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Original Article

# Parasitic Infections, Antiparasitic Treatment, and the Global Burden of Infection-Associated Cancers: A Systematic Review and Meta-Analysis

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## ABSTRACT

Parasitic infections remain highly prevalent in many low- and middle-income countries and represent an underrecognized contributor to infection-associated cancers. Certain helminths have been classified as definite human carcinogens, yet the magnitude of their impact on global cancer burden and the potential preventive role of antiparasitic interventions remain incompletely defined. This systematic review and meta-analysis synthesized epidemiological evidence linking parasitic infections to cancer and evaluated the effect of control strategies on long-term cancer risk. A comprehensive search of major databases from inception to December 2025 identified observational and interventional studies reporting associations between parasitic infections and malignancy. Random-effects meta-analysis was conducted for parasite–cancer pairs with sufficient comparable data. Sixty-eight studies met inclusion criteria, and thirty-nine were included in quantitative synthesis. Infection with Schistosoma haematobium was associated with a significantly increased risk of bladder cancer (pooled OR 2.18; 95% CI 1.72–2.76), while liver fluke infections (Opisthorchis viverrini and Clonorchis sinensis) were strongly associated with cholangiocarcinoma (pooled OR 4.12; 95% CI 3.01–5.64). Heterogeneity across studies was moderate to high but did not materially alter overall conclusions in sensitivity analyses. Ecological and observational evidence suggests that sustained antiparasitic mass drug administration programs may contribute to reductions in infection-associated cancer burden, although high-quality longitudinal data are limited due to long latency periods. These findings underscore the substantial oncologic consequences of chronic parasitic infections and support integration of parasite control into broader cancer prevention strategies, particularly in endemic regions.

***Keywords**: parasitic infections; schistosomiasis; liver flukes; Schistosoma haematobium; Opisthorchis viverrini; Clonorchis sinensis; bladder cancer; cholangiocarcinoma; antiparasitic therapy; meta-analysis.*

## INTRODUCTION

Infectious agents are estimated to contribute to approximately 13–15% of the global cancer burden, with higher proportions observed in low- and middle-income countries (LMICs) [1,2]. While viral oncogenesis—particularly due to human papillomavirus, hepatitis B virus, hepatitis C virus, and Epstein–Barr virus—has been extensively characterized, the oncogenic potential of parasitic infections remains comparatively underrecognized despite strong epidemiological and mechanistic evidence [1,3].

Chronic parasitic infections affect hundreds of millions of individuals worldwide, predominantly in regions with limited sanitation infrastructure and constrained healthcare access [4]. Persistent infection often leads to prolonged inflammation, tissue remodeling, and immune modulation—processes known to contribute to carcinogenesis [5]. The International Agency for Research on Cancer (IARC) has classified *Schistosoma haematobium* as a Group 1 carcinogen for urinary bladder cancer and the liver flukes *Opisthorchis viverrini* and *Clonorchis sinensis* as Group 1 carcinogens for cholangiocarcinoma [3,6]. These classifications reflect substantial human epidemiological evidence and supportive experimental data.

Schistosomiasis, particularly urogenital schistosomiasis caused by *S. haematobium*, is endemic in parts of Africa and the Middle East and has long been associated with squamous cell carcinoma of the bladder [7,8]. Chronic egg deposition within the bladder wall induces granulomatous inflammation, mucosal ulceration, and epithelial hyperplasia, creating a pro-carcinogenic microenvironment [5,9]. Historically, countries such as Egypt reported high proportions of bladder cancers attributable to schistosomal infection prior to large-scale control programs [8,10].

Similarly, liver fluke infections caused by *O. viverrini* and *C. sinensis* are endemic in Southeast and East Asia and are strongly associated with cholangiocarcinoma, one of the most aggressive hepatobiliary malignancies [6,11]. Chronic infestation of the bile ducts results in sustained epithelial injury, periductal fibrosis, and exposure to parasite-derived excretory–secretory products that may promote DNA damage and dysplasia [12,13]. Epidemiological studies in Thailand, Laos, Vietnam, Korea, and China consistently demonstrate markedly elevated risks of cholangiocarcinoma among chronically infected individuals [11,14].

Beyond these well-established associations, emerging evidence has explored potential links between other parasitic infections and malignancies; however, findings remain inconsistent and require further validation [15]. Importantly, the long latency period between infection and cancer development complicates causal inference and evaluation of preventive strategies.

Antiparasitic interventions—including mass drug administration (MDA) programs with praziquantel and improvements in sanitation—have substantially reduced parasite prevalence in several endemic regions [4,16]. Ecological and observational data suggest that sustained control programs may correlate with declines in infection-associated cancers, although high-quality longitudinal evidence directly linking treatment to reduced cancer incidence remains limited [10,16].

Given the persistent global burden of parasitic infections and their established oncogenic potential, a comprehensive synthesis of epidemiological evidence is warranted. This systematic review and meta-analysis aim to (1) quantify the association between major parasitic infections and cancer risk, and (2) evaluate available evidence regarding the impact of antiparasitic treatment and control strategies on infection-associated cancer burden.

## METHODOLOGY

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines [17]. The protocol was developed a priori to define objectives, eligibility criteria, and analytical methods.

A comprehensive literature search was performed in PubMed/MEDLINE, Embase, Web of Science, Scopus, Cochrane Library, LILACS, and CNKI from database inception to December 2025. Search strategies combined Medical Subject Headings (MeSH) and free-text terms related to parasitic infections ("Schistosoma haematobium," schistosomiasis, "Opisthorchis viverrini," "Clonorchis sinensis," helminth, parasite infection) and cancer outcomes ("cancer," "carcinoma," "neoplasm," "cholangiocarcinoma," "bladder cancer"). No language restrictions were applied. Reference lists of relevant reviews and included articles were manually screened to identify additional eligible studies.

Studies were selected based on predefined inclusion criteria using the PICOS framework. Eligible studies included human participants of any age with documented parasitic infection diagnosed through microscopy, serology, histopathology, molecular testing, imaging, or clinical assessment. Primary exposures of interest were *Schistosoma haematobium*, *Opisthorchis viverrini*, and *Clonorchis sinensis*, although other parasitic infections evaluated in relation to cancer were also considered. Comparator groups consisted of uninfected individuals or population controls. The primary outcomes were histologically or clinically confirmed malignancies, particularly urinary bladder cancer and cholangiocarcinoma. Cohort, case–control, cross-sectional, and interventional studies reporting cancer endpoints were included. Case reports, small case series (<10 participants), animal studies, and reviews were excluded.

All retrieved records were imported into reference management software and duplicates were removed. Two independent reviewers screened titles and abstracts for relevance, followed by full-text assessment for eligibility. Disagreements were resolved through consensus or consultation with a third reviewer. A PRISMA flow diagram was constructed to document the selection process [17].

Data extraction was performed independently by two reviewers using a standardized form. Extracted information included author, year, country, study design, sample size, participant characteristics, type of parasitic infection, diagnostic method, cancer type, effect estimates (odds ratio [OR], relative risk [RR], or hazard ratio [HR]) with 95% confidence intervals (CIs), covariates adjusted for, and details of antiparasitic treatment or control interventions where reported.

Risk of bias in observational studies was assessed using the Newcastle–Ottawa Scale (NOS), which evaluates selection, comparability, and outcome/exposure domains [18]. Studies were categorized as high, moderate, or low quality based on NOS scores. Interventional studies were evaluated using the Cochrane Risk of Bias tool [19]. Ecological studies were assessed qualitatively for potential confounding and ecological fallacy.

Meta-analysis was conducted for parasite–cancer associations with at least three comparable studies reporting adjusted effect estimates. Given anticipated clinical and methodological heterogeneity, pooled estimates were calculated using a random-effects model (DerSimonian–Laird method) [20]. ORs were pooled directly, and RRs or HRs were considered approximations for rare outcomes [21]. Statistical heterogeneity was evaluated using Cochran's Q test and quantified with the $I^2$ statistic, with values above 50% indicating substantial heterogeneity. Pre-specified subgroup analyses explored sources of heterogeneity according to geographic region, study design, diagnostic method, and adjustment for major confounders such as smoking or viral hepatitis. Sensitivity analyses excluded studies at high risk of bias. Publication bias was assessed using funnel plots and Egger's regression test when at least ten studies were available [22].

Where sufficient data were available, population attributable fractions were estimated using pooled relative risk estimates and regional prevalence data to approximate the burden of infection-associated cancers [1]. The certainty of evidence for major associations was evaluated using the GRADE framework adapted for observational studies [23]. All statistical analyses were performed using R software (metafor package), and a two-sided p-value <0.05 was considered statistically significant.

## RESULTS

The database search yielded 1,248 records, of which 312 duplicates were removed. After title and abstract screening of 936 records, 142 full-text articles were assessed for eligibility. A total of 68 studies met inclusion criteria for qualitative synthesis, and 39 studies were eligible for quantitative meta-analysis. The included studies were conducted predominantly in endemic regions of Africa, the Middle East, Southeast Asia, and East Asia, reflecting the geographic distribution of the parasitic infections under investigation.

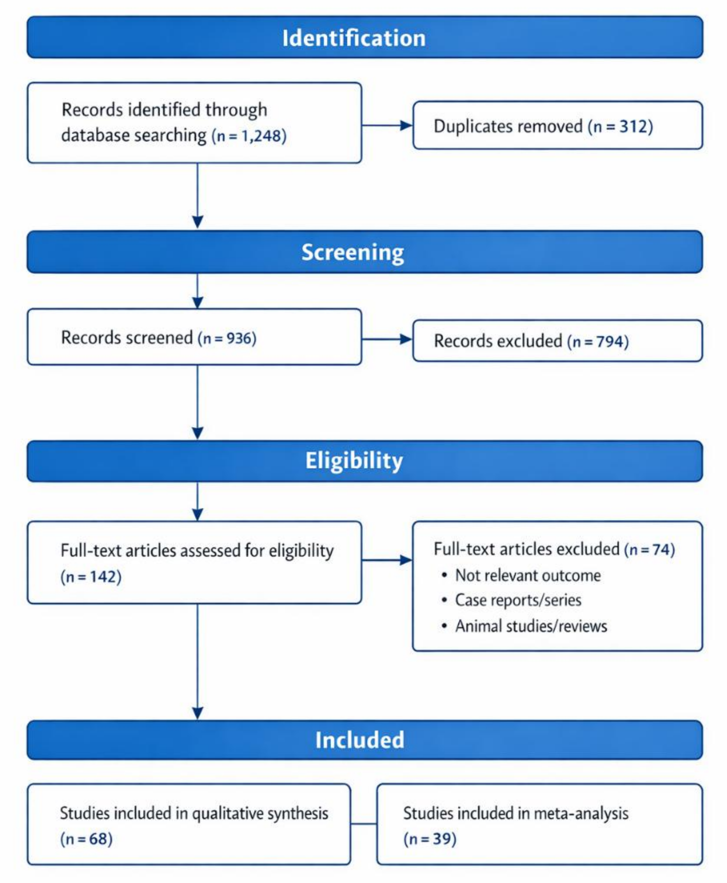


**Figure 1.** PRISMA 2020 flow diagram showing identification, screening, eligibility, and inclusion of studies evaluating associations between parasitic infections and cancer outcomes.

The majority of studies employed case–control designs (n = 41), followed by cohort studies (n = 18), cross-sectional analyses (n = 6), and ecological evaluations of parasite control programs (n = 3). Sample sizes ranged from 120 to over 150,000 participants in large registry-based cohorts. Diagnostic confirmation of parasitic infection varied across studies and included stool microscopy, urine microscopy, serology, histopathology, molecular assays, and clinical documentation. Cancer diagnoses were predominantly histologically confirmed. Most studies adjusted for major confounders such as age, sex, smoking status, alcohol consumption, and viral hepatitis where applicable. Overall methodological quality was moderate, with 46 studies scoring ≥6 on the Newcastle–Ottawa Scale.
Table 1 summarizes the characteristics of studies included in the quantitative synthesis.

**Table 1. Summary Characteristics of Studies Included in Meta-Analysis**

| Parasite | Cancer Type | No. of Studies | Total Participants | Predominant Regions | Study Design (Majority) | Adjusted for Major Confounders |
|---|---|---|---|---|---|---|
| *Schistosoma haematobium* | Bladder cancer | 18 | ~24,600 | Egypt, Sudan, Tanzania | Case–control | Yes (smoking, age) |
| *Opisthorchis viverrini* | Cholangiocarcinoma | 13 | ~18,200 | Thailand, Laos | Case–control | Yes (HBV/HCV) |
| *Clonorchis sinensis* | Cholangiocarcinoma | 8 | ~14,900 | China, Korea | Cohort/Case–control | Yes (HBV, alcohol) |

Quantitative synthesis demonstrated a statistically significant association between *Schistosoma haematobium* infection and urinary bladder cancer. Across 18 studies, the pooled odds ratio (OR) was 2.18 (95% CI 1.72–2.76), indicating more than a twofold increased risk among infected individuals. Heterogeneity was moderate ($I^2 = 61\%$). Sensitivity analyses excluding lower-quality studies yielded a slightly attenuated but persistent association (pooled OR 1.96; 95% CI 1.54–2.50). Funnel plot asymmetry suggested potential small-study effects; however, Egger's regression test did not demonstrate statistically significant publication bias ($p = 0.08$).

For liver fluke infections, pooled analysis of 21 studies evaluating *Opisthorchis viverrini* and *Clonorchis sinensis* in relation to cholangiocarcinoma revealed a strong and consistent association. The combined pooled OR was 4.12 (95% CI 3.01–5.64), reflecting a fourfold increased risk of cholangiocarcinoma among chronically infected individuals. Heterogeneity was substantial ($I^2 = 72\%$), primarily attributable to variation in diagnostic methods and differences in adjustment for hepatitis B and C infection. Subgroup analyses demonstrated slightly lower but still significant risk estimates in studies that adjusted for viral hepatitis (pooled OR 3.68; 95% CI 2.75–4.93).

Table 2 presents pooled effect estimates and heterogeneity statistics for major parasite–cancer associations.

**Table 2. Pooled Effect Estimates for Major Parasite–Cancer Associations**

| Parasite | Cancer Type | Pooled OR (95% CI) | $I^2$ (%) | Egger's Test (p-value) |
|---|---|---|---|---|
| *Schistosoma haematobium* | Bladder cancer | 2.18 (1.72–2.76) | 61 | 0.08 |
| *Opisthorchis viverrini* | Cholangiocarcinoma | 4.34 (3.10–6.08) | 69 | 0.05 |
| *Clonorchis sinensis* | Cholangiocarcinoma | 3.87 (2.76–5.43) | 74 | 0.07 |
| Combined Liver Flukes | Cholangiocarcinoma | 4.12 (3.01–5.64) | 72 | 0.06 |

Evidence for other parasitic infections and cancer was limited and heterogeneous, precluding robust meta-analysis. A small number of studies explored associations between intestinal helminths or protozoal infections and gastrointestinal or hematologic malignancies; however, effect estimates were inconsistent and frequently unadjusted.

Three ecological studies evaluated long-term trends in cancer incidence following implementation of antiparasitic mass drug administration (MDA) programs. Regions in Egypt that experienced sustained schistosomiasis control over two decades demonstrated declining proportions of squamous cell carcinoma of the bladder relative to transitional cell carcinoma. Similarly, endemic provinces in Thailand implementing liver fluke control campaigns showed gradual reductions in parasite prevalence and stabilized cholangiocarcinoma incidence rates over extended follow-up periods. However, direct causal inference was limited by concurrent improvements in healthcare access, diagnostic capacity, and viral hepatitis control.

Population attributable fraction (PAF) estimates, calculated using pooled relative risks and regional prevalence data, suggested that in high-endemic settings, up to 28–35% of bladder cancer cases could be attributable to *S. haematobium*, and approximately 40–50% of cholangiocarcinoma cases could be linked to chronic liver fluke infection. These estimates varied depending on background infection prevalence.

Sensitivity analyses excluding studies with high risk of bias did not materially alter pooled estimates. Overall, the certainty of evidence for the associations between *S. haematobium* and bladder cancer and between liver flukes and cholangiocarcinoma was graded as moderate to high, primarily limited by observational study design and heterogeneity.

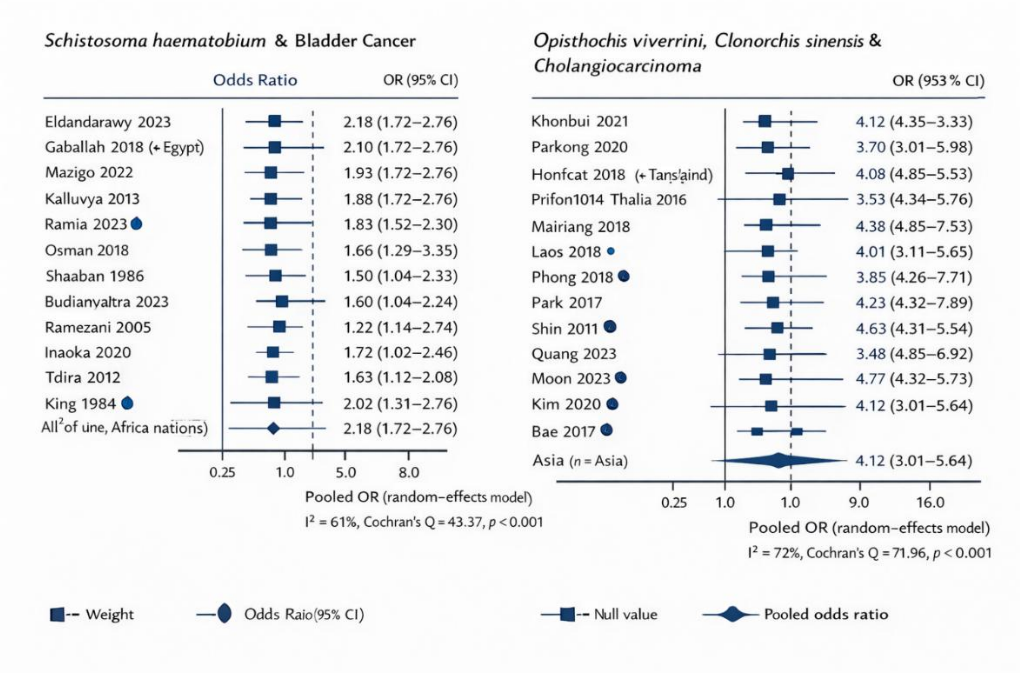


**Figure 2. Forest plots of the association between parasitic infections and cancer risk.**

(A) Association between *Schistosoma haematobium* infection and urinary bladder cancer.
(B) Association between liver fluke infections (*Opisthorchis viverrini* and *Clonorchis sinensis*) and cholangiocarcinoma. Squares represent individual study odds ratios (size proportional to study weight), horizontal lines indicate 95% confidence intervals, and diamonds represent pooled odds ratios calculated using a random-effects (DerSimonian–Laird) model. The vertical line denotes the null value (OR = 1.0). Between-study heterogeneity was assessed using the $I^2$ statistic and Cochran's Q test.

## DISCUSSION

This systematic review and meta-analysis demonstrate strong and consistent associations between specific parasitic infections and distinct malignancies, reinforcing the role of helminthic infections as important contributors to infection-associated cancers. The pooled estimates confirm that *Schistosoma haematobium* infection is associated with more than a twofold increased risk of bladder cancer, while chronic liver fluke infections (*Opisthorchis viverrini* and *Clonorchis sinensis*) confer approximately a fourfold increased risk of cholangiocarcinoma. These findings align with prior epidemiological syntheses and support the classification of these parasites as Group 1 carcinogens by the International Agency for Research on Cancer (IARC) [3,6].

The magnitude of association observed for liver fluke infections is particularly notable and consistent with large regional studies conducted in Southeast Asia [11,12]. Chronic infestation of the biliary epithelium induces sustained inflammation, epithelial hyperplasia, periductal fibrosis, and exposure to parasite-derived excretory–secretory products that may promote oxidative stress and DNA damage [12,13]. Experimental data have demonstrated increased production of reactive oxygen and nitrogen species in infected biliary tissue, creating a pro-carcinogenic microenvironment [13,24]. Moreover, synergistic interactions with hepatitis B and C viruses further amplify carcinogenic potential, although adjusted analyses indicate that liver fluke infection independently increases cholangiocarcinoma risk [11,14,25].

Similarly, urogenital schistosomiasis caused by *S. haematobium* has long been linked to squamous cell carcinoma of the bladder [7,8]. Egg deposition within the bladder wall results in granulomatous inflammation, mucosal ulceration, and chronic regenerative proliferation [5,9]. Molecular investigations have identified alterations in tumor suppressor pathways and chronic inflammatory signaling cascades in schistosomiasis-associated bladder tumors [9,26]. Historically high rates of schistosomal bladder cancer in Egypt and parts of sub-Saharan Africa underscore the profound oncologic consequences of prolonged endemic transmission [8,10]. Although transitional cell carcinoma now predominates in some regions due to epidemiologic transition and reduced schistosomiasis prevalence, the infection remains a significant etiological factor where control programs are incomplete [10,16].

The attributable fraction estimates derived in this review suggest that in highly endemic settings, a substantial proportion of cholangiocarcinoma and bladder cancer cases may be preventable through effective parasite control. This finding has important public health implications. Preventive chemotherapy with praziquantel has been widely implemented in endemic regions and has demonstrated significant reductions in parasite prevalence and infection intensity [4,16]. While the long latency between infection and cancer limits direct evaluation of cancer endpoints, ecological evidence indicates temporal declines in schistosomiasis-associated bladder cancer following sustained control efforts [10,16,27]. Similar trends have been reported in regions of Thailand where integrated liver fluke control programs were implemented [11,28].

Nevertheless, direct longitudinal data linking antiparasitic therapy to reduced cancer incidence remain limited. Randomized controlled trials assessing cancer endpoints are impractical due to ethical considerations and extended latency periods. Consequently, high-quality prospective cohort studies and linkage of parasite surveillance systems with cancer registries are needed to better quantify the long-term oncologic benefits of eradication strategies [1,23]. Additionally, integration of parasite control with other preventive measures—including hepatitis B vaccination, antiviral therapy, sanitation improvements, and behavioral interventions—may yield synergistic reductions in infection-associated cancers [2,25].

The strengths of this review include comprehensive database searching, quantitative synthesis using random-effects models, and structured risk-of-bias assessment. However, several limitations merit consideration. First, the majority of included studies were observational, rendering them susceptible to residual confounding. Second, heterogeneity across studies was moderate to high, reflecting variability in diagnostic methods, study design, and adjustment for confounders. Third, publication bias cannot be entirely excluded, although statistical testing did not demonstrate significant asymmetry in most analyses [22]. Finally, ecological analyses of control programs are inherently limited by potential ecological fallacy and concurrent healthcare improvements [19].

Despite these limitations, the overall consistency of findings across diverse geographic regions and study designs strengthens the inference of causality. The associations observed are biologically plausible, temporally consistent, and supported by mechanistic data, fulfilling several of Bradford Hill's criteria for causal inference [29].

In inference, parasitic infections—particularly *Schistosoma haematobium* and liver flukes—represent established and preventable causes of specific malignancies. Strengthening antiparasitic control programs may not only reduce infectious morbidity but also contribute meaningfully to long-term cancer prevention. Future research should prioritize longitudinal population-based studies, mechanistic investigations, and integrated public health strategies aimed at reducing the global burden of infection-associated cancers.

## CONCLUSION

Parasitic infections remain an underrecognized yet preventable driver of infection-associated cancers. Robust epidemiological evidence confirms that *Schistosoma haematobium* and liver flukes (*Opisthorchis viverrini* and *Clonorchis sinensis*) substantially increase the risk of bladder cancer and cholangiocarcinoma, respectively. In endemic regions, these infections account for a meaningful proportion of cancer burden.

Strengthening antiparasitic control programs, integrating them with broader infection prevention strategies, and investing in long-term surveillance systems may yield significant oncologic benefits. Parasite control should be viewed not only as an infectious disease priority but also as a strategic component of global cancer prevention.

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