SYSTEMATIC REVIEW

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

Rodrigo M. Carrillo-Larco, J. Gonzalo Acevedo-Rodriguez, Carlos Altez-Fernandez, Karol Ortiz-Acha, Cesar Ugarte-Gil

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

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; registered on 16/10/18.
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)

Author roles: Carrillo-Larco RM: Conceptualization, Formal Analysis, Investigation, Methodology, Writing – Original Draft Preparation, Writing – Review & Editing; Acevedo-Rodriguez JG: Formal Analysis, Investigation, Writing – Review & Editing; Altez-Fernandez C: Investigation, Methodology, Writing – Review & Editing; Ortiz-Acha K: Investigation, Methodology, Writing – Review & Editing; Ugarte-Gil C: Conceptualization, Investigation, Methodology, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: R.M.C.-L. has been supported by a Strategic Award, Wellcome Trust-Imperial College Centre for Global Health Research (100693), and Imperial College London Wellcome Trust Institutional Strategic Support Fund [Global Health Clinical Research Training Fellowship] (294834 ISSF ICL). R.M.C.-L. is supported by a Wellcome Trust International Training Fellowship (214185).

Copyright: © 2019 Carrillo-Larco RM et al. This is an open access article distributed under the terms of the Creative Commons Attribution Licence, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Carrillo-Larco RM, Acevedo-Rodriguez JG, Altez-Fernandez C et al. Is there an association between cutaneous leishmaniasis and skin cancer? A systematic review [version 1; peer review: 1 approved] Wellcome Open Research 2019, 4:110 (https://doi.org/10.12688/wellcomeopenres.15367.1)

First published: 23 Jul 2019, 4:110 (https://doi.org/10.12688/wellcomeopenres.15367.1)
**Introduction**

Globally, non-melanoma skin cancer was among the top ten malignancies with the highest incidence in 2016. A key driver of this high incidence is the aging of the population. 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 illnesses. 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 cancer.

Despite the pathophysiological background and reviews which summarized case reports, 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). The work and reporting adhered to the PRISMA guidelines.

**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. 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 (three through Ovid), Scopus and Web of Science. The search was conducted from inception to December 15, 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. 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); discrepancies were solved by consensus among the reviewers. We did not systematically search grey literature, yet we argue 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.

**Results**

**Study selection**

As presented in Figure 1, 1,429 titles and abstracts were screened, and six 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, 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, along with solid physiopathology pathways (Table 2), 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>
<thead>
<tr>
<th>Engine</th>
<th>Combined Search Terms</th>
</tr>
</thead>
</table>
| Ovid, including Embase, Medline and Global Health | 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$.mp.  
12. skin neoplasm$.mp.  
13. (basal ADJ0 cell ADJ0 carcinoma$1) OR (basal ADJ0 cell ADJ0 neoplasm$1) OR (basal ADJ0 cell ADJ0 cancer$1)  
14. (squamous ADJ0 cell ADJ0 carcinoma$1) OR (squamous ADJ0 cell ADJ0 neoplasm$1) OR (squamous ADJ0 cell ADJ0 cancer$1)  
15. (epidermoid ADJ0 carcinoma$1) OR (epidermoid ADJ0 cell ADJ0 neoplasm$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 neoplasm*)) OR (ALL((basal W/O cell W/O carcinoma*) OR (basal W/O cell W/O neoplasm*) OR (basal W/O cell W/O cancer*))))) OR (ALL((squamous W/O cell W/O carcinoma*) OR (squamous W/O cell W/O neoplasm*) OR (squamous W/O cell W/O cancer*))))) OR (ALL((epidermoid W/O carcinoma*) OR (epidermoid W/O cell W/O neoplasm*) OR (epidermoid W/O cell W/O cancer*)))) NOT DBCOLL(medl) 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 neoplasm*)) OR (TS=((basal W/O cell W/O carcinoma*) OR (basal W/O cell W/O neoplasm*) OR (basal W/O cell W/O cancer*))))) OR (TS=((squamous W/O cell W/O carcinoma*) OR (squamous W/O cell W/O neoplasm*) OR (squamous W/O cell W/O cancer*))))) OR (TS=((epidermoid W/O carcinoma*) OR (epidermoid W/O cell W/O neoplasm*) OR (epidermoid W/O cell W/O cancer*)))) AND DOCUMENT TYPES: (Article) |
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.


Basal cell carcinoma arising in scars of old CL lesions (i.e., dysplastic changes). Scars and sun exposure are risk factors for malignancies.


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 et al., 1988).


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.

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

<table>
<thead>
<tr>
<th>Reference</th>
<th>Proposed physiopathology pathway(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwing A, Pomares C, Majoar A, Boyer L, Marty P, Michel G. Leishmania infection: Misdiagnosis as cancer and tumor-promoting potential. Acta Trop. 2018. pii: S0001-706X(18)31322-6.</td>
<td>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.</td>
</tr>
<tr>
<td>Kargi E, Güngör E, Aslan G, Erdogan B. Epidermoid carcinoma in cutaneous leishmaniasis scar. Ann Plast Surg. 2001;46(6):657-8.</td>
<td>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 et al., 1988).</td>
</tr>
<tr>
<td>Suster S, Ronnen M. Basal cell carcinoma arising in a Leishmania scar. Int J Dermatol. 1988;27(3):175-6.</td>
<td>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.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reference</th>
<th>Proposed physiopathology pathway(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwing A, Pomares C, Majoar A, Boyer L, Marty P, Michel G. Leishmania infection: Misdiagnosis as cancer and tumor-promoting potential. Acta Trop. 2018. pii: S0001-706X(18)31322-6.</td>
<td>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.</td>
</tr>
<tr>
<td>Kargi E, Güngör E, Aslan G, Erdogan B. Epidermoid carcinoma in cutaneous leishmaniasis scar. Ann Plast Surg. 2001;46(6):657-8.</td>
<td>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 et al., 1988).</td>
</tr>
<tr>
<td>Suster S, Ronnen M. Basal cell carcinoma arising in a Leishmania scar. Int J Dermatol. 1988;27(3):175-6.</td>
<td>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.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reference</th>
<th>Proposed physiopathology pathway(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwing A, Pomares C, Majoar A, Boyer L, Marty P, Michel G. Leishmania infection: Misdiagnosis as cancer and tumor-promoting potential. Acta Trop. 2018. pii: S0001-706X(18)31322-6.</td>
<td>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.</td>
</tr>
<tr>
<td>Kargi E, Güngör E, Aslan G, Erdogan B. Epidermoid carcinoma in cutaneous leishmaniasis scar. Ann Plast Surg. 2001;46(6):657-8.</td>
<td>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 et al., 1988).</td>
</tr>
<tr>
<td>Suster S, Ronnen M. Basal cell carcinoma arising in a Leishmania scar. Int J Dermatol. 1988;27(3):175-6.</td>
<td>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.</td>
</tr>
</tbody>
</table>
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


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

Grant information

R.M.C-.L. has been supported by a Strategic Award, Wellcome Trust-Imperial College Centre for Global Health Research (100693), and Imperial College London Wellcome Trust Institutional Strategic Support Fund [Global Health Clinical Research Training Fellowship] (294834 ISSF ICL). R.M.C-.L. is supported by a Wellcome Trust International Training Fellowship (214185).

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

References


Open Peer Review

Current Peer Review Status: ✓

Version 1

Reviewer Report 02 August 2019

https://doi.org/10.21956/wellcomeopenres.16787.r36033

© 2019 Khalifeh I. This is an open access peer review report distributed under the terms of the Creative Commons Attribution Licence, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

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.