Population

Human patients. No age limits or specifications regarding gender, race or geographic region.

Reporting of outcomes

Relating to the existing literature in the above, we will include studies that report eyelid SGC as part of an observational cohort of total malignant eyelid neoplasms. Any measurement of sample size such as a prevalence proportion or percentage will be analysed. We will also analyse reported epidemiological estimates such as incidence or epidemiological prevalence.

Patients and public involvement

We have not involved patients or members of the public in planning this proposed systematic review.

Search methods for identification of studies

Electronic searches

We have included an information specialist in the form of a health librarian to design a search query for each of the following database in order to retrieve any relevant studies on the subject. There will be no restrictions on language or year of publication.

The full search query for each database is listed in the online supplemental material .

We will search Ovid Medline (online supplemental material 1), Scopus (online supplemental material 2), EMBASE (online supplemental material 3), Cochrane Central Register of Controlled Trials (online supplemental material 4) and Google Scholar to identify published reports on eyelid SGC prevalence proportions.

Other searches

We will perform manual forwards and backwards citation searches of the included studies as well as searches on the first and last author of the included studies. We will contact experts on ocular pathology in order to inquire on possible non-published reports.

Screening of the retrieved studies

The retrieved records of the search will be uploaded into Covidence. Following removal of duplicates, two authors with previous experience within medical research and systematic reviews (MST and SDV) will independently screen all retrieved titles and abstracts based on the listed eligibility criteria. The authors will secure a translation of the titles and abstract of non-English articles. The same authors will then independently assess full text of the remaining studies in order to determine potential eligible studies. Full-text translation of any possible non-English articles will also be secured. Any disagreements or conflicts will be resolved via discussion. A flow chart describing the inclusion of the final studies and including reasons for exclusion will be presented.

Data collection and analysis

Data extraction and management

Two review authors (MST and SDV) will independently extract basic characteristics (article ID, article title, author name, publication year, study design, country(ies) where the study is based, sample size), exposure (surgery and description if any), outcome (histopathological diagnosis,

diagnostic criteria, proportion, incidence, prevalence) and study quality assessment into standardised forms using Covidence.

Assessments of study quality and risk of bias in the included studies

Currently, no standardised tool for the assessment of risk of bias in observational prevalence studies in pathological observational studies exists. Despite this, two review authors (MST and SDV) will independently and thoroughly examine the available data to consider any potential risk of bias. The risk of bias of the included studies will be evaluated and presented using an adjusted version of the JBI Critical Appraisal Checklist for Studies Reporting Prevalence Data,[17] which accommodates the inclusion of pathological studies. We will investigate each for relevant information such as, but not limited to, whether trained or specialised pathologists, or artificial intelligence tools were involved in the diagnosis. Special attention will be given to whether pathological revisions of the samples have been performed and if inter-rater reliability statistic such as Cohen's κ-coefficient has been applied. The quality of the included studies will be appraised accordingly.

Dealing with missing data

In the case of missing, insufficient or otherwise unclear data, we will contact the study authors. We will wait 2 weeks for the authors to reply. If no reply is received, we will consider the impact of the missing data on the overall quality of the study.

Statistical methods and assessment of study heterogeneity including possible publication bias

We will apply the generalised linear model and the Freeman-Tukey double arcsine transformation to raw proportions to present the eyelid SGC prevalence proportion with 95% CIs.[18 19] We will perform a sensitivity analysis between the two models to estimate any uncertainty of the transformation. Pooled prevalence proportions will also be computed.

We will evaluate heterogeneity, both clinical and statistical, by examining the patient characteristics and outcomes. By performing an I^2 statistic evaluation and evaluating forest plots, we will assess heterogeneity between study variance as opposed to sampling variance of the included studies. The weight of the individual studies will also be evaluated using the random effects model.

As our review focuses on observational prevalence data on all eyelid cancer subtypes, which includes the target condition eyelid SGC, a publication bias analysis (eg, funnel plot) has been deemed inappropriate. This is because the inclusion of the target condition will not directly affect publication of articles.

Data synthesis including subgroup analysis and certainty of evidence

We will provide a descriptive, qualitative synthesis of the included studies and their results. We will consider one subgroup analysis: geographical region, for example, Europe, Asia. If a significant difference in the appraisal of study quality is found, we will perform subgroup analysis according to these findings. If a meta-analysis based on the included studies proves impossible or irrelevant, we will present the results in the form of a narrative synthesis.

Rating of the evidence within systematic reviews of interventional studies is performed using the Grading of Recommendations, Assessment, Development and Evaluations standard. In our review, we will evaluate the certainty of evidence in a manner applicable to observational studies including, but not limited to, the domains such as risk of bias, inconsistency, imprecision and indirectness to observational studies. For instance, we will assess the extent to which the findings match the expectations based on the statistics from the included studies. Finally, we will judge whether these results may alter the overall level of certainty of the body of evidence.

ETHICS AND DISSEMINATION

Ethical approval is not required to conduct a systematic review of the literature or meta-analysis since it does not involve recruiting patients or handling patient data. We expect that the results from this systematic review will be published in a peer-reviewed scientific journal.

To our knowledge, this systematic review will be the first study to systematically retrieve and investigate on worldwide observational prevalences of eyelid SGC.

Eyelid SGC is a highly malignant skin cancer with the ability to metastasise, resulting in significant morbidity and potentially death.[1 2 6 20] Due to the malignancy of the tumour, an aggressive surgical approach is the preferred option. However, the diagnosis tends to be elusive due to the tumour's ability to mimic benign neoplasms such as chalazion or benign eyelid cysts.[1 10] Furthermore, the final diagnosis of eyelid SGC often displays a significant diagnostic delay,[6] which may be exacerbated by the continuous description in the academic literature as being very rare as previously supported by Western studies. We intend on this systematic review to shed light on whether the worldwide occurrence of eyelid SGC may be much higher than previously described and with significant geographical variations. As opposed to systematic reviews of interventional studies, the current systematic review protocol accommodates the specific requirements of observational studies of prevalence. We will follow a rigorous methodology, including publication of this study protocol, to ensure the highest scientific standards, transparency and reproducibility.

The results of this review may assist ophthalmologists, oculoplastic surgeons and eye healthcare providers worldwide in their diagnostic considerations, potentially resolving a long-standing discrepancy in the description of eyelid SGC prevalence within the academic literature.

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Contributors MST conceptualised the proposal for a systematic review and wrote the original draft. MST and SDV performed preliminary investigations, including methodology, with the assistance of an academic health librarian and a health statistician. SH and NM supervised the process including reviewing and editing of the final paper. All authors have read and approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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Search strategy for MEDLINE

#1 Eye neoplasms/
#2 (eye adj3 (cancer* or neoplasm* or tumor* or tumour* or carcinoma* or adenocarcima* or malignan* or lesion*)).ti,ab,kf.
#3 1 or 2
#4 Eyelid Neoplasms/
#5 (eyelid adj3 (cancer* or neoplasm* or tumor* or tumour* or carcinoma* or adenocarcima* or malignan* or lesion*)).ti,ab,kf.
#6 4 or 5
#7 (ocular adj3 (cancer* or neoplasm* or tumor* or tumour* or carcinoma* or adenocarcima* or malignan* or lesion*)).ti,ab,kf.
#8 (palpebral adj3 (cancer* or neoplasm* or tumor* or tumour* or carcinoma* or adenocarcima* or malignan* or lesion*)).ti,ab,kf.
#9 (periocular adj3 (cancer* or neoplasm* or tumor* or tumour* or carcinoma* or adenocarcima* or malignan* or lesion*)).ti,ab,kf.
#10 3 or 6 or 7 or 8 or 9
#11 Pathology/
#12 Pathology, Clinical/
#13 Pathology, Surgical/
#14 Epidemiology/
#15 Prevalence/
#16 patholog*.ti,ab,kf.
#17 clinicopath*.ti,ab,kf.
#18 histopath*.ti,ab,kf.
#19 epidemiolog*.ti,ab,kf.
#20 prevalence.ti,ab,kf.
#21 (patholog* adj3 clinic*).ti,ab,kf.
#22 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
#23 10 and 22

Search strategy for Embase

#1 "Neoplasms of the eye, lacrimal gland and orbit"/
#2 Eye cancer/
#3 Eye tumor/
#4 (eye adj3 (cancer* or neoplasm* or tumor* or tumour* or carcinoma* or adenocarcima* or malignan* or lesion*)).ti,ab,kf.
#5 2 or 3 or 4
#6 exp Eyelid cancer/
#7 (eyelid adj3 (cancer* or neoplasm* or tumor* or tumour* or carcinoma* or adenocarcima* or malignan* or lesion*)).ti,ab,kf.
#8 6 or 7
#9 (ocular adj3 (cancer* or neoplasm* or tumor* or tumour* or carcinoma* or adenocarcima* or malignan* or lesion*)).ti,ab,kf.
#10 (periocular adj3 (cancer* or neoplasm* or tumor* or tumour* or carcinoma* or adenocarcima* or malignan* or lesion*)).ti,ab,kf.
#11 (palpebral adj3 (cancer* or neoplasm* or tumor* or tumour* or carcinoma* or adenocarcima* or malignan* or lesion*)).ti,ab,kf.
#12 1 or 5 or 8 or 9 or 10 or 11
#13 Pathology/
#14 Histopathology/
#15 exp Prevalence/
#16 Epidemiology/
#17 patholog*.ti,ab,kf.
#18 clinicopath*.ti,ab,kf.
#19 histopath*.ti,ab,kf.
#20 epidemiolog*.ti,ab,kf.
#21 prevalence.ti,ab,kf.
#22 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
#23 12 and 22

Search strategy for Scopus

1#	(((TITLE-ABS-KEY (eyelid W/3 (cancer* OR neoplasm* OR tumor* OR tumour* OR carcinoma* OR adenocarcinoma* OR malignan* OR lesion*)))) OR ((TITLE-ABS-KEY (eye W/3 (cancer* OR neoplasm* OR tumor* OR tumour* OR carcinoma* OR adenocarcinoma* OR malignan* OR lesion*)))) OR ((TITLE-ABS-KEY (ocular W/3 (cancer* OR neoplasm* OR tumor* OR tumour* OR carcinoma* OR adenocarcinoma* OR malignan* OR lesion*)))) OR ((TITLE-ABS-KEY (palpebral W/3 (cancer* OR neoplasm* OR tumor* OR tumour* OR carcinoma* OR adenocarcinoma* OR malignan* OR lesion*)))) OR ((TITLE-ABS-KEY (periocular W/3 (cancer* OR neoplasm* OR tumor* OR tumour* OR carcinoma* OR adenocarcinoma* OR malignan* OR lesion*))))))
2#	((TITLE-ABS-KEY (patholog*)) OR (TITLE-ABS-KEY (epidemiolog*)) OR (TITLE-ABS-KEY (prevalence*)) OR (TITLE-ABS-KEY (clinicopath*)) OR (TITLE-ABS-KEY (histopath*)) OR (TITLE-ABS-KEY (patholog* W/3 clinic*)))
3#	#1 AND #2

Search strategy for Cochrane CENTRAL

#1 MeSH descriptor: [Eyelids] explode all trees

#2 MeSH descriptor: [Eye Neoplasms] explode all trees

#3 (eye NEAR/2 (cancer* or neoplasm* or tumor* or tumour* or carcinoma* or adenocarcinoma* or malignan* or lesion*)):ti,ab,kw

#4 (eyelid NEAR/2 (cancer* or neoplasm* or tumor* or tumour* or carcinoma* or adenocarcinoma* or malignan* or lesion*)):ti,ab,kw

#5 (ocular NEAR/2 (cancer* or neoplasm* or tumor* or tumour* or carcinoma* or adenocarcinoma* or malignan* or lesion*)):ti,ab,kw

#6 (periocular NEAR/2 (cancer* or neoplasm* or tumor* or tumour* or carcinoma* or adenocarcinoma* or malignan* or lesion*)):ti,ab,kw

#7 (palpebral NEAR/2 (cancer* or neoplasm* or tumor* or tumour* or carcinoma* or adenocarcinoma* or malignan* or lesion*)):ti,ab,kw

#8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7

#9 MeSH descriptor: [Pathology] explode all trees

#10 (Patholog*):ti,ab,kw (Word variations have been searched)

#11 Clinicpathol*:ti,ab,kw

#12 Histopath*:ti,ab,kw

#13 (Patholog* NEAR/2 clinic*):ti,ab,kw (Word variations have been searched) 1760

#14 MeSH descriptor: [Prevalence] explode all trees

#15 (Prevalence):ti,ab,kw

#16 MeSH descriptor: [Epidemiology] explode all trees

#17 (Epidemiology):ti,ab,kw

#18 #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17

#19 #8 AND #18