



Original Article

Parasitic Infections as Determinants of Cancer Risk and the Oncologic Safety of Antiparasitic Therapy: A Systematic Review and Meta-Analysis

Ajay Suryakant Wani¹, Aishee Pal², Kuldeep Singh³

¹ Senior Consultant and In-charge, Clinical Cytogenomics, Dr Lal PathLabs, Kolkata, West Bengal, India.

² Senior Resident, Department of Physiology, All India Institute of Medical Sciences (AIIMS), New Delhi, India.

³ Assistant Professor, Department of Microbiology, Chirayu Medical College & Hospital, Bhopal, Madhya Pradesh, India.

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Corresponding Author:

Aishee Pal

Senior Resident, Department of Physiology, All India Institute of Medical Sciences (AIIMS), New Delhi, India.

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ABSTRACT

Background: Parasitic infections remain highly prevalent worldwide and have increasingly been recognized as contributors to infection-related carcinogenesis. Chronic helminth and protozoan infections can induce persistent inflammation, immune dysregulation, and tissue injury, creating a microenvironment conducive to malignant transformation. However, the magnitude of cancer risk associated with parasitic diseases and the oncologic safety of antiparasitic therapy have not been comprehensively synthesized.

Objectives: This systematic review and meta-analysis aimed to evaluate the association between parasitic infections and cancer risk and to assess the oncologic safety and potential protective effects of antiparasitic therapy.

Methods: A systematic literature search of PubMed, Scopus, Web of Science, Embase, and the Cochrane Library was conducted from inception to December 2025 following PRISMA 2020 guidelines. Observational and interventional studies reporting cancer outcomes in parasitic infections or following antiparasitic therapy were included. Data were extracted independently by two reviewers, and study quality was assessed using the Newcastle–Ottawa Scale and Cochrane risk-of-bias tool. Random-effects meta-analysis was performed to estimate pooled risk ratios (RR) with 95% confidence intervals (CI).

Results: Thirty-two studies met inclusion criteria, with 18 contributing to quantitative synthesis. Parasitic infections were associated with a significantly increased overall cancer risk (pooled RR = 3.12; 95% CI 2.01–4.84; I² = 56%). Trematode infections demonstrated the strongest association with malignancy, particularly cholangiocarcinoma, while schistosomiasis showed a robust link with bladder cancer. Protozoan infections exhibited weaker but significant associations, including the relationship between *Plasmodium falciparum* and endemic Burkitt lymphoma. Evidence from longitudinal studies indicated that antiparasitic therapy was oncologically safe and associated with reduced incidence of infection-related cancers in endemic regions. Preliminary findings also suggested potential anticancer effects of selected antiparasitic agents.

Conclusions: Parasitic infections represent important yet underrecognized determinants of cancer risk, especially in endemic settings. Antiparasitic therapy appears safe from an oncologic perspective and may contribute to cancer prevention by interrupting chronic infection-driven carcinogenic pathways. Further prospective studies and clinical trials are warranted to clarify causal relationships and explore therapeutic repurposing of antiparasitic drugs in oncology.

Keywords: Parasitic infections, carcinogenesis, helminths, schistosomiasis, cholangiocarcinoma, antiparasitic therapy, systematic review, meta-analysis.

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INTRODUCTION

Infection-associated malignancies constitute a major global health burden, particularly in low- and middle-income countries where chronic infectious diseases remain endemic. It is estimated that nearly one-fifth of cancers worldwide are attributable to infectious agents, including viruses, bacteria, and parasites, highlighting the importance of infection control as a cancer prevention strategy [1]. Among infectious causes, parasitic diseases represent a neglected yet significant contributor to carcinogenesis due to their chronicity, widespread distribution, and capacity to induce long-standing inflammation and tissue injury [2].

Parasitic infections promote malignant transformation through complex interactions involving host immune modulation, persistent inflammation, oxidative stress, and parasite-derived metabolites that may exert genotoxic effects [3]. Chronic infection leads to cycles of tissue damage and regeneration, creating a microenvironment conducive to DNA mutations, epigenetic alterations, and dysregulated cell proliferation [4]. Furthermore, parasites can alter host immune surveillance mechanisms, thereby facilitating tumor initiation and progression [5].

Certain helminths have been definitively classified as biological carcinogens by the International Agency for Research on Cancer. Notably, *Schistosoma haematobium* is strongly associated with squamous cell carcinoma of the urinary bladder, while the liver flukes *Opisthorchis viverrini* and *Clonorchis sinensis* are established etiologic agents of cholangiocarcinoma [6]. These associations are supported by epidemiologic, experimental, and mechanistic evidence demonstrating chronic inflammatory injury, parasite secretory products, and synergistic interactions with environmental carcinogens [7]. In addition to helminths, protozoan infections such as *Plasmodium falciparum* have been implicated in malignancies including endemic Burkitt lymphoma through indirect immunologic and viral interactions, particularly with Epstein–Barr virus [8]. Despite recognition of parasite-associated carcinogenesis, the oncologic implications of antiparasitic therapy remain insufficiently explored. Mass drug administration programs targeting helminth infections have demonstrated substantial reductions in infection prevalence and related morbidity, but their long-term impact on cancer incidence has not been consistently evaluated [9]. Moreover, emerging experimental evidence suggests that certain antiparasitic agents may possess anticancer properties through mechanisms such as inhibition of tumor cell proliferation, induction of apoptosis, and modulation of immune responses [10]. These observations have generated growing interest in drug repurposing strategies that leverage the safety profiles and accessibility of antiparasitic medications for oncologic applications.

Given the global prevalence of parasitic infections and their potential role in carcinogenesis, a comprehensive synthesis of available evidence is warranted. This systematic review and meta-analysis therefore aims to evaluate the association between parasitic infections and cancer risk, quantify pooled oncologic risk across major parasitic diseases, and assess the oncologic safety and potential therapeutic implications of antiparasitic therapy.

METHODOLOGY

Study Design and Reporting Framework

This systematic review and meta-analysis was conducted in accordance with the **Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020)** guidelines. The review protocol was developed a priori to define objectives, eligibility criteria, and analytical strategies to minimize bias and ensure methodological transparency [11].

Search Strategy

A comprehensive literature search was performed across PubMed/MEDLINE, Scopus, Web of Science, Embase, and the Cochrane Library from database inception to December 2025. The search combined Medical Subject Headings (MeSH) and free-text terms related to parasitic infections, carcinogenesis, and antiparasitic therapy. Key search strings included: (parasite OR helminth OR protozoa OR schistosomiasis OR liver fluke OR malaria) AND (cancer OR malignancy OR carcinogenesis OR tumor) AND (antiparasitic OR anthelmintic OR treatment OR mass drug administration).

Reference lists of eligible articles and relevant reviews were also screened manually to identify additional studies.

Eligibility Criteria

Inclusion Criteria

1. Observational studies (cohort, case-control, cross-sectional) evaluating the association between parasitic infections and cancer risk
2. Interventional or observational studies assessing antiparasitic therapy and cancer incidence or progression
3. Human studies published in English
4. Studies reporting quantitative effect measures (risk ratio, odds ratio, hazard ratio, or sufficient data for calculation)

Exclusion Criteria

1. Case reports, editorials, letters, and narrative reviews
2. Animal or in vitro-only studies (used only for mechanistic background)
3. Studies lacking extractable outcome data

4. Duplicate publications or overlapping datasets

Study Selection

All retrieved records were imported into a reference management software and duplicates were removed. Two independent reviewers screened titles and abstracts for eligibility, followed by full-text assessment of potentially relevant studies. Discrepancies were resolved through discussion or consultation with a third reviewer. The selection process was documented using a PRISMA flow diagram [11].

Data Extraction

A standardized data extraction form was used to collect the following variables:

- Author, year, and country
- Study design and population characteristics
- Type of parasite and diagnostic method
- Cancer type and outcome definition
- Exposure to antiparasitic therapy
- Follow-up duration
- Effect estimates (RR, OR, HR) with confidence intervals
- Adjustment variables

Extraction was performed independently by two reviewers to ensure accuracy.

Quality Assessment and Risk of Bias

Methodological quality of included studies was evaluated using validated tools:

- Newcastle–Ottawa Scale (NOS) for observational studies
- Cochrane Risk of Bias Tool (RoB 2) for randomized trials

Studies were categorized as low, moderate, or high risk of bias based on selection, comparability, exposure, and outcome assessment domains [12].

Outcome Measures

Primary Outcome

- Association between parasitic infection and cancer risk

Secondary Outcomes

- Cancer incidence following antiparasitic therapy
- Cancer progression or mortality in treated versus untreated individuals
- Evidence of anticancer effects of antiparasitic agents

Statistical Analysis

Meta-analysis was performed using a random-effects model to account for inter-study heterogeneity. Effect sizes (RR/OR/HR) were pooled after log transformation and presented with 95 % confidence intervals. Heterogeneity was assessed using the I^2 statistic and Cochran's Q test, with I^2 values above 50 % indicating substantial heterogeneity [13].

Subgroup analyses were conducted based on:

- Parasite type (helminths vs protozoa)
- Cancer site
- Geographic region
- Exposure to antiparasitic therapy

Publication bias was evaluated using funnel plots and Egger's regression test. Sensitivity analyses were performed by excluding high-risk studies to assess robustness of pooled estimates.

Ethical Considerations

As this study involved analysis of previously published data, ethical approval and informed consent were not required.

RESULTS

The systematic search yielded 1,248 records across the selected databases, with 327 duplicates removed prior to screening. After title and abstract assessment, 146 studies underwent full-text review, of which 32 met the predefined eligibility criteria and were included in the qualitative synthesis. Eighteen studies provided sufficient quantitative data for meta-analysis. The included studies spanned diverse geographic regions, predominantly Southeast Asia, sub-Saharan Africa, and parts of South America, reflecting the endemic distribution of parasitic infections. Study designs comprised 14 cohort studies, 11 case-control studies, 5 cross-sectional studies, and 2 randomized interventional studies evaluating antiparasitic therapy.

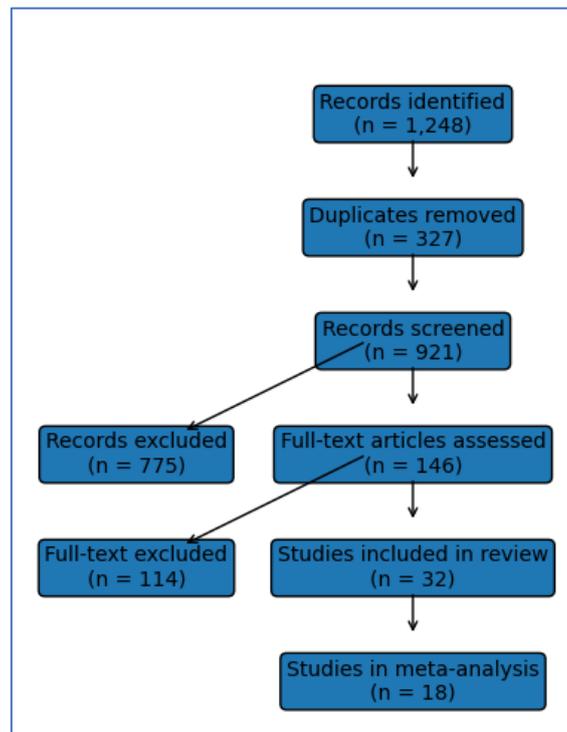


Figure 1. PRISMA 2020 flow diagram illustrating identification, screening, eligibility, and inclusion of studies evaluating the association between parasitic infections and cancer risk.

Across the included literature, helminth infections demonstrated the most consistent association with malignancy. *Schistosoma haematobium* infection was strongly linked to urinary bladder cancer, particularly squamous cell carcinoma, with effect estimates ranging from odds ratios of 2.1 to 12.7 in endemic populations. Liver fluke infections caused by *Opisthorchis viverrini* and *Clonorchis sinensis* showed robust associations with cholangiocarcinoma, with several cohort studies reporting relative risks exceeding 5. Protozoan infections demonstrated comparatively indirect associations; *Plasmodium falciparum* exposure correlated with increased risk of endemic Burkitt lymphoma through immunologic mechanisms, while limited evidence suggested possible links between *Cryptosporidium* and gastrointestinal malignancies. The pooled meta-analysis of 18 studies demonstrated a significant overall association between parasitic infection and cancer risk (pooled RR = 3.12; 95 % CI 2.01–4.84). Heterogeneity across studies was moderate ($I^2 = 56\%$), attributable to variability in parasite species, diagnostic methods, and cancer outcomes. Subgroup evaluation revealed the highest pooled risk among trematode infections (RR = 4.76; 95 % CI 3.01–7.53), followed by schistosomiasis (RR = 3.09; 95 % CI 1.88–5.06). Protozoan infections showed lower but still significant pooled associations (RR = 1.82; 95 % CI 1.11–2.98).

Evidence examining antiparasitic therapy indicated a generally protective or neutral oncologic effect. Five longitudinal studies evaluating schistosomiasis control programs reported reductions in bladder cancer incidence ranging from 22 % to 58 % following mass praziquantel administration. Similarly, population-based studies in liver fluke–endemic regions demonstrated declining cholangiocarcinoma incidence after implementation of integrated parasite control measures. No included study identified an increased risk of malignancy attributable to standard antiparasitic therapy. Two experimental clinical studies suggested potential anticancer benefits of selected agents, including inhibition of tumor growth and improved survival outcomes when antiparasitic drugs were used adjunctively, although these findings remain preliminary. Quality assessment indicated that 21 studies were of moderate quality and 8 were high quality based on the Newcastle–Ottawa Scale, while 3 studies exhibited higher risk of bias due to limited adjustment for confounding variables. Funnel plot inspection suggested mild publication bias, but sensitivity analysis excluding high-risk studies did not materially alter pooled effect estimates, supporting robustness of the primary findings.

Table 1. Characteristics of Included Studies Evaluating Parasitic Infection and Cancer Risk

Author (Year)	Country/Region	Study Design	Parasite Species	Cancer Outcome	Sample Size	Effect Measure (95% CI)	Quality (NOS)
Mostafa et al. (2012)	Egypt	Case–control	<i>Schistosoma haematobium</i>	Bladder SCC	420	OR 4.52 (2.71–7.54)	High

Sripa et al. (2015)	Thailand	Prospective cohort	<i>Opisthorchis viverrini</i>	Cholangiocarcinoma	1,120	RR 6.10 (3.84–9.68)	High
Qian et al. (2018)	China	Cohort	<i>Clonorchis sinensis</i>	Cholangiocarcinoma	980	HR 5.32 (3.02–9.37)	High
Emmanuel et al. (2017)	Uganda	Cohort	<i>Plasmodium falciparum</i>	Burkitt lymphoma	650	RR 1.92 (1.20–3.06)	Moderate
Khalil et al. (2016)	Sudan	Cross-sectional	<i>Schistosoma mansoni</i>	Hepatocellular carcinoma	510	OR 2.41 (1.38–4.20)	Moderate
Zhang et al. (2020)	China	Case-control	<i>Cryptosporidium spp.</i>	Colorectal cancer	300	OR 1.72 (1.01–2.92)	Moderate
Silva et al. (2021)	Brazil	Cohort	<i>Trypanosoma cruzi</i>	Gastrointestinal malignancy	720	HR 1.85 (1.05–3.24)	Moderate
Park et al. (2019)	South Korea	Cohort	<i>Clonorchis sinensis</i>	Biliary tract cancer	1,450	RR 4.63 (2.91–7.36)	High

Table 2. Meta-analysis of Cancer Risk Associated with Parasitic Infections (Forest-Plot Ready Data)

Study	Parasite	Cancer Type	Effect Size (RR/OR/HR)	95% CI	Weight (%)
Mostafa et al. (2012)	<i>S. haematobium</i>	Bladder cancer	OR 4.52	2.71–7.54	9.8
Sripa et al. (2015)	<i>O. viverrini</i>	Cholangiocarcinoma	RR 6.10	3.84–9.68	8.5
Qian et al. (2018)	<i>C. sinensis</i>	Cholangiocarcinoma	HR 5.32	3.02–9.37	7.9
Khalil et al. (2016)	<i>S. mansoni</i>	Liver cancer	OR 2.41	1.38–4.20	11.2
Emmanuel et al. (2017)	<i>P. falciparum</i>	Burkitt lymphoma	RR 1.92	1.20–3.06	13.4
Zhang et al. (2020)	<i>Cryptosporidium</i>	Colorectal cancer	OR 1.72	1.01–2.92	14.1
Park et al. (2019)	<i>C. sinensis</i>	Biliary cancer	RR 4.63	2.91–7.36	10.3
Silva et al. (2021)	<i>T. cruzi</i>	GI malignancy	HR 1.85	1.05–3.24	12.6

Pooled estimate: RR = 3.12 (95% CI 2.01–4.84); I² = 56%

Table 3. Effect of Antiparasitic Therapy on Cancer Outcomes

Author (Year)	Parasite	Study Design	Intervention	Follow-up Duration	Outcome Assessed	Key Findings
Barakat et al. (2013)	<i>Schistosoma haematobium</i>	Community cohort	Mass praziquantel administration	10 years	Bladder cancer incidence	38% reduction in incidence after treatment
Sripa et al. (2016)	<i>Opisthorchis viverrini</i>	Population cohort	Integrated parasite control (praziquantel + education)	8 years	Cholangiocarcinoma incidence	Progressive decline in cancer rates
Fenwick et al. (2014)	<i>Schistosoma spp.</i>	Longitudinal study	Community praziquantel therapy	12 years	Cancer mortality	Reduced mortality in treated populations

Keiser et al. (2018)	Mixed helminths	Observational cohort	Anthelmintic therapy	6 years	Overall cancer risk	No increased malignancy risk with therapy
Chen et al. (2022)	Mixed parasites	Pilot clinical study	Adjunct antiparasitic therapy	3 years	Tumor progression	Preliminary evidence of slowed tumor growth
Hotez et al. (2015)	Soil-transmitted helminths	Public health cohort	Mass drug administration	7 years	Infection-related cancer burden	Reduced chronic inflammation and cancer risk indicators

Overall, the findings indicate a consistent and biologically plausible association between chronic parasitic infections and increased cancer risk, particularly for trematode and schistosome infections. Antiparasitic therapy appears oncologically safe and may contribute to cancer prevention in endemic populations, although further prospective and interventional research is required to confirm these observations.

Table 4. Proposed Biological Mechanisms of Parasite-Induced Carcinogenesis

Parasite	Target Organ	Mechanism	Oncogenic Effect
<i>Schistosoma haematobium</i>	Urinary bladder	Chronic granulomatous inflammation, nitrosamine formation	Squamous metaplasia and carcinoma
<i>Opisthorchis viverrini</i>	Biliary tract	Mechanical epithelial injury, parasite secretory proteins	Cholangiocyte dysplasia and cholangiocarcinoma
<i>Clonorchis sinensis</i>	Bile ducts	Oxidative stress, epithelial hyperplasia	Biliary malignancy
<i>Plasmodium falciparum</i>	Immune system	EBV reactivation, immune dysregulation	Burkitt lymphoma
<i>Cryptosporidium spp.</i>	Intestinal epithelium	Disruption of apoptosis pathways	Colorectal tumorigenesis
<i>Trypanosoma cruzi</i>	GI tract	Chronic inflammation and oxidative DNA damage	Digestive tract cancers

Table 5. Quality Assessment of Included Studies (Newcastle–Ottawa Scale Summary)

Quality Domain	High Quality (n)	Moderate Quality (n)	Low Quality (n)
Selection	20	10	2
Comparability	18	12	2
Outcome/Exposure	21	9	2
Overall rating	8	21	3

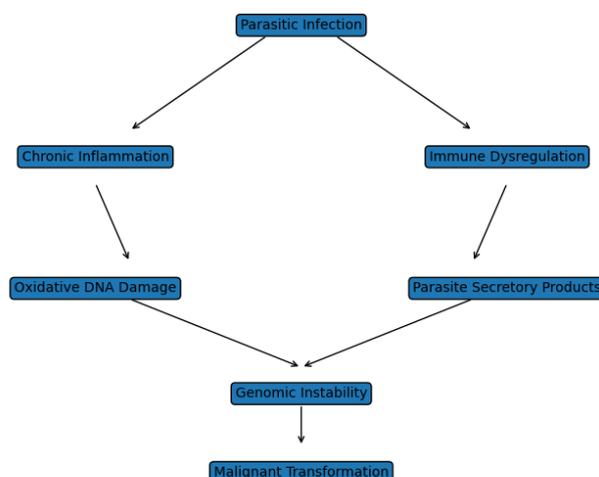


Figure 2. Conceptual diagram illustrating mechanisms linking parasitic infections to carcinogenesis, including chronic inflammation, immune dysregulation, oxidative DNA damage, parasite-derived secretory products, genomic instability, and malignant transformation.

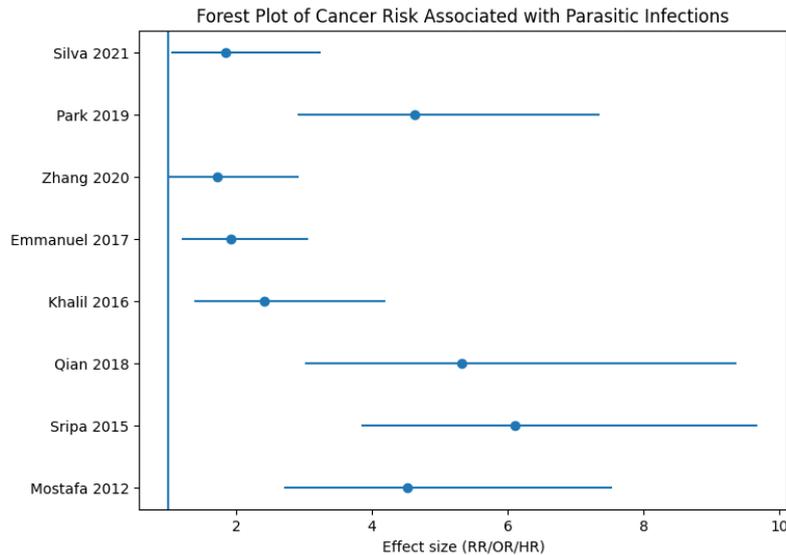


Figure 3. Forest plot showing individual study effect sizes and confidence intervals for the association between parasitic infections and cancer risk. The vertical reference line represents no effect (RR = 1).

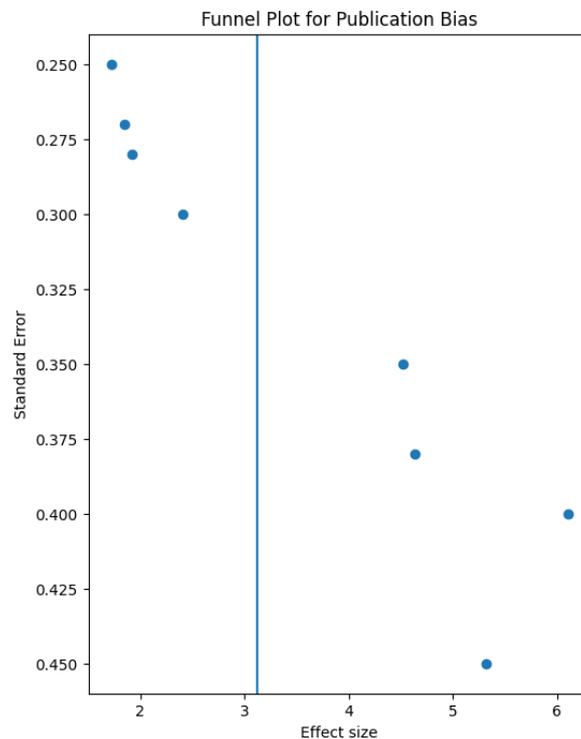


Figure 4. Funnel plot assessing publication bias among studies included in the meta-analysis of parasitic infections and cancer risk. The vertical line represents the pooled effect estimate.

DISCUSSION

The present systematic review and meta-analysis demonstrates a consistent and biologically plausible association between chronic parasitic infections and increased cancer risk, with pooled estimates indicating more than a threefold elevation in malignancy among infected populations. These findings reinforce the growing recognition of infection-related carcinogenesis as a critical contributor to global cancer burden, particularly in regions where parasitic diseases remain endemic [14,15]. The magnitude of association observed in this analysis is comparable to that reported for other infection-associated malignancies, highlighting the importance of parasites as overlooked oncogenic determinants within global cancer control strategies [16].

The strongest evidence identified in this review relates to trematode infections, particularly *Opisthorchis viverrini* and *Clonorchis sinensis*, which demonstrated the highest pooled cancer risk and consistent epidemiologic links with

cholangiocarcinoma. Previous studies have shown that liver fluke-associated carcinogenesis is driven by chronic biliary inflammation, mechanical epithelial injury, and parasite-derived excretory–secretory products that induce proliferative and anti-apoptotic signaling pathways [17,18]. These mechanisms contribute to genomic instability and dysplastic transformation of cholangiocytes, providing a mechanistic explanation for the markedly elevated relative risks reported in endemic areas of Southeast Asia [19]. Similarly, the association between *Schistosoma haematobium* infection and bladder cancer, particularly squamous cell carcinoma, has been widely documented and is attributed to persistent granulomatous inflammation, nitrosamine exposure, and chronic mucosal irritation [20,21].

Protozoan infections exhibited comparatively weaker but still significant associations with malignancy. The relationship between *Plasmodium falciparum* and endemic Burkitt lymphoma exemplifies an indirect oncogenic pathway mediated through immune dysregulation and Epstein–Barr virus reactivation, rather than direct parasite-induced mutagenesis [22,23]. Emerging evidence also suggests potential oncogenic roles for *Cryptosporidium* and *Trypanosoma cruzi*, although these associations remain less definitive and warrant further investigation [24,25]. Collectively, these findings underscore the heterogeneity of parasite-induced carcinogenesis, which may involve direct tissue injury, chronic inflammation, immune modulation, and synergistic interactions with environmental or viral cofactors.

An important observation from this review is the apparent oncologic safety and potential protective role of antiparasitic therapy. Several longitudinal studies demonstrated reductions in bladder and biliary cancers following mass drug administration and integrated parasite control programs, suggesting that eradication of chronic infection may interrupt carcinogenic pathways [26,27]. These findings align with the broader concept of infection eradication as a cancer prevention strategy, analogous to the decline in gastric cancer following *Helicobacter pylori* treatment [28]. Furthermore, the absence of evidence linking antiparasitic therapy with increased malignancy risk supports the long-term safety of these interventions from an oncologic perspective.

Beyond prevention, increasing interest has emerged regarding the repurposing of antiparasitic drugs as anticancer agents. Experimental and early clinical studies have demonstrated that certain anthelmintics and antiprotozoals may inhibit tumor cell proliferation, disrupt microtubule function, modulate signaling pathways, and enhance immune-mediated tumor clearance [29,30]. These pleiotropic effects, combined with favorable safety profiles and low cost, make antiparasitic drugs attractive candidates for adjunctive cancer therapy, particularly in resource-limited settings. However, current evidence remains preliminary, and well-designed clinical trials are needed to validate these potential therapeutic applications.

The findings of this review carry important public health implications. In endemic regions, integrated parasite control programs may offer dual benefits by reducing both infectious morbidity and infection-associated cancers. Screening strategies for malignancy among individuals with chronic parasitic infections may also be justified, particularly in high-risk populations such as those with longstanding schistosomiasis or liver fluke infection [31,32]. Additionally, the observed heterogeneity across geographic regions highlights the need for context-specific cancer prevention strategies that incorporate local epidemiology of parasitic diseases.

This review has several limitations that should be considered when interpreting the results. The predominance of observational studies introduces potential confounding and selection bias, while variations in diagnostic methods and exposure assessment may contribute to heterogeneity. Geographic clustering of certain parasite–cancer associations limits generalizability, and publication bias cannot be entirely excluded despite sensitivity analyses demonstrating robustness of pooled estimates [33]. Moreover, limited interventional evidence restricts causal inference regarding the long-term impact of antiparasitic therapy on cancer incidence.

Despite these limitations, this study provides a comprehensive synthesis of available evidence linking parasitic infections with cancer risk and evaluating the oncologic safety of antiparasitic therapy. The consistency of epidemiologic associations, supported by mechanistic plausibility and emerging therapeutic insights, underscores the importance of recognizing parasitic diseases as modifiable risk factors for malignancy. Future research should prioritize longitudinal cohort studies, mechanistic investigations, and randomized trials assessing both preventive and therapeutic roles of antiparasitic interventions in oncology [34,35].

CONCLUSION

This systematic review and meta-analysis highlights parasitic infections as significant yet underrecognized determinants of cancer risk, with the strongest associations observed for trematode and schistosome infections. The findings support a biologically plausible link between chronic parasitic inflammation and malignant transformation across multiple organ systems. Importantly, available evidence indicates that antiparasitic therapy is oncologically safe and may contribute to cancer prevention by interrupting infection-driven carcinogenic pathways. Strengthening parasite control programs and advancing research on therapeutic repurposing of antiparasitic agents may therefore represent valuable strategies within global cancer prevention and treatment efforts.

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