



SYSTEMATIC REVIEW

Is there an association between cutaneous leishmaniasis and skin cancer? A systematic review [version 1; peer review: 2 approved]

Rodrigo M. Carrillo-Larco ¹⁻³, J. Gonzalo Acevedo-Rodriguez⁴,
Carlos Altez-Fernandez⁵, Karol Ortiz-Acha⁵, Cesar Ugarte-Gil ⁴⁻⁷

¹Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, UK

²CRONICAS Centre of Excellence in Chronic Diseases, Universidad Peruana Cayetano Heredia, Lima, Peru

³Centro de Estudios de Poblacion, Universidad Catolica los Ángeles de Chimbote (ULADECH-Catolica), Chimbote, Peru

⁴Instituto de Medicina Tropical Alexander von Humboldt, Universidad Peruana Cayetano Heredia, Lima, Peru

⁵Facultad de Medicina Alberto Hurtado, Universidad Peruana Cayetano Heredia, Lima, Peru

⁶Department of Clinical Research, London School of Hygiene and Tropical Medicine, London, UK

⁷Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, USA

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Abstract

Background: Cutaneous leishmaniasis is a prevalent communicable disease in low- and middle-income countries, where non-communicable diseases like skin cancer are on the rise. However, the study of multi-morbidity or co-morbidity between communicable and non-communicable diseases is limited, and even null for some tropical or neglected diseases. Nevertheless, looking at these conditions together instead of as isolated entities in places where these illnesses exist, could show new prevention and treatment paths. We aimed to summarize and critically appraise the epidemiological evidence on the association between cutaneous leishmaniasis and skin cancer.

Methods: Following the PRISMA guidelines, we conducted a systematic review using five search engines (Embase, Medline, Global Health, Scopus and Web of Science). We sought observational studies in which the outcome was skin cancer whilst the exposure was cutaneous leishmaniasis; these conditions should have had laboratory or pathology confirmation.

Results: No epidemiological investigations have studied the association between cutaneous leishmaniasis and skin cancer. Most of the evidence about the association of interest is still based on case reports and other clinical observations rather than strong epidemiological observational studies.

Conclusions: Research is much needed to verify the repeatedly clinical observation that cutaneous leishmaniasis may be a risk factor for skin cancer. This evidence could inform and guide early diagnosis or prevention of skin cancer in survivors of cutaneous leishmaniasis or where cutaneous leishmaniasis is still highly prevalent.

Registration: PROSPERO ID [CRD42018111230](https://doi.org/10.1136/2018.01.11.2811230); registered on 16/10/18.

Open Peer Review

Reviewer Status

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	1	2
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1 **Ibrahim Khalifeh**, American University of Beirut Medical Center, Beirut, Lebanon

2 **Temmy Sunyoto** , Institute of Tropical Medicine Antwerp, Antwerp, Belgium
Institute of Tropical Medicine Antwerp, Antwerp, Belgium

Any reports and responses or comments on the article can be found at the end of the article.

Keywords

Systematic review, neglected tropical diseases, tropical medicine, neoplasms, risk factors, non-communicable diseases, multi-morbidity, syndemics

Corresponding author: Rodrigo M. Carrillo-Larco (rcarrill@ic.ac.uk)

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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Introduction

Globally, non-melanoma skin cancer was among the top ten malignancies with the highest incidence in 2016¹. A key driver of this high incidence is the aging of the population¹. Therefore, those living in low- and middle-income countries (LMICs) are at high risk, because although sanitation and health care have improved thereby delaying mortality, the preventive and treatment care for non-communicable diseases (e.g., neoplasms) is still limited.

In comparison to people in high-income countries, people in LMICs have a double burden of disease, i.e., more cases of non-communicable diseases while still facing infectious/communicable illnesses². This epidemiological profile, along with health and socio-economic inequalities, and even climate change, make it relevant to better understand infectious/communicable illnesses that may become risk factors for non-communicable diseases. In this line, cutaneous leishmaniasis (CL) have been proposed as a risk factor for skin cancer³⁻⁶.

Despite the pathophysiological background^{4,5}, and reviews which summarized case reports^{3,6}, to the best of our knowledge no other work has synthesized the epidemiological evidence on the association between CL and skin cancer. Aiming to provide robust epidemiological conclusions about the association of CL and skin cancer, we conducted a systematic review of observational studies.

Methods

Protocol and registration

This is a systematic review of the scientific literature which protocol was registered at PROSPERO ([CRD42018111230](https://doi.org/10.1111/1230)). The work and reporting adhered to the PRISMA guidelines⁷.

Eligibility criteria

We sought reports that studied men and women of any age; the study sample could have been population- or hospital-based. The comparison group included people without history of CL. The outcome of interest was skin cancer, including: basal cell carcinoma, squamous cell carcinoma and epidermoid carcinoma^{3,6}. Both the exposure and outcome of interest should have had laboratory or pathology confirmation. The eligibility criteria included observational studies with a formal comparison group, including cross-sectional, case-control and cohort studies.

Information sources and search

The search was conducted in Embase, Medline and Global Health (these three through Ovid), Scopus and Web of Science. The search was conducted from inception to December 15th, 2018; no language restrictions were set. The search terms are available in [Table 1](#).

Study selection

Following the selection criteria above described, two independent reviewers screened titles and abstracts (R.M.C.-L., J.G.A.-R., C.A.-F. and K.O.-A., working in pairs); discrepancies were solved by consensus among the reviewers. The full-text of the selected reports was studied in detail by two reviewers independently (R.M.C.-L., J.G.A.-R., C.A.-F. and K.O.-A., working in pairs); again, discrepancies were solved by consensus among the reviewers.

Ethics

This study was classified as of low risk because no human subject was studied. This is a systematic review of the scientific literature, which is public and can be accessed.

Results

Study selection

As presented in [Figure 1](#), 1,429 titles and abstracts were screened, and 6 reports were studied in detail. No reports met our selection criteria, with most of the studies being case reports or letters about the association of interest without presenting results following an epidemiological study design. Therefore, zero observational epidemiological studies have aimed to assess or quantify the association between CL and skin cancer.

Discussion

Summary of evidence

We conducted a thorough systematic review including relevant terms and several search engines, though this work could not find any epidemiological evidence on the association between CL and skin neoplasms. Although there were many case reports signalling how seemingly evident this association is in clinical practice^{3,6}, no epidemiological studies have quantified or characterized the correlation between CL and skin cancer.

Limitations

We did not systematically search grey literature, yet we argue that it would have provided few or no additional relevant references. Even if there were some references, the overall conclusion would hold: the association between CL and skin cancer has been seriously understudied.

Conclusions

Evidence based on clinical reports^{3,6}, along with solid physiopathology pathways ([Table 2](#))^{4,5}, supports the argument that the association of interest is not random or due to “bad luck”. Nonetheless, and even though both CL and skin cancer impose a non-negligible health burden with larger impact in LMICs, the epidemiological work on this association appears to be null. Research is much needed to verify (or disprove) the available evidence, thereby enabling the development of pragmatic tools to help and guide early diagnosis or prevention of skin cancer among survivors of CL.

Table 1. Search terms as used in each search engine.

1	*Leishmaniasis/	
2	skin leishmaniasis/	
3	spundia.mp.	
4	leishman\$.mp.	
5	cutaneous leishmaniasis.mp.	
6	(solitary or limited or old world or localised or diffuse or cutaneous).mp.	
7	5 and 6	
8	1 or 2 or 3 or 4 or 7	
9	skin cancer.mp.	
10	cutaneous malignanc\$.mp.	
11	skin malignanc\$.mp.	
12	skin neoplasms\$.mp.	
13	(basal ADJ0 cell ADJ0 carcinoma\$1) OR (basal ADJ0 cell ADJ0 neoplasms\$1) OR (basal ADJ0 cell ADJ0 cancer\$1)	
14	(squamous ADJ0 cell ADJ0 carcinoma\$1) OR (squamous ADJ0 cell ADJ0 neoplasms\$1) OR (squamous ADJ0 cell ADJ0 cancer\$1)	
15	(epidermoid ADJ0 carcinoma\$1) OR (epidermoid ADJ0 cell ADJ0 neoplasms\$1) OR (epidermoid ADJ0 cell ADJ0 cancer\$1)	
16	9 or 10 or 11 or 12 or 13 or 14 or 15	
17	8 and 16	
18	exp animals/ not humans.sh.	
19	17 not 18	
20	remove duplicates from 19	
Scopus	((ALL(spundia) OR ALL(leishman*) OR ALL(leishmaniasis) OR ALL(skin leishmaniasis)) OR (ALL(cutaneous leishmaniasis) AND (ALL(solitary) OR ALL(limited) OR ALL(old world) OR ALL(localised) OR ALL(diffuse) OR ALL(cutaneous)))) AND ((ALL(skin cancer) OR ALL(cutaneous malignanc*) OR ALL(skin malignanc*) OR ALL(skin neoplasms*)) OR (ALL(basal W/0 cell W/0 carcinoma*) OR (basal W/0 cell W/0 neoplasms*) OR (basal W/0 cell W/0 cancer*))) OR (ALL(squamous W/0 cell W/0 carcinoma*) OR (squamous W/0 cell W/0 neoplasms*) OR (squamous W/0 cell W/0 cancer*))) OR (ALL(epidermoid W/0 carcinoma*) OR (epidermoid W/0 cell W/0 neoplasms*) OR (epidermoid W/0 cell W/0 cancer*))) NOT DBCOLL(medi) AND (LIMIT-TO (DOCTYPE, "ar")) AND (LIMIT-TO(SUBJAREA, "MEDI"))	
Web of Science	(TS=(spundia) OR TS=(leishman*) OR TS=(leishmaniasis) OR TS=(skin leishmaniasis)) OR (TS=(cutaneous leishmaniasis) AND (TS=(solitary) OR TS=(limited) OR TS=(old world) OR TS=(localised) OR TS=(diffuse) OR TS=(cutaneous)))) AND ((TS=(skin cancer) OR TS=(cutaneous malignanc*) OR TS=(skin malignanc*) OR TS=(skin neoplasms*)) OR (TS=((basal W/0 cell W/0 carcinoma*) OR (basal W/0 cell W/0 neoplasms*) OR (basal W/0 cell W/0 cancer*))) OR (TS=((squamous W/0 cell W/0 carcinoma*) OR (squamous W/0 cell W/0 neoplasms*) OR (squamous W/0 cell W/0 cancer*))) OR (TS=((epidermoid W/0 carcinoma*) OR (epidermoid W/0 cell W/0 neoplasms*) OR (epidermoid W/0 cell W/0 cancer*)))) AND DOCUMENT TYPES: (Article)	

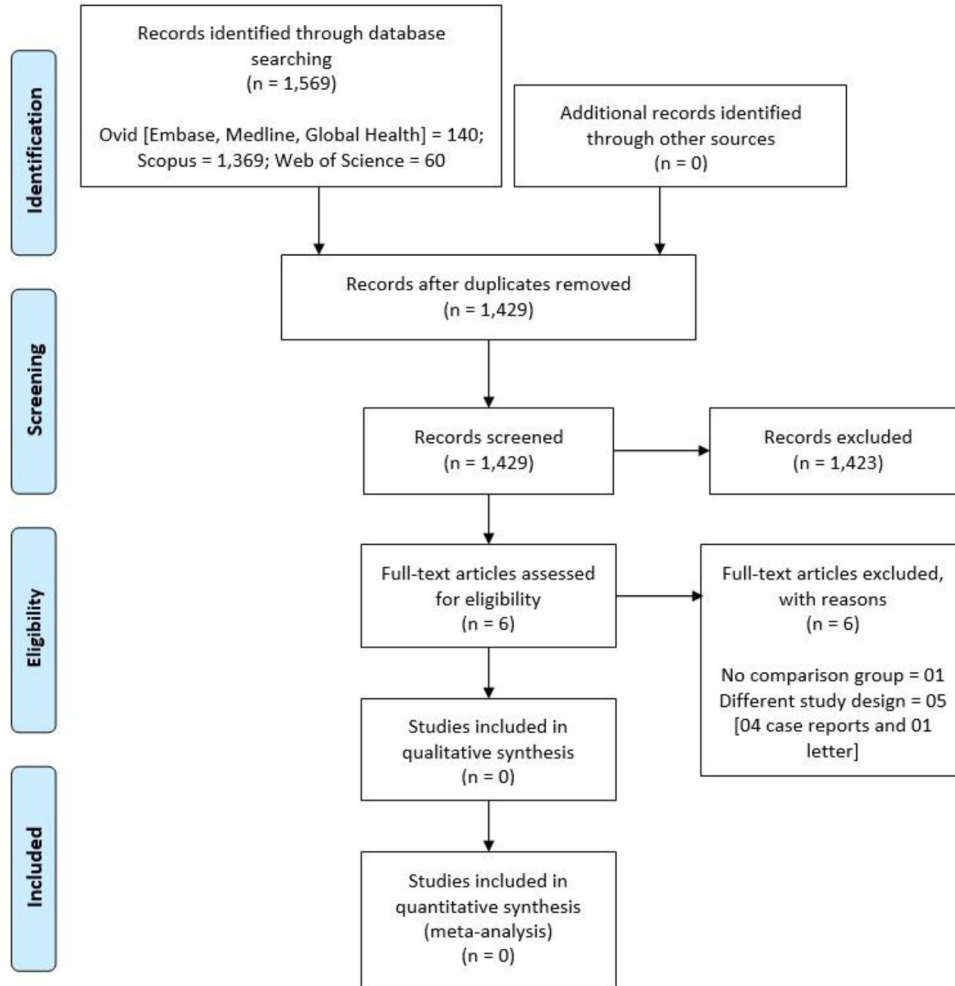


Figure 1. Flowchart of the review process.

Table 2. Selected physiopathology pathways linking cutaneous leishmaniasis (CL) as a potential risk factor for skin cancer.

Reference	Proposed physiopathology pathway(s)
Schwing A, Pomares C, Majoor A, Boyer L, Marty P, Michel G. Leishmania infection: Misdiagnosis as cancer and tumor-promoting potential. <i>Acta Trop</i> . 2018. pii: S0001-706X(18)31322-6.	Among others, this work recaps some proposed pathways: i) through disturbing the activation and functioning of inflammation cells (e.g., macrophages and dendritic cells), Leishmaniasis could be responsible for chronic inflammation, a risk factor for neoplasms; ii) Leishmaniasis may promote a micro-environment rich in Th2 response which, along with the chronic inflammation, may initiate the transition towards cancer.
Kopterides P, Mourtzoukou EG, Skopelitis E, Tsavaris N, Falagas ME. Aspects of the association between leishmaniasis and malignant disorders. <i>Trans R Soc Trop Med Hyg</i> . 2007;101(12):1181-9.	Basal cell carcinoma arising in scars of old CL lesions (i.e., dysplastic changes). Scars and sun exposure are risk factors for malignancies.
Kargi E, Güngör E, Aslan G, Erdogan B. Epidermoid carcinoma in cutaneous leishmaniasis scar. <i>Ann Plast Surg</i> . 2001;46(6):657-8.	As part of a case report summarizes previous findings suggesting that: i) the development of neoplastic lesions where there had been a CL scar known consequence; ii) the development of tumours on cutaneous scars is not new; and iii) basal cell carcinoma could be a consequence of CL lesions (from Suster <i>et al.</i> , 1988).
Suster S, Ronnen M. Basal cell carcinoma arising in a Leishmania scar. <i>Int J Dermatol</i> . 1988;27(3):175-6.	They recap an old theory suggesting that the effect of ultraviolet radiation and other environmental carcinogens may be exacerbated in tissues with a reduced vascularity and atrophy of adnexal structures, as it is the case when there are scarring processes.
	A consistent consequence seems to be that sun exposure, i.e., ultraviolet radiation, could have stronger negative on CL lesions than on lesions-free skin. Noteworthy, CL patients are mostly from rural areas or fieldworkers whom are constantly exposed to sun light. The pathophysiological evidence may suggest that these groups are of particular relevance for this association and deserves further research.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Reporting guidelines

Figshare: PRISMA checklist for article 'Is there an association between cutaneous Leishmaniasis and skin cancer? A systematic review'. <https://doi.org/10.6084/m9.figshare.8870690.v1>⁷.

The completed PRISMA checklist is available under the terms of the [Creative Commons Attribution 4.0 International license](#) (CC-BY 4.0).

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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
2. GBD 2016 Causes of Death Collaborators: **Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016.** *Lancet.* 2017; 390(10100): 1151–210.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
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[PubMed Abstract](#) | [Publisher Full Text](#)
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[PubMed Abstract](#) | [Publisher Full Text](#)
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 **Temmy Sunyoto** 

¹ Department of Public Health, Institute of Tropical Medicine Antwerp, Antwerp, Belgium

² Unit of Epidemiology and Control of Neglected Tropical Disease, Institute of Tropical Medicine Antwerp, Antwerp, Belgium

Thank you for the opportunity given to review this paper.

In this succinct text, the authors carried out a systematic review aiming to summarise available evidence on the epidemiological association between cutaneous leishmaniasis and skin cancer. The title is clear and using a question format reflects the research question and the method that was applied to answer it. The topic is also of interest, especially when relations, if any, between communicable/infectious diseases and non-communicable diseases, are rarely explored.

Reading the text truly feels as a refresher, compared to reading manuscripts with lengthy and too many details. In general, the authors have succeeded in stripping the non-essential elements and remain to the point. The procedure for systematic review was explained clearly and adhered to the standard. From the screening and identification, finally, no record/study was found to be eligible. Therefore the authors point to the inexistence of evidence between CL and skin cancer, in the published literature.

Of note, I would like to express my appreciation for this 'negative' result publication. More often than not, journals are reluctant to publish manuscripts with non-positive or non-significant results. The fact that this systematic review yielded no suitable paper would actually help to design further research questions or designs to answer this knowledge gap. In fact, this paper can serve as an example of justification on why studying this topic is important - it shows that evidence is very limited. For any epidemiological study, or maybe all studies, this literature review step is crucial and I commend again the authors and the journal for the work done.

Now more specifically, I do have some comments that I hope will be useful for the authors:

- The introduction, albeit concise, lack a bit the depth of the spectrum of cutaneous leishmaniasis, or even the critical detail of CL being a parasitic protozoan disease. CL can manifest locally, as a single lesion, or disseminated and complicated, or even the mucocutaneous forms. From Table 1 (search terms) we could glean that the authors did cover all forms of CL during the search, but for

readers not too familiar with CL it is perhaps useful to add one or two sentences that reflect the complexity of CL.

- Related to that, even though no record is included, I wonder if in the pathophysiological pathways linking CL and skin cancer (Table 2) whether the different clinical manifestations could play a role. Furthermore, at least the existing evidence can be elaborated as per the origin of the case reports/suspicion (e.g Old World vs New World).
- In the Methods section, in the first paragraph 'Protocol and Registration' - the last sentence about PRISMA guidelines is citing the figure of the paper itself. Although this is not strictly incorrect, especially with FigShare citeable characteristics, another reference (e.g Mohler, Cochrane etc) is also necessary.
- Did the authors also screen the reference list from the full-text articles or contact research groups working on the issue? To be fair, indeed this may not yield much addition, but for a systematic review I find it to be important to ensure that all information sources have been exhausted.
- In results, although the 6 full text articles were considered non-eligible to be included in the synthesis, it will be informative to understand more about them: are they case reports reporting a single patient? I know that as they are not filling inclusion criteria there is no need to elaborate, but as a curious reader, I am wondering why some are included in Table 2 (Kopterides, Schwing) and some are not.
- In terms of discussion and conclusion, the straightforward conclusion that CL and skin cancer association is understudied is valid. However, I think it will be worthwhile to expand a bit more on the recommendations for future research, and not just broadly in terms of 'enabling the development of pragmatic tools to help and guide early diagnosis or prevention of skin cancer among survivors of CL'. As the authors have stated, the double burden of diseases is important in LMIC, so this paper should also serve as a call to increase awareness in the context where the diagnosis and treatment are limited for patients with either condition.

Looking forward to seeing the next version and again thank you to the authors' team for the attention to the neglected yet intriguing aspect of CL.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Not applicable

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: I am a medical doctor with advanced training in epidemiology, public health and tropical medicines (MD, DTMH, MPH, PhD). My expertise is on leishmaniasis, neglected diseases and access to medicines.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 02 August 2019

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Ibrahim Khalifeh

Department of Pathology and Laboratory Medicine, American University of Beirut Medical Center, Beirut, Lebanon

The manuscript entitled “Is there an association between cutaneous leishmaniasis and skin cancer? A systematic review” studied the potential correlation between cutaneous leishmaniasis (CL) and skin cancer. The aim of this review is to study the link between these two diseases, which has not been well elucidated before. The manuscript is clear, concise and well written.

In the Introduction, authors covered both diseases succinctly, and enlighten the need of new studies correlating them.

The results covered around 1,400 studies without a clear identification of an association between CL and skin cancer. Authors summarized reports with relevant evidence about the correlation between these two diseases. Thus, presentation of a high number of studies along with no studies providing a clear association between CL and skin cancer is worth investigating, and sheds light on the necessity of new approaches for a better guidance and diagnosis.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Yes

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.
