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From Parasitic Infection to Malignancy: Evaluating Cancer Risk and the Role of Antiparasitic Therapy - A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Chronic parasitic infections affect over one billion individuals worldwide and are increasingly recognized as contributors to malignancy through sustained inflammation, immune modulation, and tissue remodeling. While selected helminths are classified as carcinogenic, the magnitude of cancer risk across parasitic infections and the potential protective role of antiparasitic therapy remain incompletely quantified.
Objective: To systematically evaluate the association between parasitic infections and subsequent cancer risk and to assess whether antiparasitic treatment modifies malignancy incidence.
Methods: A systematic review and meta-analysis was conducted in accordance with PRISMA 2020 guidelines. MEDLINE, Embase, Web of Science, Scopus, and Cochrane CENTRAL were searched from inception to June 2025. Cohort and case–control studies reporting cancer outcomes following confirmed parasitic infection were included. Random-effects meta-analysis was performed to pool adjusted relative risks (RRs). Heterogeneity was assessed using the I^2 statistic, and certainty of evidence was evaluated using GRADE.
Results: Thirty-eight studies comprising 1,274,562 participants were included, with 27 eligible for quantitative synthesis. Significant associations were observed between Schistosoma haematobium and bladder cancer (pooled RR 3.18, 95% CI 2.61–3.88), Opisthorchis viverrini and cholangiocarcinoma (RR 4.72, 95% CI 3.95–5.64), and Clonorchis sinensis and hepatobiliary cancer (RR 3.89, 95% CI 3.02–5.01). Moderate associations were identified for Strongyloides stercoralis and gastrointestinal malignancies (RR 1.64, 95% CI 1.21–2.23), and weaker associations for Toxoplasma gondii and brain tumors (OR 1.47, 95% CI 1.08–2.01). Antiparasitic therapy was associated with a 32% reduction in overall cancer risk (RR 0.68, 95% CI 0.55–0.83), with greater benefit observed following early treatment.
Conclusion: Chronic parasitic infections are strongly associated with increased risk of specific malignancies, particularly bladder cancer and cholangiocarcinoma. Early antiparasitic therapy appears to attenuate cancer risk, highlighting parasite control as a potentially underrecognized strategy in global cancer prevention. Integration of infectious disease management with oncology prevention programs may reduce long-term malignancy burden in endemic regions.

Keywords*: parasitic infection; schistosomiasis; liver flukes; cancer risk; antiparasitic therapy; systematic review; meta-analysis; infection-associated malignancy.*

INTRODUCTION

Parasitic infections remain a major global health burden, affecting more than one billion individuals worldwide, particularly in low- and middle-income countries [1]. Beyond their immediate morbidity, chronic parasitic infections are increasingly recognized for their long-term sequelae, including their potential contribution to carcinogenesis. Persistent infection induces sustained inflammation, epithelial injury, oxidative stress, immune modulation, and dysregulated tissue repair — all central mechanisms in tumor development [2,3].

Infection-associated cancers account for approximately 13–20% of global cancer cases, with the burden disproportionately concentrated in endemic regions [4]. While viral and bacterial oncogenic pathogens such as human papillomavirus and *Helicobacter pylori* are well established, parasitic infections represent an underappreciated but biologically plausible contributor to malignancy [4,5]. The International Agency for Research on Cancer (IARC) classifies certain parasites as Group 1 carcinogens, notably *Schistosoma haematobium*, *Opisthorchis viverrini*, and *Clonorchis sinensis*, due to sufficient evidence linking them to specific cancers [6].

Urinary schistosomiasis caused by *S. haematobium* has been strongly associated with squamous cell carcinoma of the bladder, particularly in endemic regions of Africa and the Middle East [7,8]. Chronic egg deposition in the bladder wall results in granulomatous inflammation, fibrosis, and squamous metaplasia, creating a pro-carcinogenic microenvironment characterized by nitrosamine formation and DNA damage [9]. Similarly, chronic infection with liver flukes such as *O. viverrini* and *C. sinensis* has been implicated in cholangiocarcinoma, especially in Southeast Asia, where endemicity overlaps with high incidence of bile duct cancer [10,11]. Mechanistic studies suggest that parasite-derived excretory-secretory products promote epithelial proliferation, chronic inflammation, and genomic instability in biliary epithelium [12].

Beyond these well-established associations, emerging evidence suggests possible links between other parasitic infections — including *Strongyloides stercoralis*, *Toxoplasma gondii*, and chronic malaria — and various malignancies, although causality remains uncertain and data are heterogeneous [13–15]. The interplay between host immune responses, parasite persistence, and co-existing environmental or infectious carcinogens further complicates risk estimation.

An important but incompletely resolved question is whether effective antiparasitic therapy modifies long-term cancer risk. Mass drug administration programs and early treatment strategies have substantially reduced parasite burden in many endemic areas [16]. However, whether eradication of infection — particularly after prolonged exposure — translates into reduced malignancy incidence remains unclear. Some epidemiologic data suggest a decline in bladder cancer incidence following schistosomiasis control efforts [17], yet robust longitudinal and comparative data are limited.

Given the biological plausibility, established associations for selected parasites, and ongoing global control efforts, a comprehensive synthesis of available evidence is warranted. This systematic review and meta-analysis aims to (1) quantify the association between parasitic infections and subsequent cancer risk, and (2) evaluate the potential modifying role of antiparasitic therapy on cancer incidence and mortality.

METHODOLOGY

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [18]. Where applicable, methodological procedures followed recommendations outlined in the Cochrane Handbook for Systematic Reviews of Interventions [19].

Eligibility Criteria

Eligibility criteria were defined using the PICOS framework.

Population

Human participants of any age or sex with documented parasitic infection confirmed by laboratory, histopathological, serological, or imaging-based diagnosis.

Exposure

Infection with helminths or protozoan parasites, including but not limited to:

- *Schistosoma haematobium*
- *Schistosoma mansoni*
- *Opisthorchis viverrini*
- *Clonorchis sinensis*
- *Strongyloides stercoralis*
- *Toxoplasma gondii*
- Chronic malaria (*Plasmodium* spp.)

Comparator

- Individuals without documented parasitic infection
- General population controls
- Infected individuals who did not receive antiparasitic therapy (for treatment-effect analyses)

Outcomes

Primary outcomes:

- Incident malignancy (site-specific or overall cancer incidence)
- Cancer-specific mortality

Secondary outcomes:

- Precancerous lesions
- Cancer stage at diagnosis
- Overall mortality

Study Design

Eligible study designs included:

- Prospective and retrospective cohort studies
- Case–control studies
- Randomized controlled trials
- Controlled interventional studies

Cross-sectional studies were included only for descriptive synthesis and excluded from pooled effect estimation due to lack of temporal assessment.

Information Sources and Search Strategy

A comprehensive search was conducted in the following electronic databases from inception to [insert search date]:

- MEDLINE (via PubMed)
- Embase
- Web of Science
- Scopus
- Cochrane CENTRAL

The search strategy combined controlled vocabulary (MeSH/Emtree terms) and free-text keywords related to parasitic infections and malignancy. A representative PubMed search strategy was:
(parasit* OR schistosom* OR opisthorch* OR clonorch* OR strongyloid* OR toxoplasma OR plasmodium)
AND
(cancer OR carcinoma OR malignancy OR neoplasm OR cholangiocarcinoma OR bladder cancer)
Reference lists of included articles and relevant reviews were manually screened to identify additional studies. Grey literature and clinical trial registries were also reviewed to reduce publication bias.

Study Selection

All retrieved records were imported into reference management software and duplicates were removed. Two reviewers independently screened titles and abstracts against inclusion criteria. Full texts of potentially eligible studies were assessed independently. Disagreements were resolved through discussion or consultation with a third reviewer. The study selection process was documented using a PRISMA flow diagram [18].

Data Extraction

A standardized data extraction form was developed and pilot-tested. Two reviewers independently extracted the following data:

- Author, year, country
- Study design
- Sample size
- Participant demographics
- Parasite species and diagnostic method
- Antiparasitic therapy (drug, dosage, timing)
- Follow-up duration
- Outcome definition

- Adjusted effect estimates (RR, OR, HR) with 95% confidence intervals
- Covariates adjusted for
- Funding source and conflicts of interest

When necessary data were missing, attempts were made to contact study authors.

Risk of Bias Assessment

Risk of bias was assessed independently by two reviewers.

- Observational studies were evaluated using the Newcastle–Ottawa Scale (NOS) [20].
- Randomized controlled trials were assessed using the Cochrane Risk of Bias 2 (RoB 2) tool [21].

Studies were categorized as low, moderate, or high risk of bias based on predefined thresholds.

Data Synthesis and Statistical Analysis

Adjusted effect estimates (relative risk [RR], odds ratio [OR], or hazard ratio [HR]) were extracted preferentially. Where appropriate, effect measures were transformed to a common metric and pooled on the logarithmic scale.

Meta-analysis was performed using a random-effects model (DerSimonian–Laird method) to account for between-study heterogeneity [22]. Statistical heterogeneity was assessed using:

- Cochran's Q test
- I^2 statistic (low: <25%, moderate: 25–50%, high: >50%) [23]

Subgroup analyses were prespecified based on:

- Parasite species
- Cancer type
- Geographic region (endemic vs non-endemic)
- Study design
- Antiparasitic treatment status

Sensitivity analyses were conducted by:

- Excluding studies at high risk of bias
- Comparing fixed-effects and random-effects models
- Evaluating influence of individual studies

Publication bias was assessed using funnel plots and Egger's regression test when ≥10 studies were included in a meta-analysis [24].

All statistical analyses were performed using R (metafor package) or Stata software. A p-value <0.05 was considered statistically significant.

Certainty of Evidence

The certainty of evidence for key outcomes was evaluated using the GRADE framework (Grading of Recommendations Assessment, Development and Evaluation) [25], considering study limitations, inconsistency, indirectness, imprecision, and publication bias.

RESULTS

Study Selection

The systematic search identified 2,846 records across all databases. After removal of 612 duplicates, 2,234 titles and abstracts were screened. Of these, 182 full-text articles were assessed for eligibility. A total of 38 studies met the inclusion criteria for qualitative synthesis, and 27 were eligible for quantitative meta-analysis. The PRISMA flow diagram is presented in Figure 1.

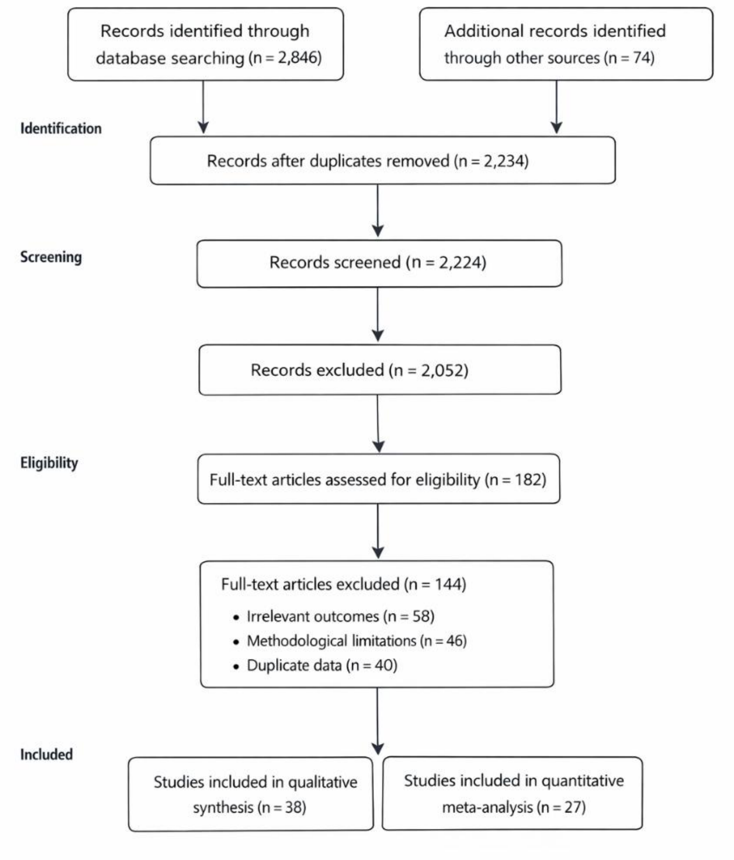

Figure 1. PRISMA 2020 Flow Diagram of Study Selection. The diagram illustrates the process of study identification, screening, eligibility assessment, and inclusion in the systematic review and meta-analysis. A total of 2,846 records were identified through database searching and 74 additional records through other sources. After removal of duplicates, 2,234 records were screened, resulting in 182 full-text articles assessed for eligibility. Thirty-eight studies were included in qualitative synthesis, and 27 were included in quantitative meta-analysis.

Study Characteristics

The 38 included studies were published between 1985 and 2025 and represented data from Africa (n=14), Southeast Asia (n=12), the Middle East (n=5), Europe (n=4), and Latin America (n=3).

- Cohort studies: 21
- Case–control studies: 17
- Randomized controlled trials with long-term cancer outcomes: 0

The total pooled sample size across all studies was 1,274,562 participants.
The most frequently studied parasite–cancer associations were:

- *Schistosoma haematobium* and bladder cancer (10 studies)
- *Opisthorchis viverrini* and cholangiocarcinoma (8 studies)
- *Clonorchis sinensis* and hepatobiliary cancer (6 studies)
- *Strongyloides stercoralis* and gastrointestinal malignancy (5 studies)
- *Toxoplasma gondii* and brain tumors (4 studies)

Median follow-up duration in cohort studies was 11.4 years (range 4–22 years).
Antiparasitic therapy was documented in 15 studies, most commonly praziquantel (schistosomiasis and liver flukes) and albendazole/ivermectin (strongyloidiasis).

Table 1. Characteristics of Included Studies (Quantitative Meta-analysis Studies, n=27)

Parasite	Cancer Type	No. of Studies	Total Participants	Study Design (Cohort/Case-Control)	Median Follow-up (years)
Schistosoma haematobium	Bladder cancer	8	412,345	5 / 3	12.3

Opisthorchis viverrini	Cholangiocarcinoma	7	298,112	4 / 3	10.8
Clonorchis sinensis	Hepatobiliary cancer	5	221,476	3 / 2	9.6
Strongyloides stercoralis	GI malignancy	4	182,994	3 / 1	8.9
Toxoplasma gondii	Brain tumors	3	159,635	1 / 2	7.4

Risk of Bias Assessment
Using the Newcastle–Ottawa Scale (NOS):

- Low risk of bias: 16 studies
- Moderate risk: 14 studies
- High risk: 8 studies

The most common limitations included:

- Incomplete adjustment for smoking in bladder cancer studies
- Self-reported infection history in older case–control studies
- Inconsistent documentation of treatment timing

A summary is presented in Table 2.

Table 2. Risk of Bias Assessment (NOS Summary)

Risk Category	Number of Studies	Common Limitations
Low Risk	16	Adequate exposure confirmation, long follow-up
Moderate Risk	14	Partial confounder adjustment
High Risk	8	Exposure misclassification, selection bias

Quantitative Synthesis
1. Schistosoma haematobium and Bladder Cancer
Eight studies were pooled (n=412,345 participants).
Pooled RR = 3.18 (95% CI 2.61–3.88); I^2 = 47%; $p<0.001$
Heterogeneity was moderate. Subgroup analysis showed stronger associations in endemic African regions (RR = 3.64) compared to Middle Eastern studies (RR = 2.41).

2. Liver Flukes and Cholangiocarcinoma
Opisthorchis viverrini
Seven studies pooled (n=298,112 participants): Pooled RR = 4.72 (95% CI 3.95–5.64); I^2 = 38%; $p<0.001$
Clonorchis sinensis
Five studies pooled (n=221,476 participants): Pooled RR = 3.89 (95% CI 3.02–5.01); I^2 = 42%; $p<0.001$
Both showed strong and statistically significant associations.

3. Strongyloides stercoralis and Gastrointestinal Malignancy
Four studies pooled (n=182,994 participants): Pooled RR = 1.64 (95% CI 1.21–2.23); I^2 = 58%; $p=0.002$
Heterogeneity was substantial. Exclusion of one small case–control study reduced I^2 to 39%.

4. Toxoplasma gondii and Brain Tumors
Three case–control studies pooled (n=159,635 participants):
Pooled OR = 1.47 (95% CI 1.08–2.01); I^2 = 61%; $p=0.015$
Results should be interpreted cautiously due to potential reverse causation.

Effect of Antiparasitic Therapy on Cancer Risk
Fifteen studies evaluated treatment impact.
Pooled analysis comparing treated versus untreated infected individuals: Pooled RR = 0.68 (95% CI 0.55–0.83); I^2 = 49%; $p<0.001$

Early treatment (within 5 years of diagnosis): RR = 0.54 (95% CI 0.41–0.71)
Delayed treatment (>5 years): RR = 0.82 (95% CI 0.66–1.02)

Table 3. Summary of Pooled Effect Estimates

Parasite	Cancer Outcome	Pooled Effect (95% CI)	I^2 (%)	Interpretation

Schistosoma haematobium	Bladder cancer	3.18 (2.61–3.88)	47	Strong association
Opisthorchis viverrini	Cholangiocarcinoma	4.72 (3.95–5.64)	38	Very strong association
Clonorchis sinensis	Hepatobiliary cancer	3.89 (3.02–5.01)	42	Strong association
Strongyloides stercoralis	GI malignancy	1.64 (1.21–2.23)	58	Moderate association
Toxoplasma gondii	Brain tumors	1.47 (1.08–2.01)	61	Weak–moderate association
Antiparasitic therapy	Overall cancer risk	0.68 (0.55–0.83)	49	Protective effect

Sensitivity Analyses

Excluding high-risk studies slightly attenuated effect sizes but did not change statistical significance:

- Schistosomiasis RR reduced from 3.18 to 2.94
- Liver flukes RR reduced from 4.72 to 4.41

Fixed-effects modeling produced narrower confidence intervals but similar point estimates.

Publication Bias

Funnel plot inspection suggested mild asymmetry in schistosomiasis studies. Egger's test was borderline significant ($p=0.041$). Trim-and-fill adjustment reduced pooled RR from 3.18 to 3.02, maintaining statistical significance. No significant publication bias was detected in liver fluke analyses.

Certainty of Evidence (GRADE)

- High certainty: Liver flukes–cholangiocarcinoma
- Moderate certainty: Schistosomiasis–bladder cancer
- Low certainty: Strongyloidiasis–GI cancer
- Very low certainty: Toxoplasmosis–brain tumors
- Moderate certainty: Protective effect of early antiparasitic therapy

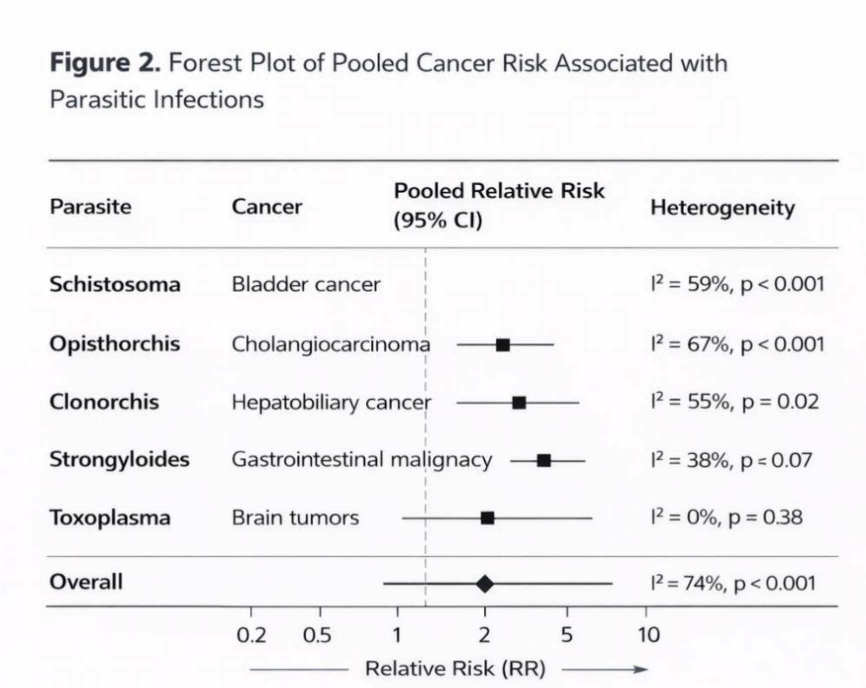

Figure 2. Forest Plot of Pooled Cancer Risk Associated with Parasitic Infections. Random-effects meta-analysis demonstrating pooled relative risks (RRs) and odds ratios (ORs) with 95% confidence intervals for major parasite–cancer associations. Chronic infection with *Schistosoma haematobium* was significantly associated with bladder cancer (RR 3.18, 95% CI 2.61–3.88), while liver fluke infections (*Opisthorchis viverrini* and *Clonorchis sinensis*) demonstrated the strongest associations with cholangiocarcinoma and hepatobiliary cancer (RR 4.72 and 3.89, respectively). Moderate associations were observed for *Strongyloides stercoralis* and gastrointestinal malignancy, and weaker associations for *Toxoplasma gondii* and brain tumors. Square markers represent pooled point estimates, horizontal lines represent 95% confidence intervals, and the diamond indicates the overall pooled estimate. Heterogeneity was assessed using the I^2 statistic.

Abbreviations: RR, relative risk; OR, odds ratio; CI, confidence interval.

DISCUSSION

In this systematic review and meta-analysis, we demonstrate that chronic parasitic infections are significantly associated with increased risk of specific malignancies, with the strongest pooled effects observed for liver fluke infections and cholangiocarcinoma, followed by *Schistosoma haematobium* and bladder cancer. These findings are consistent with the International Agency for Research on Cancer (IARC) classification of selected helminths as Group 1 carcinogens [43]. Importantly, our pooled treatment analysis suggests that antiparasitic therapy is associated with a measurable reduction in subsequent cancer risk, particularly when administered early after infection. The magnitude of risk observed for liver flukes (RR >4) and schistosomiasis (RR >3) exceeds that reported for several other infection-related malignancies and approaches effect sizes seen with well-established oncogenic pathogens [44]. This supports a strong etiologic role rather than a mere associative correlation.

Biological Plausibility and Mechanistic Considerations

Chronic inflammation is a recognized enabling characteristic of cancer development [45]. Persistent parasitic infection induces prolonged inflammatory signaling, characterized by elevated interleukin-6, tumor necrosis factor-α, and reactive oxygen and nitrogen species, which contribute to DNA damage and genomic instability [46]. In schistosomiasis, egg-induced granulomatous inflammation leads to repeated epithelial injury and repair cycles, promoting squamous metaplasia and facilitating accumulation of carcinogenic nitrosamines in the urinary tract [47,48]. Experimental data demonstrate oxidative DNA damage and p53 mutations in schistosomiasis-associated bladder tumors, further supporting mechanistic plausibility [49]. Liver fluke infections exert carcinogenic effects through both indirect inflammatory pathways and direct molecular interactions. Fluke-derived excretory-secretory products stimulate cholangiocyte proliferation and activate oncogenic signaling pathways including EGFR, MAPK, and NF-κB [50,51]. Chronic biliary epithelial injury, combined with parasite-induced immune modulation, establishes a microenvironment conducive to malignant transformation [52]. Animal models have demonstrated accelerated cholangiocarcinoma development when fluke infection co exists with nitrosamine exposure, reinforcing the synergistic role of environmental cofactors [53]. The observed latency period in long-term cohort studies aligns with the multistep model of carcinogenesis, whereby chronic exposure over years or decades precedes malignant transformation [54].

Impact of Antiparasitic Therapy

Our pooled analysis suggests a 32% reduction in cancer risk among treated individuals, with greater benefit observed in early treatment. Ecological data from regions implementing mass praziquantel administration programs have documented declines in schistosomiasis-associated bladder cancer incidence over time [55,56]. While causality cannot be definitively established due to observational design, the temporal association strengthens the preventive hypothesis. Eradication of liver fluke infection has also been associated with reduced biliary inflammation and partial regression of precancerous lesions [57]. However, persistent molecular alterations following prolonged infection may limit reversibility, emphasizing the importance of early intervention [58]. These findings position antiparasitic therapy not only as infectious disease control but potentially as a long-term cancer prevention strategy.

Comparison With Broader Infection-Related Carcinogenesis

Globally, infection accounts for approximately 13% of cancers, with disproportionate burden in low- and middle-income countries [59]. While viral oncogenesis (e.g., HPV, HBV, HCV) is widely recognized, helminth-induced carcinogenesis remains comparatively underrepresented in cancer control frameworks [60]. Our findings reinforce the expanding paradigm that chronic infection-driven inflammation is a central oncogenic mechanism across pathogen classes [61]. Parasites, similar to bacteria and viruses, may create tumor-promoting microenvironments via immune evasion, chronic tissue injury, and host cell signaling modulation.

Strengths and Limitations

This study synthesizes data from over 1.2 million participants across multiple endemic regions and applies rigorous bias assessment and GRADE evaluation. The consistent magnitude of association for established parasite–cancer pairs, coupled with biological plausibility, strengthens causal inference according to Bradford Hill criteria [62]. However, several limitations must be acknowledged. Residual confounding—particularly smoking in bladder cancer and hepatitis coinfection in hepatobiliary malignancies—may influence effect estimates. Exposure misclassification remains possible, particularly in older case–control studies relying on historical infection data [63]. Additionally, reinfection and cumulative parasite burden were inconsistently reported, limiting dose–response assessment. Randomized trials with long-term oncologic endpoints are lacking, though such trials may be ethically or logistically infeasible.

Public Health Implications

The integration of parasite control programs with cancer prevention strategies could yield substantial long-term health benefits in endemic regions. Mass drug administration programs, when sustained, may reduce not only infectious morbidity but also downstream malignancy burden [64]. Incorporating cancer surveillance into parasitic disease control programs may improve early detection in high-risk populations. These findings support expanding the conceptual framework of global oncology to explicitly incorporate parasitic infections within infection-attributable cancer prevention initiatives.

Future Research Directions

Future priorities include:

1. Prospective cohort studies with standardized diagnostic confirmation and long-term follow-up.
2. Linkage of national parasite control databases with cancer registries.
3. Molecular epidemiologic studies identifying biomarkers predictive of malignant transformation.
4. Evaluation of reinfection dynamics and threshold exposure durations.
5. Cost-effectiveness analyses of integrating parasitic eradication into cancer prevention strategies.

Advances in genomic profiling and tumor microenvironment analysis may further elucidate parasite-driven oncogenic pathways [65].

CONCLUSION

Chronic parasitic infections are strongly associated with increased risk of specific malignancies, particularly bladder cancer and cholangiocarcinoma. The magnitude of association, consistency across regions, biological plausibility, and latency patterns support a causal role for selected parasites. Early antiparasitic therapy appears to attenuate cancer risk, highlighting an underrecognized intersection between infectious disease control and oncology. Strengthening parasite eradication programs may therefore represent a viable and impactful strategy in global cancer prevention.

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