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

Methods and Analysis

We will search Ovid Medline, EMBASE, Cochrane Central, Scopus as well as grey literature to identify published reports on eyelid SGC prevalence proportions to clarify the commonness of the tumor. 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 Checklist 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 is 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.

Ethics and Dissemination

This proposed systematic review will be the first study to examine the available evidence on prevalence proportions of eyelid SGC in relation to other eyelid tumors. The results may shed light upon a long-standing academic disparity of the scientific literature. This systematic review does not require ethical approval.

Trial registration number: CRD42023487141

Strengths and limitations of this study

- This will be the first systematic investigation eyelid sebaceous gland carcinoma prevalence data from pathology studies.
- 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.
- The quality of this study and protocol, has been accommodated to studies on observational data. We will assess the quality of the included studies using a recognized tool designed for use in prevalence studies.

1. 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) arise from the sebaceous glands in the skin, and on the eyelids they arise from the Meibomian - and Zeis glands associated with the eyelashes. In contrast to basal cell carcinoma (BCC) of the eyelids, eyelid SGC displays an aggressive local behavior[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 tumor.

Controversies regarding the epidemiology of this malignant eyelid tumor 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 tumor[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 hypothesize that eyelid SGC is more common on a world-wide scale than the previous academic consensus and common phrasing in the literature as outlined in the above suggest. 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 of total eyelid tumors published worldwide. Secondary, to report the geographical variances of these reports.

2. 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 (MOOSE)[12,13] and in addition was elaborated using the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols (PRISMA-P)[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].

2.1 Eligibility criteria

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

2.1.1 Study designs

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

2.1.2 Condition

Eyelid SGC with a confirmed histopathologic diagnosis.

2.1.3 Context

Eyelid neoplasms with a confirmed histopathologic 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.

2.1.4 Population

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

2.1.5 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 analyzed. We will also analyze reported epidemiologic estimates such as incidence or epidemiologic prevalence.

2.1.6 Patients and public involvement

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

2.2 Search methods for identification of studies

2.2.1 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.

We will search

Ovid Medline,

Scopus,

Embase

Cochrane Central Register of Controlled Trials (CENTRAL)

Google Scholar to identify any grey literature.

2.2.2 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.

2.3 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 (MT and SV) 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.

2.4 Data collection and analysis

2.4.1 Data extraction and management

Two review authors (MT and SV) 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 standardized forms using Covidence.

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

Currently, no standardized tool for the assessment of risk of bias (RoB) in observational prevalence studies in pathological observational studies exists. Despite this, two review authors (MT and SV) 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 the JBI Critical Appraisal Checklist for Studies Reporting Prevalence Data[17] and the quality of the included studies will be appraised accordingly.

2.4.3 Dealing with missing data

In the case of missing, insufficient, or otherwise unclear data, we will contact the study authors. We will wait two 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.

2.4.4 Statistical methods and assessment of study heterogeneity including possible publication bias

We will apply the generalized linear model and the Freeman-Tukey double arcsine transformation to raw proportions to present the Eyelid SGC prevalence proportion with 95% CI intervals[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 (e.g. funnel plot) has been deemed inappropriate. This is because the inclusion of the target condition will not directly affect publication of articles.

2.4.5 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, e.g. Europe, Asia. If a significant differences 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 GRADE 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; risk of bias, inconsistency, imprecision and indirectness to observational studies and judge whether these results may alter the overall level of certainty of the body of evidence.

3. Ethics and Dissemination

Ethical approval is not required in order to conduct a systematic review of the literature or meta-analysis, as no patients will be recruited, nor any patient data handled. We expect that the results from this systematic review to 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 metastasize, resulting in significant morbidity and potentially death[1,2,6,20]. Due to the malignancy of the tumor an aggressive surgical approach is the preferred option. However, the diagnosis tends to be elusive due to the tumors ability to mask as a benign neoplasm such as chalazion or a benign cysts of the eyelid[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 upon 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 achieve the highest scientific standards, transparency, and reproducibility.
The results of this review may aid the diagnostic thinking of ophthalmologists, oculoplastic surgeons, and eye health-care providers worldwide and hopefully resolve a long-standing discrepancy of the description of eyelid SGC prevalence in the academic literature.

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Author contributions

MT conceptualized the proposal for a systematic review and wrote the original draft. MT and SV performed preliminary investigations, including methodology, and with the help 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.

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Table 1.

Search strategy for MEDLINE

#1	Eye neoplasms/
#2	(eye adj3 (cancer* or neoplasm* or tumor* or tumour* 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 malignan* or lesion*)).ti,ab,kf.
#6	4 or 5
#7	(ocular adj3 (cancer* or neoplasm* or tumor* or tumour* or malignan* or lesion*)).ti,ab,kf.
#8	(palpebral adj3 (cancer* or neoplasm* or tumor* or tumour* or malignan* or lesion*)).ti,ab,kf.
#9	(periocular adj3 (cancer* or neoplasm* or tumor* or tumour* 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

Appendix 1.

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 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 malignan* or lesion*)).ti,ab,kf.
#8 6 or 7
#9 (ocular adj3 (cancer* or neoplasm* or tumor* or tumour* or malignan* or lesion*)).ti,ab,kf.
#10 (periocular adj3 (cancer* or neoplasm* or tumor* or tumour* or malignan* or lesion*)).ti,ab,kf.
#11 (palpebral adj3 (cancer* or neoplasm* or tumor* or tumour* 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

Appendix 2.

Search strategy for Scopus

1#	(((TITLE-ABS-KEY (eyelid W/3 (neoplasm* OR cancer* OR neoplasm* OR tumor* OR tumour* OR malignan* OR lesion*)))) OR ((TITLE-ABS-KEY (eye W/3 (neoplasm* OR cancer* OR neoplasm* OR tumor* OR tumour* OR malignan* OR lesion*)))) OR ((TITLE-ABS-KEY (ocular W/3 (neoplasm* OR cancer* OR neoplasm* OR tumor* OR tumour* OR malignan* OR lesion*)))) OR ((TITLE-ABS-KEY (palpebral W/3 (neoplasm* OR cancer* OR neoplasm* OR tumor* OR tumour* OR malignan* OR lesion*)))) OR ((TITLE-ABS-KEY (periocular W/3 (neoplasm* OR cancer* OR neoplasm* OR tumor* OR tumour* 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

Appendix 3.

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 malignan* or lesion*)):ti,ab,kw

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

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

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

#7 (palpebral NEAR/2 (cancer* or neoplasm* or tumor* or tumour* 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

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D, et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	Title line 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐	n/a
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	41
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	4-9
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	254-257
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☐	n/a
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	261-262
Sponsor	5b	Provide name for the review funder and/or sponsor	☐	☐	n/a
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☐	n/a
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	69-78
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	80-83
METHODS					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	97-120
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	131-153
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	Presented in tables
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	157-160
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	157-164
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	170-174
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	170-174
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	124-127
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	178-183
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	210-219
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	194-219
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	194-219
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	213-214
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	203-206
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	216-219

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Abstract

Introduction

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

Methods and Analysis

We will search Ovid Medline, EMBASE, Cochrane Central, Scopus as well as grey literature to identify published reports on eyelid SGC prevalence proportions to clarify the commonness of the tumor. 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 Checklist 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 is 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 upon 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 pathologic specialty.

Trial registration number: CRD42023487141

Strengths and limitations of this study

- The quality of this study and protocol, has been accommodated to studies 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 recognized tool designed for use in prevalence studies.

1. 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) arise from the sebaceous glands in the skin, and on the eyelids they arise from the Meibomian - and Zeis glands associated with the eyelashes. In contrast to basal cell carcinoma (BCC) of the eyelids, eyelid SGC displays an aggressive local behavior[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 tumor.

Controversies regarding the epidemiology of this malignant eyelid tumor 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 tumor[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 hypothesize that eyelid SGC is more common on a world-wide scale than the previous academic consensus and common phrasing in the literature as outlined in the above suggest. 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 of total eyelid tumors published worldwide. Secondary, to report the geographical variances of these reports.

2. 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 (MOOSE)[12,13] and in addition was elaborated using the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols (PRISMA-P)[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].

2.1 Eligibility criteria

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

2.1.1 Study designs

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

2.1.2 Condition

Eyelid SGC with a confirmed histopathologic diagnosis.

2.1.3 Context

Eyelid neoplasms with a confirmed histopathologic 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.

2.1.4 Population

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

2.1.5 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 analyzed. We will also analyze reported epidemiologic estimates such as incidence or epidemiologic prevalence.

2.1.6 Patients and public involvement

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

2.2 Search methods for identification of studies

2.2.1 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 supplemental material.

We will search

Ovid Medline (supplemental material 1),

Scopus (supplemental material 2),

Embase (supplemental material 3),

Cochrane Central Register of Controlled Trials (CENTRAL) (supplemental material 4),

Google Scholar to identify any grey literature.

2.2.2 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.

2.3 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 (MT and SV) 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.

2.4 Data collection and analysis

2.4.1 Data extraction and management

Two review authors (MT and SV) 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 standardized forms using Covidence.

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

Currently, no standardized tool for the assessment of risk of bias (RoB) in observational prevalence studies in pathological observational studies exists. Despite this, two review authors (MT and SV) 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 specialized pathologists, or AI tools were involved in the diagnosis. Special attention will be given to whether pathologic 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.

2.4.3 Dealing with missing data

In the case of missing, insufficient, or otherwise unclear data, we will contact the study authors. We will wait two 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.

2.4.4 Statistical methods and assessment of study heterogeneity including possible publication bias

We will apply the generalized linear model and the Freeman-Tukey double arcsine transformation to raw proportions to present the Eyelid SGC prevalence proportion with 95% CI intervals[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 (e.g. funnel plot) has been deemed inappropriate. This is because the inclusion of the target condition will not directly affect publication of articles.

2.4.5 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, e.g. Europe, Asia. If a significant differences 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 GRADE 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; risk of bias, inconsistency, imprecision and indirectness to observational studies e.g. to what extend do 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.

3. Ethics and Dissemination

Ethical approval is not required in order to conduct a systematic review of the literature or meta-analysis, as no patients will be recruited, nor any patient data handled. We expect that the results from this systematic review to 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 metastasize, resulting in significant morbidity and potentially death[1,2,6,20]. Due to the malignancy of the tumor an aggressive surgical approach is the preferred option. However, the diagnosis tends to be elusive due to the tumors ability to mask as a benign neoplasm such as chalazion or a benign cysts of the eyelid[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 upon 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 achieve the highest scientific standards, transparency, and reproducibility.

The results of this review may aid the diagnostic thinking of ophthalmologists, oculoplastic surgeons, and eye health-care providers worldwide and hopefully resolve a long-standing discrepancy of the description of eyelid SGC prevalence in the academic literature.

Acknowledgements

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Author contributions

MT conceptualized the proposal for a systematic review and wrote the original draft. MT and SV performed preliminary investigations, including methodology, and with the help 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.

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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 pathолog*.ti,ab,kf.
#17 clinicopath*.ti,ab,kf.
#18 histopath*.ti,ab,kf.
#19 epidemiolog*.ti,ab,kf.
#20 prevalence.ti,ab,kf.
#21 (pathолog* 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

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D, et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	Title line 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐	n/a
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	42
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	4-9
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	263-266
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☐	n/a
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	270-271
Sponsor	5b	Provide name for the review funder and/or sponsor	☐	☐	n/a
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☐	n/a
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	68-77

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	78-82
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	96-115
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	132-157
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	Presented in suppl. mat.
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	159-168
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	159-178
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	159-178
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	172-178
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	123-126
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	180-197
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	210-222
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	199-228

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	199-228
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	221-222
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	211-214
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	223-228