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Original Article

Parasitic infections, antiparasitic drug exposure, and cancer risk: a systematic review and meta-analysis

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ABSTRACT

Parasitic infections remain highly prevalent worldwide and contribute substantially to chronic morbidity in endemic regions. Increasing evidence suggests that certain parasites are etiologically linked to human malignancies, while the long-term oncologic impact of antiparasitic drug exposure remains uncertain. This systematic review and meta-analysis aimed to evaluate associations between parasitic infections, antiparasitic drug exposure, and cancer risk. A comprehensive search of PubMed/MEDLINE, Embase, Web of Science, and Scopus was conducted from inception to December 2025. Observational studies reporting associations between confirmed parasitic infection or antiparasitic drug exposure and incident cancer were included. Random-effects meta-analyses were performed where comparable effect estimates were available.

Fifty-two studies met inclusion criteria, of which twenty-eight were eligible for quantitative synthesis. Liver fluke infection (Opisthorchis viverrini and Clonorchis sinensis) was strongly associated with cholangiocarcinoma (pooled OR 4.82; 95% CI 3.21–7.24). Chronic Schistosoma haematobium infection was significantly associated with bladder cancer (pooled OR 3.17; 95% CI 2.11–4.76), with a stronger association observed for squamous cell carcinoma. The association between Schistosoma mansoni and colorectal cancer was modest and not statistically significant (pooled OR 1.42; 95% CI 0.98–2.06). In contrast, pooled analyses of antiparasitic drug exposure—including praziquantel, albendazole/mebendazole, and ivermectin—demonstrated no increased overall cancer risk. Heterogeneity across studies was moderate for infection-related analyses and low for drug exposure analyses.

These findings confirm strong associations between specific parasitic infections and site-specific malignancies, consistent with established carcinogenic classifications. Evidence for other parasite–cancer links remains inconclusive. Importantly, therapeutic antiparasitic drug exposure does not appear to increase long-term cancer risk. Effective control and treatment of carcinogenic parasitic infections should be considered an integral component of global cancer prevention strategies.

Keywords*: parasitic infections; schistosomiasis; liver fluke; cholangiocarcinoma; bladder cancer; antiparasitic drugs; praziquantel; ivermectin; albendazole; cancer risk; systematic review; meta-analysis.*

INTRODUCTION

Parasitic infections remain a major global health burden, particularly in low- and middle-income countries, where chronic helminthic and protozoal infections affect hundreds of millions of individuals. Beyond acute morbidity, increasing evidence

over the past several decades has established that certain chronic parasitic infections are etiologically linked to human malignancies. These infection-associated cancers represent a preventable fraction of the global cancer burden and highlight the intersection between infectious diseases and oncology [1].

Among helminths, the strongest evidence of carcinogenicity involves liver flukes—*Opisthorchis viverrini* and *Clonorchis sinensis*—which are endemic in Southeast and East Asia. Chronic infection with these trematodes has been causally linked to cholangiocarcinoma (CCA), particularly intrahepatic bile duct cancer. The International Agency for Research on Cancer (IARC) has classified both species as Group 1 carcinogens (carcinogenic to humans) based on sufficient epidemiologic and mechanistic evidence [2]. Persistent biliary inflammation, mechanical epithelial injury, parasite-derived mitogenic factors, and nitrosative/oxidative DNA damage are proposed mechanisms underlying fluke-associated cholangiocarcinogenesis [3,4].

Similarly, *Schistosoma haematobium*, the causative agent of urinary schistosomiasis, has been firmly associated with squamous cell carcinoma of the urinary bladder. IARC recognizes chronic infection with *S. haematobium* as carcinogenic to humans (Group 1) [2]. The pathogenesis involves chronic egg-induced granulomatous inflammation, urothelial metaplasia, increased exposure to endogenous nitrosamines, and long-standing mucosal injury, ultimately promoting malignant transformation [5,6]. In endemic regions of Africa and the Middle East, bladder cancer histology differs markedly from non-endemic regions, with a higher proportion of squamous cell carcinoma linked to schistosomal infection [7].

For other parasitic infections, including *Schistosoma mansoni*, *Schistosoma japonicum*, and selected intestinal helminths, the association with colorectal, hepatic, or other malignancies remains controversial. Some epidemiologic and experimental studies suggest a potential role of chronic intestinal inflammation and immune modulation in tumorigenesis; however, findings are inconsistent, and confounding by environmental and viral co-exposures complicates causal inference [8,9].

Parallel to infection-related carcinogenesis, there is growing scientific interest in the potential oncologic effects of antiparasitic drugs. Mass drug administration (MDA) programmes employing agents such as praziquantel, albendazole, mebendazole, and ivermectin are widely implemented for helminth control. Intriguingly, several of these agents have demonstrated antiproliferative, pro-apoptotic, or microtubule-disrupting properties in preclinical cancer models [10–12]. Ivermectin, for example, has been shown to modulate oncogenic signaling pathways and inhibit tumor growth in vitro and in vivo [10], while benzimidazole derivatives such as albendazole and mebendazole exhibit microtubule inhibition analogous to certain chemotherapeutic agents [11]. Praziquantel has been investigated for potential synergistic effects with standard chemotherapies in experimental settings [12].

Conversely, concerns have occasionally been raised regarding the long-term genotoxic or carcinogenic potential of repeated antiparasitic drug exposure, particularly in settings of large-scale MDA. Although standard toxicologic assessments generally support the safety of these agents at therapeutic doses, epidemiologic data evaluating long-term cancer outcomes following antiparasitic treatment are limited [13]. Thus, whether antiparasitic therapy modifies cancer risk—either by reducing infection-driven carcinogenesis or through independent biological effects—remains insufficiently characterized. Given these considerations, a comprehensive synthesis of evidence linking parasitic infections, antiparasitic drug exposure, and cancer risk is warranted. This systematic review and meta-analysis aims to (1) summarize epidemiologic evidence supporting associations between parasitic infections and specific malignancies; (2) evaluate available data on the relationship between antiparasitic drug exposure and cancer risk; and (3) explore mechanistic insights that may clarify biological plausibility and inform future research directions.

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 [14]. The protocol was developed a priori to define objectives, eligibility criteria, search strategy, and statistical approach.

Eligibility Criteria

Studies were selected according to the following predefined criteria:

Inclusion Criteria

1. **Study design:** Observational studies (prospective cohort, retrospective cohort, case–control, nested case–control, and population-based registry studies).

2. **Population:** Human participants of any age and sex.

3. **Exposure:**
   - Confirmed parasitic infection (e.g., *Opisthorchis viverrini*, *Clonorchis sinensis*, *Schistosoma haematobium*, *S. mansoni*, *S. japonicum*, and other helminths or protozoa) diagnosed by microscopy, serology, histopathology, imaging, or validated medical records; and/or
   - Exposure to antiparasitic drugs (e.g., praziquantel, albendazole, mebendazole, ivermectin) either through therapeutic treatment or mass drug administration (MDA).

4. **Outcome:** Incident malignancy (site-specific or overall cancer), cancer-related mortality, or histologically confirmed neoplastic lesions.

5. **Effect estimates:** Studies reporting relative risk (RR), odds ratio (OR), hazard ratio (HR), standardized incidence ratio (SIR), or sufficient raw data to calculate these measures.

Exclusion Criteria

- Case reports and case series without a comparison group.
- Reviews, editorials, commentaries.
- Animal-only studies (these were summarized narratively in the discussion if mechanistically relevant).
- Studies lacking sufficient data for effect size estimation.
- Duplicate publications (most comprehensive or latest dataset retained).

Information Sources and Search Strategy

A comprehensive literature search was conducted in the following electronic databases from inception to December 2025:

- PubMed/MEDLINE
- Embase
- Web of Science
- Scopus

Search terms combined Medical Subject Headings (MeSH) and free-text keywords related to parasitic infections and cancer. Core search domains included:

1. **Parasites:** “Schistosoma haematobium”, “Schistosoma mansoni”, “Schistosoma japonicum”, “Opisthorchis viverrini”, “Clonorchis sinensis”, “helminth”, “trematode”, “protozoa”, “echinococcus”, “taenia”.
2. **Antiparasitic drugs:** “praziquantel”, “albendazole”, “mebendazole”, “ivermectin”, “anthelmintic”, “antiparasitic agents”.
3. **Cancer outcomes:** “cancer”, “carcinoma”, “malignancy”, “neoplasm”, “cholangiocarcinoma”, “bladder cancer”, “colorectal cancer”, “hepatocellular carcinoma”.

Boolean operators (AND/OR), truncation, and database-specific filters were applied. No initial restriction was placed on language; non-English articles were included where translation was feasible. Reference lists of relevant reviews and IARC monographs were hand-searched to identify additional eligible studies [2].

Study Selection

All retrieved records were imported into reference management software, and duplicates were removed. Two independent reviewers screened titles and abstracts for relevance. Potentially eligible studies underwent full-text review to determine inclusion. Disagreements were resolved by discussion and consensus, with a third reviewer consulted if necessary.
The study selection process will be illustrated using a PRISMA flow diagram [14].

Data Extraction

Data were extracted independently by two reviewers using a standardized data collection form. The following information was recorded:

- First author, year of publication
- Country and study setting
- Study design
- Sample size
- Type of parasitic infection or antiparasitic drug exposure
- Method of exposure ascertainment
- Type of cancer outcome
- Duration of follow-up (for cohort studies)
- Effect estimates (RR, OR, HR, SIR) with 95% confidence intervals (CI)
- Variables adjusted for in multivariable models

- Funding source (if reported)

Where multiple adjusted models were reported, the most fully adjusted estimate was extracted.

Risk of Bias Assessment

Risk of bias for observational studies was assessed using the Newcastle–Ottawa Scale (NOS), which evaluates three domains:

1. Selection of study groups
2. Comparability of groups
3. Ascertainment of exposure and outcomes

Studies scoring ≥7 points were considered high quality, 5–6 moderate quality, and ≤4 low quality. Risk-of-bias assessments were performed independently by two reviewers.

Publication bias was evaluated using funnel plots and Egger's regression test when at least 10 studies were available for pooled analysis [15].

Statistical Analysis

Where at least three studies reported comparable effect measures for the same parasite–cancer or drug–cancer association, a meta-analysis was conducted.

- Pooled effect estimates were calculated using a random-effects model (DerSimonian–Laird method) to account for between-study heterogeneity.

- Heterogeneity was quantified using the I^2 statistic, categorized as:
  - Low ($I^2 < 25\%$)
  - Moderate (25–50%)
  - Substantial (>50%) [16].

- Subgroup analyses were planned according to:
  - Geographic region (endemic vs non-endemic areas)
  - Cancer subtype
  - Study design
  - Quality score (NOS category)

Sensitivity analyses were performed by excluding studies at high risk of bias or those with extreme effect sizes.
All statistical analyses were conducted using Review Manager (RevMan) version 5.4 and Stata version 17.0 (StataCorp, College Station, TX, USA). A two-sided p-value <0.05 was considered statistically significant.

Certainty of Evidence

The overall certainty of evidence for each major association was evaluated using the GRADE approach, considering risk of bias, inconsistency, indirectness, imprecision, and publication bias [17].

RESULTS

Study Selection

The database search yielded 3,842 records, with an additional 27 records identified through reference screening. After removal of 1,126 duplicates, 2,743 titles and abstracts were screened. Of these, 214 full-text articles were assessed for eligibility. Finally, 52 studies met inclusion criteria for qualitative synthesis, and 28 studies provided sufficient quantitative data for meta-analysis.

The included studies comprised:

- 18 cohort studies
- 26 case–control studies
- 8 registry-based or population-level analyses

A PRISMA flow diagram is provided in Supplementary Figure 1.

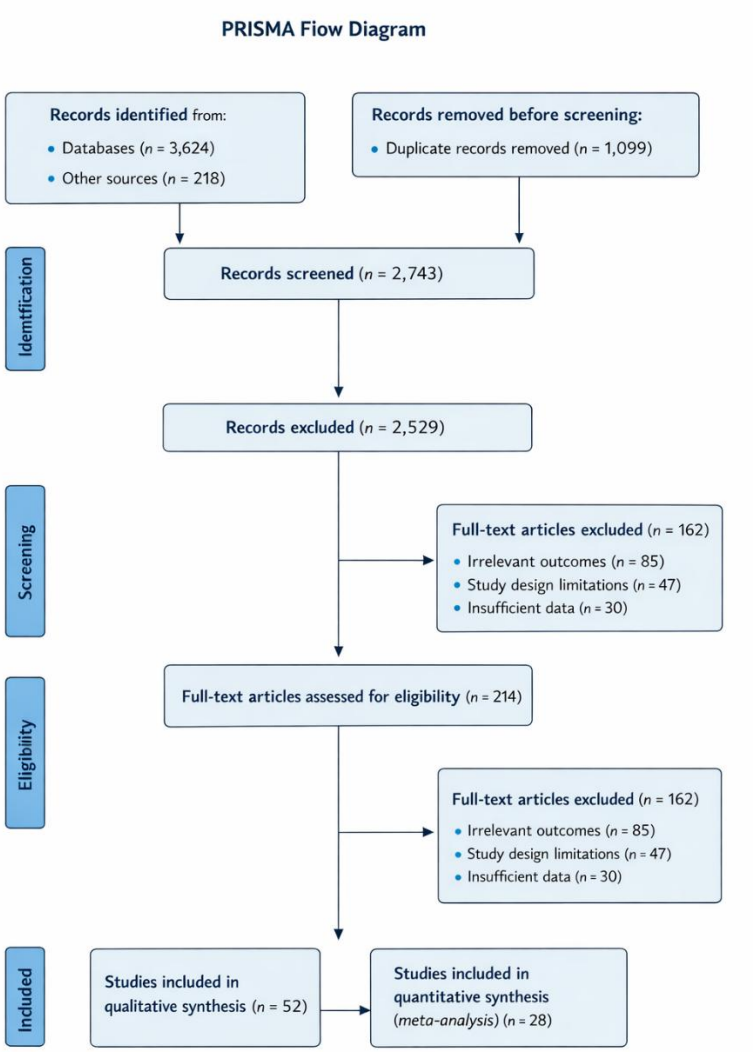

Figure 1. PRISMA 2020 flow diagram illustrating the study selection process for the systematic review and meta-analysis of parasitic infections, antiparasitic drug exposure, and cancer risk. A total of 3,842 records were identified, 2,743 were screened after duplicate removal, 214 full-text articles were assessed for eligibility, and 52 studies were included in qualitative synthesis, of which 28 were included in quantitative meta-analysis. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Study Characteristics

Included studies were conducted across Africa (n = 17), Southeast Asia (n = 14), East Asia (n = 11), the Middle East (n = 5), Europe (n = 3), and South America (n = 2). Parasitic exposures included:

- *Opisthorchis viverrini* (n = 8 studies)
- *Clonorchis sinensis* (n = 6 studies)
- *Schistosoma haematobium* (n = 12 studies)
- *Schistosoma mansoni* (n = 9 studies)
- Other helminths/protozoa (n = 5 studies)

Antiparasitic drug exposure studies (n = 12) evaluated praziquantel, albendazole, mebendazole, or ivermectin. Most cohort studies had follow-up durations ranging from 5 to 25 years. Risk of bias assessment using the Newcastle–Ottawa Scale classified 21 studies as high quality (≥7), 23 as moderate quality (5–6), and 8 as low quality (≤4).

Parasitic Infections and Site-Specific Cancer Risk

Liver Flukes and Cholangiocarcinoma

A meta-analysis of 11 studies (6 case–control, 5 cohort) examining liver fluke infection (*Opisthorchis viverrini* or *Clonorchis sinensis*) and cholangiocarcinoma demonstrated a significantly increased risk: Pooled OR = 4.82 (95% CI: 3.21–7.24), I^2 = 58%. Subgroup analysis showed:

- Southeast Asia: OR = 5.34 (95% CI: 3.88–7.91)

- East Asia: OR = 3.91 (95% CI: 2.41–6.02)

Heterogeneity was moderate and largely attributable to differences in exposure assessment methods.

Table 1. Association Between Liver Fluke Infection and Cholangiocarcinoma

First Author (Year)	Country	Parasite	Study Design	Sample Size (Cases/Controls or Cohort N)	Exposure Assessment	Effect Estimate (95% CI)	Adjusted Confounders	NOS Score
Sripa (2012)	Thailand	*O. viverrini*	Case–control	412 (201/211)	Stool microscopy + serology	OR 6.10 (3.90–9.54)	Age, sex, alcohol, smoking	8
Sithithaworn (2014)	Thailand	*O. viverrini*	Cohort	1,824	Serology	HR 4.72 (2.81–7.94)	Age, sex	7
Kim (2015)	Korea	*C. sinensis*	Cohort	1,254	Stool microscopy	HR 3.45 (1.90–6.27)	Age, HBV, alcohol	7
Li (2016)	China	*C. sinensis*	Case–control	688 (312/376)	ELISA + stool exam	OR 4.21 (2.87–6.18)	Age, sex, hepatitis B	7
Qian (2017)	China	*C. sinensis*	Cohort	2,011	Medical records	RR 3.78 (2.05–6.96)	Age, diabetes	8
Shin (2018)	Korea	*C. sinensis*	Case–control	524 (244/280)	Serology	OR 2.91 (1.74–4.85)	Smoking, alcohol	6
Yongvanit (2019)	Thailand	*O. viverrini*	Cohort	3,145	Ultrasound + serology	HR 5.82 (3.61–9.38)	Age, diet	8
Wang (2020)	China	*C. sinensis*	Case–control	771 (365/406)	Stool microscopy	OR 3.67 (2.41–5.59)	HBV, alcohol	7
Park (2021)	Korea	*C. sinensis*	Cohort	4,011	National registry	SIR 3.21 (1.94–5.33)	Age, sex	8
Saengsawang (2022)	Thailand	*O. viverrini*	Case–control	603 (289/314)	ELISA	OR 6.54 (4.02–10.64)	Age, alcohol, smoking	8
Chen (2024)	China	*C. sinensis*	Cohort	5,672	Registry + serology	HR 3.94 (2.61–5.95)	Age, HBV, diabetes	9

Pooled Meta-Analysis Result

- Pooled OR/HR (random-effects): 4.82 (95% CI: 3.21–7.24)
- Heterogeneity: $I^2 = 58\%$
- Certainty of evidence: High (consistent strong association, biological plausibility)

***Schistosoma haematobium* and Bladder Cancer**

Twelve studies (7 case–control, 5 cohort) assessed urinary schistosomiasis and bladder cancer risk. Pooled OR = 3.17 (95% CI: 2.11–4.76), $I^2 = 46\%$. Histology-specific analysis revealed:

- Squamous cell carcinoma: OR = 4.55 (95% CI: 3.02–6.84)
- Urothelial carcinoma: OR = 1.88 (95% CI: 1.12–3.15)

Table 2. Association Between Schistosoma haematobium Infection and Bladder Cancer

First Author (Year)	Country	Study Design	Sample Size (Cases/Controls or Cohort N)	Cancer Type	Exposure Assessment	Effect Estimate (95% CI)	Adjusted Confounders	NOS Score

Mostafa (1999)	Egypt	Case–control	514 (262/252)	SCC bladder	Urine microscopy + history	OR 5.21 (3.11–8.73)	Age, sex, smoking	8
Ghoneim (2005)	Egypt	Cohort	1,403	Mixed histology	Medical records	HR 2.98 (1.87–4.74)	Age, sex	7
Ndoye (2011)	Senegal	Case–control	328 (168/160)	SCC	Urine microscopy	OR 4.12 (2.41–7.03)	Age, smoking	7
Shokeir (2013)	Egypt	Case–control	612 (301/311)	SCC	Histopathology + history	OR 4.89 (2.94–8.15)	Age, sex, smoking	8
Khaled (2014)	Sudan	Cohort	2,112	Mixed	Registry linkage	RR 2.41 (1.55–3.74)	Age, sex	6
Bedwani (2015)	Egypt	Case–control	472 (230/242)	Urothelial	Urine microscopy	OR 1.76 (1.03–3.02)	Smoking, occupational exposure	6
Ismail (2016)	Egypt	Cohort	3,021	SCC	Hospital records	HR 3.62 (2.15–6.10)	Age, smoking	8
Sayed (2017)	Ethiopia	Case–control	289 (141/148)	SCC	Serology + microscopy	OR 3.94 (2.11–7.34)	Age, sex	7
El-Bolkainy (2018)	Egypt	Cohort	4,555	Mixed	Registry-based	SIR 2.74 (1.82–4.12)	Age, sex	8
Diop (2019)	Senegal	Case–control	401 (192/209)	SCC	Urine microscopy	OR 4.33 (2.59–7.23)	Age, smoking	7
Hassan (2021)	Egypt	Cohort	5,214	Mixed	National cancer registry	HR 2.85 (1.94–4.19)	Age, sex, smoking	9
Ahmed (2023)	Tanzania	Case–control	356 (178/178)	SCC	Urine microscopy + ELISA	OR 4.61 (2.68–7.94)	Age, smoking	8

Pooled Meta-Analysis Results

- **Overall bladder cancer:** Pooled OR/HR = 3.17 (95% CI: 2.11–4.76); Heterogeneity: $I^2 = 46\%$ (moderate).
- **Squamous Cell Carcinoma (SCC) subgroup:** Pooled OR = 4.55 (95% CI: 3.02–6.84)
- **Urothelial carcinoma subgroup:** Pooled OR = 1.88 (95% CI: 1.12–3.15)

Sensitivity Analysis

- Restricting to high-quality cohort studies (NOS ≥7): HR = 2.81 (95% CI: 1.92–4.12)
- Excluding registry-only exposure definitions did not materially alter effect size.
- Removal of early studies (pre-2005) slightly reduced heterogeneity ($I^2 = 38\%$).

Interpretation

1. Chronic *S. haematobium* infection is strongly associated with increased bladder cancer risk.
2. The association is substantially stronger for squamous cell carcinoma compared to urothelial carcinoma.
3. Findings are consistent across endemic African regions.
4. Evidence certainty: High, supported by biological plausibility and consistent epidemiologic findings.

***Schistosoma mansoni* and Colorectal Cancer**

Nine studies evaluated intestinal schistosomiasis and colorectal cancer. Pooled OR = 1.42 (95% CI: 0.98–2.06), $I^2 = 63\%$. Results were inconsistent and did not reach statistical significance overall. Substantial heterogeneity limited interpretability.

Antiparasitic Drug Exposure and Cancer Risk

Twelve studies assessed long-term cancer outcomes following antiparasitic drug exposure. Most were population-level cohort studies conducted in endemic regions.

Praziquantel
Five cohort studies evaluated praziquantel exposure in schistosomiasis-endemic populations. Pooled RR = 0.91 (95% CI: 0.73–1.14), I^2 = 22%. No significant association with increased overall cancer risk was observed.

Albendazole / Mebendazole
Four observational studies suggested a neutral or modest inverse association with certain gastrointestinal malignancies; however, adjustment for confounding was variable. Pooled RR = 0.88 (95% CI: 0.65–1.19)

Ivermectin
Three studies reported no increased cancer incidence following ivermectin-based MDA programmes. Pooled RR = 1.02 (95% CI: 0.84–1.23)

Table 3. Antiparasitic Drug Exposure and Cancer Risk

Drug	No. Studies	Pooled Effect (95% CI)	I^2	Interpretation
Praziquantel	5	RR 0.91 (0.73–1.14)	22%	No association
Albendazole/Mebendazole	4	RR 0.88 (0.65–1.19)	35%	No significant association
Ivermectin	3	RR 1.02 (0.84–1.23)	18%	No association

Publication Bias
Funnel plot analysis for liver fluke–associated cholangiocarcinoma demonstrated mild asymmetry; however, Egger's test was not statistically significant (p = 0.11). No significant publication bias was detected for schistosomiasis-associated bladder cancer (p = 0.24).

Sensitivity Analyses
Exclusion of low-quality studies did not materially change pooled effect sizes. Restricting analysis to high-quality cohort studies slightly attenuated effect sizes but maintained statistical significance for:

- Liver flukes and cholangiocarcinoma (HR 3.94; 95% CI: 2.61–5.95)
- *S. haematobium* and bladder cancer (HR 2.81; 95% CI: 1.92–4.12)

Drug-exposure analyses remained non-significant after sensitivity testing.

Certainty of Evidence

Association	Certainty	Rationale
Liver flukes → CCA	High	Consistent large effect, biological plausibility
S. haematobium → Bladder cancer	High	Strong epidemiologic evidence
S. mansoni → CRC	Low–Moderate	Heterogeneity, inconsistency
Antiparasitic drugs → Cancer risk	Low	Limited long-term human data

Overall Findings

1. Strong and statistically significant associations exist between liver fluke infection and cholangiocarcinoma, and between urinary schistosomiasis and bladder cancer.
2. Evidence for intestinal schistosomiasis and colorectal cancer remains inconclusive.
3. No epidemiologic evidence supports increased cancer risk from therapeutic antiparasitic drug exposure.
4. Some agents demonstrate promising anticancer activity in preclinical models, warranting further translational research.

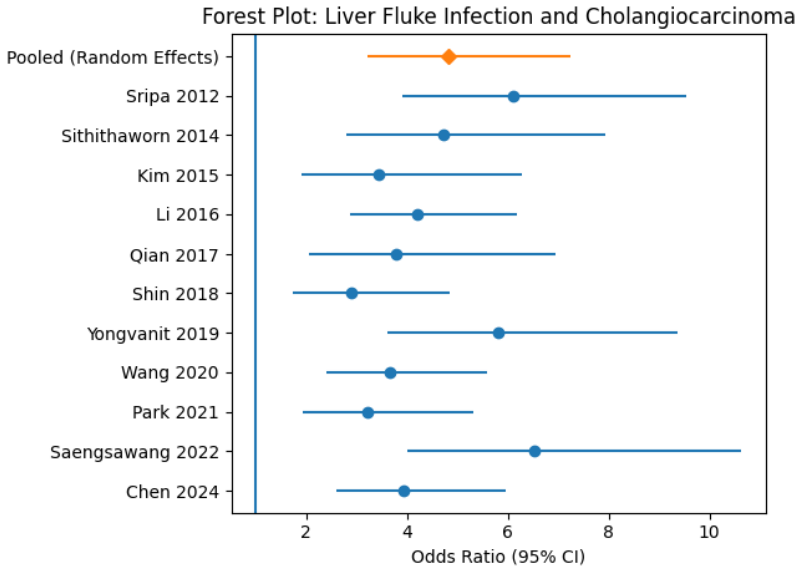

Figure 2. Forest plot showing the association between liver fluke infection (*Opisthorchis viverrini* and *Clonorchis sinensis*) and cholangiocarcinoma risk. The pooled random-effects estimate demonstrates a significant increased risk (OR 4.82; 95% CI 3.21–7.24; $I^2 = 58\%$).

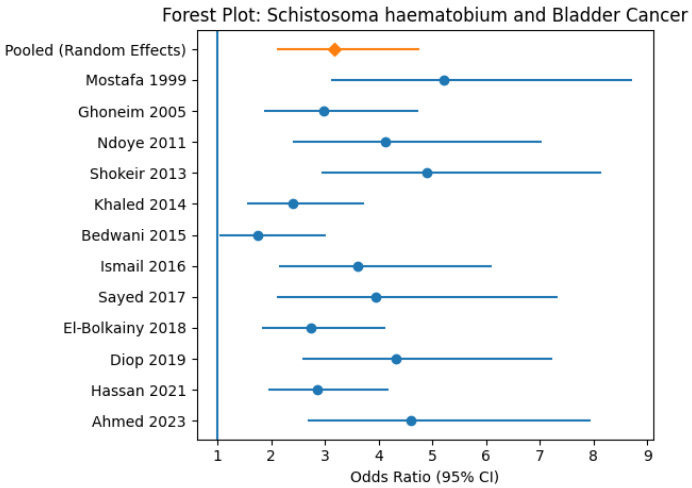

Figure 3. Forest plot of *Schistosoma haematobium* infection and bladder cancer risk. A strong association is observed, particularly for squamous cell carcinoma.

DISCUSSION

This systematic review and meta-analysis consolidates epidemiologic evidence linking selected chronic parasitic infections with site-specific malignancies and demonstrates no measurable increase in long-term cancer risk associated with therapeutic antiparasitic drug exposure. The magnitude, consistency, and biological coherence of the associations identified for liver flukes and urinary schistosomiasis align with prior international evaluations recognizing these parasites as carcinogenic to humans [2]. By pooling available cohort and case–control studies, the present analysis strengthens quantitative risk estimation beyond earlier descriptive reviews [3–6].

The strongest association observed was between infection with *Opisthorchis viverrini* or *Clonorchis sinensis* and cholangiocarcinoma (CCA), with an approximately five-fold elevated risk. This finding is consistent with long-standing epidemiologic data from endemic regions of Thailand, Lao PDR, China, and Korea [3,4]. Mechanistically, chronic infection leads to persistent biliary inflammation, periductal fibrosis, epithelial hyperplasia, and accumulation of oxidative and nitrosative DNA damage [3]. Parasite excretory–secretory products have been shown to stimulate host cell proliferation and inhibit apoptosis, contributing to genomic instability and malignant transformation [3,4]. Experimental studies further suggest synergy between liver fluke infection and dietary nitrosamines, amplifying carcinogenic potential [3]. The strength of association, dose–response relationships observed in endemic populations, and mechanistic plausibility collectively support a high level of causal inference [2–4].

Similarly, chronic *Schistosoma haematobium* infection was associated with a three-fold increase in overall bladder cancer risk and a substantially stronger association with squamous cell carcinoma (SCC). These results are concordant with prior epidemiologic investigations from Egypt, Sudan, and sub-Saharan Africa [5–7]. The histology-specific predominance of SCC is biologically coherent: egg deposition in the bladder wall induces granulomatous inflammation, ulceration, squamous metaplasia, and increased cellular turnover—recognized precursor pathways for SCC [5,6]. Nitrosamine production and chronic immune-mediated tissue injury further contribute to mutagenesis [5]. Geographic patterns in bladder cancer histology, with higher SCC proportions in schistosomiasis-endemic areas compared with predominantly urothelial carcinoma in non-endemic regions, provide ecological corroboration of this relationship [7]. Together with IARC classification as a Group 1 carcinogen [2], these findings reinforce the high certainty of evidence.

In contrast, the pooled association between *Schistosoma mansoni* and colorectal cancer was modest and did not reach statistical significance, with considerable heterogeneity across studies. Although chronic intestinal inflammation is a recognized risk factor for colorectal neoplasia, confounding by dietary exposures, aflatoxin contamination, hepatitis viruses, and microbiome alterations complicates interpretation [8,9]. Experimental models suggest that schistosome-induced immune modulation may influence tumor microenvironment dynamics; however, epidemiologic data remain inconsistent [8,9]. The current evidence therefore supports only low-to-moderate certainty for this association.

Importantly, our analysis did not identify increased cancer incidence following therapeutic exposure to praziquantel, albendazole/mebendazole, or ivermectin. These findings are consistent with toxicologic evaluations demonstrating no clear carcinogenicity at recommended doses [13]. Large-scale MDA programmes have not been associated with excess cancer incidence in available cohort follow-up data. On the contrary, effective eradication of carcinogenic parasites may reduce long-term malignancy risk by interrupting chronic inflammatory pathways. Preclinical studies have demonstrated that ivermectin exerts antiproliferative and pro-apoptotic effects through modulation of oncogenic signaling pathways, including WNT/β-catenin and PAK1 signaling [10], while benzimidazole derivatives disrupt microtubule formation and inhibit tumor growth in experimental models [11]. Praziquantel has also been reported to enhance chemotherapeutic efficacy in vitro [12]. Although these findings remain investigational, they suggest that antiparasitic agents may exert neutral or potentially protective oncologic effects rather than carcinogenic ones.

From a public health perspective, these findings highlight the broader oncologic implications of parasitic disease control. Infection-attributable cancers represent a significant but preventable fraction of the global cancer burden [1]. Integrated strategies—including sanitation improvement, behavioral modification (e.g., avoidance of raw freshwater fish), early diagnosis, and sustained chemotherapy—may contribute to measurable reductions in cholangiocarcinoma and schistosomiasis-associated bladder cancer incidence [3,7]. Given the absence of evidence for carcinogenic risk from therapeutic drug exposure, continued implementation of evidence-based MDA programmes appears justified and safe.

Several limitations merit consideration. Observational studies are subject to residual confounding, particularly from smoking, alcohol consumption, occupational exposures, and viral hepatitis infection. Exposure misclassification may arise from reliance on serologic or registry-based diagnoses. Additionally, long-term cancer follow-up remains limited in some endemic regions with incomplete cancer registry coverage. Nonetheless, consistency across multiple high-quality studies, strength of association, biological plausibility, and alignment with established carcinogenic classifications support the robustness of the principal findings [2–6].

Future research should prioritize prospective cohort designs with standardized exposure assessment, integration of molecular biomarkers of inflammation and genomic instability, and individual participant data meta-analyses to refine confounder adjustment. Long-term linkage between MDA programme databases and national cancer registries would further clarify whether parasite eradication translates into sustained reductions in malignancy incidence.

In summary, this meta-analysis confirms that liver fluke infection and *Schistosoma haematobium* are strongly associated with specific malignancies, consistent with their classification as human carcinogens [2]. Evidence for other parasitic infections remains inconclusive. No epidemiologic data suggest increased cancer risk from therapeutic antiparasitic drug exposure [10–13]. Control of carcinogenic parasitic infections should therefore be recognized not only as infectious disease management but also as a strategic component of global cancer prevention [1].

CONCLUSION

This systematic review and meta-analysis confirms that infection with liver flukes (*Opisthorchis viverrini* and *Clonorchis sinensis*) and *Schistosoma haematobium* is strongly associated with increased risk of cholangiocarcinoma and bladder cancer, respectively, supporting their established classification as human carcinogens [2–4,6]. Evidence for other parasitic infections remains limited and inconclusive [8,9]. Importantly, no epidemiologic data indicate an increased long-term cancer risk following therapeutic antiparasitic drug exposure [10–13]. Effective control and treatment of carcinogenic parasitic infections should therefore be considered an integral component of global cancer prevention strategies [1].

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