Global epidemiology of *Giardia duodenalis* infection in cancer patients: a systematic review and meta-analysis

Farzad Mahdavi, Alireza Sadrebazzaz, Amir Modarresi Chahardehi, Roya Badali, Mostafa Omidiane, Soheil Hassanipour and Ali Asghari

*Department of Medical Parasitology and Mycology, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran; bRazi Vaccine and Serum Research Institute, Agricultural Research, Education and Extension Organization, Mashhad, Iran; cIntegrative Medicine Cluster, Advanced Medical and Dental Institute, Universiti Sains Malaysia, Bertam, Kepala Batas, 13200, Penang, Malaysia; dDepartment of Microbiology, Faculty of Basic Sciences, Ardabil Branch, Islamic Azad University, Ardabil, Iran; eDepartment of Medical Parasitology and Mycology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran; fGastrointestinal and Liver Diseases Research Center, Guilan University of Medical Sciences, Rasht, Iran

*Corresponding author: Tel: +989120236311; E-mail: a_asghari@sums.ac.ir

Received 29 January 2021; revised 28 March 2021; editorial decision 27 April 2021; accepted 2 May 2021

**Background:** Application of chemotherapeutics in cancer patients may provide an immunosuppressive milieu, favourable for parasitic infections. *Giardia duodenalis* is an important zoonotic intestinal parasite responsible for diarrhoea in humans worldwide.

**Methods:** The present systematic review and meta-analysis was conducted to estimate the prevalence of *G. duodenalis* and respective odds ratios (ORs) in cancer patients around the globe. Four online databases—PubMed, Scopus, Web of Science and Google Scholar—were carefully explored for relevant literature without time limitation until 28 November 2020. Meta-analysis was done based on a random effects model to pool the estimations and define 95% confidence intervals (CIs).

**Results:** The overall weighted prevalence of *G. duodenalis* infection in cancer patients was calculated to be 6.9% (95% CI 0.5 to 9.3) globally, based on data from 32 studies. Although not statistically significant, eight case–control studies revealed that cancer patients were 1.24 times (95% CI 0.66 to 2.31; *p* = 0.501) more exposed to *G. duodenalis* infection than healthy controls. Moreover, the prevalence of infection was not significantly associated with quantitative variables, including publication year (regression coefficient = −0.0135, *p* = 0.578), sample size (regression coefficient = −0.0007, *p* = 0.074) and human development index (regression coefficient = −1.6263, *p* = 0.419). Also, subgroup analysis of the pooled *G. duodenalis* infection was performed for publication year, World Health Organization regions, countries, continents, cancer types and country income.

**Conclusions:** Altogether, the epidemiology of *G. duodenalis* infection and its associated risk factors in immunocompromised individuals, especially cancer patients, is still open to question and deserves comprehensive investigations.

**Keywords:** cancer patients, *Giardia duodenalis*, *Giardia intestinalis*, *Giardia lamblia*, meta-analysis, odds ratios (ORs), prevalence, systematic review.

**Introduction**

A quarter of the world suffers from inadequate hygienic settings and diagnostic options, leading to underestimated and/or chronic parasitic infections, which are a major cause of morbidity and mortality worldwide. Such infections are also overlooked in industrialized nations due to their low prevalence and the fact that they do not have pathognomonic signs. Thus they are a silent threat, particularly in immunocompromised individuals undergoing chemotherapy, leading to hyperinfection by parasitic as well as other infectious agents. The flagellated diplomonad protozoan *Giardia duodenalis* (also known as *Giardia intestinalis* and *Giardia lamblia*) is the most common species of the genus.
Giardia, infecting various mammals, including domestic animals and humans.5–7 In total, epidemiological investigations through 2011 show that approximately 280 million human diarrhoea cases occur annually due to Giardia infection, particularly in children <5 y of age, and with a varying prevalence of 0.4–7.5% in developed countries and to 8–30% in underdeveloped countries. Nevertheless, the true prevalence of the parasite is significantly underestimated and much work is needed to accurately clarify this issue.6–8

The life cycle of G. duodenalis occurs in canine, feline and human hosts. In brief, the parasite encysts in the intestine of susceptible infected humans/animals and the cystic stages are shed to the environment via faeces.9 Human infection primarily occurs via the faecal–oral route by consumption of cyst-contaminated food or water and contact with infected hosts.10,11 Following excystation by gastric acid and pancreatic enzymes, each cyst releases two motile pear-shaped trophozoites that colonize the duodenum and jejunum and consume bile salts, which further provokes deconjugation and lipid metabolism dysfunction.12 In total, disease manifestation depends on the parasite genotype and infective dose as well as host-related factors such as nutritional and immunological status.13 Since September 2004, giardiasis was included in the Neglected Diseases Initiatives of the World Health Organization (WHO), due to its negative effect on child health and pregnancy as well as being in parallel with poverty.11

The infection is usually asymptomatic. While clinical giardiasis is frequently associated with children <5 y of age or pre-school children living in poor sanitary environments, elderly people and patients with immunodeficiency manifest a variety of gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal cramps and epigastric pain, bloating and progressive weight loss.14–16 Notably, chronic Giardia infection in children, particularly in developing countries, may be associated with growth retardation and cognitive impairment.17 Faecal microscopy is routinely used for the diagnosis of G. duodenalis infection. Also, immunodiagnostic assays such as enzyme-linked immunosorbent assay (ELISA) for antibody or copro-antigen detection as immunodiagnostic assays such as enzyme-linked immunosorbent assay (ELISA) for antibody or copro-antigen detection as well as molecular techniques are applicable.18 According to several genetic markers, including small subunit ribosomal RNA (SSU-rRNA) and the triosephosphate isomerase (tpi), glutamate dehydrogenase (gdh) and β-giardin (bg) genes, eight morphologically indistinguishable assemblages of G. duodenalis have been confirmed, comprising assemblages A and B (humans and other mammals), C and D (dog and other canids), E (hoofed animals), F (cats), G (rodents) and H (pinnipeds). A single G. duodenalis isolate can actually be assigned to different assemblages based on the above-mentioned markers. Identification of the same assemblages or multilocus genotypes in humans and animals of a particular region implicates a zoonotic infection, although the actual role of zoonotic pathways is highly neglected in the epidemiology of giardiasis.14–19–21 Humans are mostly infected by assemblages A and B, and to a lesser extent by assemblages C, E and F.22–24 Assemblages A and B are further subtyped into A1 (mostly zoonotic), A1I (mostly anthroponotic), A1II (hoofed animals), B1III and BIV. Convincing evidence suggest that assemblage B is more virulent and prevalent in outbreaks than assemblage A. However, there exists no scientific basis to correlate the course of the infection and/or clinical symptoms to G. duodenalis assemblages.12–14

More than 2 decades of investigation on Giardia pathogenicity indicate that disease initiation and progression is a multifactorial process, being associated with parasitic, host, nutritional, environmental and immunological factors.25,26 An in-depth look at Giardia pathogenicity shows intestinal barrier dysfunction, elevation of enterocyte apoptosis, host lymphocyte activation, a shortage of brush-border microvilli and atrophy of the intestinal villi, which entails epithelial maladaptation and malabsorption, hypersecretion of anions and subsequent acute diarrhoea. This cascade of events may also facilitate bacterial invasion towards the submucosal layers. Proteomic profiling of Giardia trophozoites demonstrated that cysteine proteases, especially cathespin L (cat(L))-like and cathepsin B (catB)-like enzymes, may be associated with the increased pathophysiological responses during giardiasis.27–29

Diarrhoea is a prominent cause of death in immunocompromised people, with particular emphasis on children <5 y of age. G. duodenalis is known as one of the significant agents of diarrhoea in mammals, including humans, along with rotavirus, Cryptosporidium species, Escherichia coli, Clostridium difficile and Shigella species. The disease in people with a healthy immune status is self-limiting, without a clinical course, whereas immunocompromised patients may experience harsh clinical outcomes.30–32 Therefore the importance of giardiasis in cancer patients and its proven pathogenicity led us to implement the first global systematic review and meta-analysis on the pooled prevalence of Giardia infection and respective odds ratios (ORs) in cancer patients compared with healthy individuals and the associated risk factors.

**Methods**

**Systematic search strategy and selection criteria**

The results of the present systematic review and meta-analysis were reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist.33 Two expert investigators (AA and SH) searched four English electronic databases (PubMed, Scopus, Google Scholar and Web of Science) without a time limitation until 28 November 2020 to retrieve articles investigating the prevalence of G. duodenalis in cancer patients globally. For this purpose, the following search keywords were used alone or in combination: ‘intestinal parasites’, ‘parasitic infections’, ‘giardiasis’, ‘Giardia duodenalis’, ‘Giardia intestinalis’, ‘Giardia lamblia’, ‘prevalence’, ‘epidemiology’, ‘frequency’, ‘occurrence’, ‘cancer’, ‘neoplasm’, ‘malignancy’, ‘tumor’, and ‘carcinoma’ using OR and/or AND Boolean operators. A set of keywords was employed for better exploration of relevant literature regarding cancer patients (Table 1). Also, the bibliographies of related papers were scrutinized to extract papers not found through database searching.

Initial screening was only based on the abstract and title of papers. After duplicate removal, the full texts of eligible articles were obtained via online databases. Evaluation of eligibility was done by four trained investigators and possible disagreements were settled by discussion and consensus with the fifth reviewer. The following inclusion criteria were used for qualified studies: the study population was limited to cancer patients;
peer-reviewed original papers without any geographical and time limitation until 28 November 2020; cross-sectional studies investigating G. duodenalis prevalence in a particular sample size of cancer patients; case–control studies reporting cancer (as exposure) and G. duodenalis infection (as outcome) having specified ORs; and molecular- and/or microscopy-based studies evaluating stool samples regarding G. duodenalis infection. Those studies that did not meet the inclusion criteria, including case studies, reviews, letters, studies on non-cancerous immunocompromised patients and/or immunocompetent individuals, animal studies, seroprevalence reports, experimentally infected individuals, studies without prevalence reports and studies with unclear/confusing information were excluded from the present review. The following variables were extracted using a predesigned checklist for each study: first author’s last name, quality assessment score, publication year, implementation year, continent, country, WHO region, country income, study type, cancer type, total sample size, infected sample size and Human Development Index (HDI). In the present study, information about country income was obtained from the World Bank https://datahelpdesk.worldbank.org, which has been updated through 2019.

Quality assessment and data extraction
The quality of the papers was another parameter required for the inclusion of relevant records. For this purpose, Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Studies Reporting Prevalence Data was employed. Those articles that scored 4–6 and 7–10 points were deemed moderately and highly qualified, respectively. Accordingly, articles with a score of ≤ 3 points were excluded from this systematic review.

Data synthesis and statistical analysis
Statistical analyses were conducted using the Comprehensive Meta-Analysis version 3 software (Biostat, Englewood, NJ, USA). The prevalence of G. duodenalis infection in cancer patients was assessed by computing pooled prevalence and 95% confidence intervals (CIs) using a random effects model. This model is used in the case of heterogeneity, which provides the distribution of true effect sizes among published papers. Subgroup analyses were used to estimate the weighted frequency of G. duodenalis infection based on WHO regions, geographical distribution, country incomes, publication years, continents, cancer types and HDI. Weighted odds ratios (WORs) and 95% CIs were calculated to correlate the G. duodenalis infection to cancer patients and their respective control groups. Also, any variations in the finally calculated WORs were evaluated by sensitivity analysis. The results were shown as forest plots of the weighted prevalence (with 95% CI) of G. duodenalis infection in cancer patients. The funnel plot was used to check the probability of publication bias during the analysis. Meta-regression was used to assess the possible association between variables such as publication year, sample size and HDI index with G. duodenalis prevalence in cancer patients. Heterogeneity between studies was assessed using the I^2 index, so that I^2 values <25%, 25–50% and >50% were considered to have low, moderate and high heterogeneity, respectively. P-values <0.05 were considered statistically significant.

Results
Summary of the systematic search
Figure 1 provides a flowchart summarizing the procedure of the systematic search strategy and selection of qualified studies. In brief, our primary systematic searching identified 11 721 papers. After initial screening based on title and abstract along with removal of duplicates, 104 articles were subjected to the complete review process by trained investigators. Of these, 32 papers qualified to be included in the present systematic review and meta-analysis.

Qualitative and quantitative characteristics of included studies
The main characteristics of the included papers are provided in Table 2. According to geographical location, most studies (14 papers) were from Iran, followed by 3 from Turkey, 3 from Egypt, 2 from Brazil, 2 from India, and 1 each from...
Studies identified through international database search (n=11721)

Studies remained after removal of the duplicates (n=8506)

Studies excluded after title and abstract screening (n=8402)

Full-text papers assessed for eligibility (n=104)

Papers excluded for various reasons (n=72)

Studies remained for qualitative and quantitative analyses (n=32)

Figure 1. Flowchart of the included eligible studies in the systematic review.

Indonesia,59 Iraq,60 Malaysia,61 Mexico,62 Poland,63 Uganda,64 Uzbekistan65 and Yemen.66 Overall, 21 studies were from Asia (3706 individuals), followed by 4 studies from Africa (2268 individuals), 4 from Europe (687 individuals), 2 from South America (143 individuals) and 1 from North America (77 individuals). The sample size ranged from 10 to 1771 individuals and the oldest study was conducted in 1997.57 A total of 26 studies were done among patients having mixed cancer types, followed by 4 and 2 studies on patients with haematological malignancies (HMs) and colorectal cancer (CRC), respectively. Based on the epidemiological design of studies, 27 were cross-sectional studies, whereas only 8 had a case-control design. Among all included studies, 27 assessed the *Giardia* infection by faecal microscopy and 5 studies used both microscopic and molecular techniques. The JBI checklist found that 6 articles had high quality (>6 points) and the remaining 26 had moderate quality (4–6 points) (Supplementary File 1).

Pooled prevalence of *G. duodenalis* infection in cancer patients

The estimated weighted prevalence of *G. duodenalis* infection in cancer patients was computed to be 6.9% (95% CI 0.5 to 9.3) (Figure 2). The heterogeneity analysis illustrates that there was high-level, significant heterogeneity in our meta-analysis regarding cancer patients ($Q=272.464, I^2=88.6\%, p=0.000$).

Association of cancer patients with *G. duodenalis* infection

Of the eight case-control studies conducted in four countries worldwide, the estimated pooled random effects ORs of cancer patients compared with their controls was calculated to be 1.24 (95% CI 0.66 to 2.31; $p=0.501$) for infection with *G. duodenalis*. In other words, cancer patients were 1.24 times more
| Author, year | Implementation year | Country | Cases | Controls | Total sample size, n | Prevalence, % | Study type | Diagnostic method | Cancer type | Quality score | Reference |
|-------------|---------------------|---------|-------|----------|---------------------|---------------|------------|------------------|-------------|---------------|----------|
| Rudrapatna, 1997 | UC | India | 1029 | - | 3.1 | C-S | Mic | Mixed | 4 | 57 |
| Menon, 1999 | 1996–1997 | Malaysia | 50 | - | 6 | C-S | Mic | Mixed | 4 | 61 |
| Togeh, 2000 | 1996–1997 | Iran | 261 | 200 | 13.8 | C-S | Mic | HM | 5 | 48 |
| Tasava, 2000 | 1997–1998 | Turkey | 206 | 200 | 6.8 | C-C | Mic | Mixed | 4 | 60 |
| Gharavi, 2003 | UC | Iran | 141 | 70 | 17 | C-C | Mic | HM | 6 | 40 |
| Robinson, 2006 | 1997–2001 | Uganda | 1771 | - | 3.5 | C-S | Mic | Mixed | 4 | 64 |
| Monsef, 2008 | 2005–2006 | Iran | 190 | - | 5.8 | C-S | Mic | Mixed | 4 | 45 |
| Idris, 2010 | 2008–2009 | Indonesia | 10 | - | 10 | C-S | Mic | Mixed | 7 | 59 |
| Hazrati-Tappeh, 2011 | 2007–2008 | Iran | 101 | - | 7.9 | C-S | Mic | Mixed | 4 | 62 |
| El-Mahallawy, 2011 | 2008–2009 | Egypt | 271 | 60 | 5.2 | C-C | Mic | Mixed | 5 | 54 |
| Sulzyc-Bielicka, 2012 | 2009–2010 | Poland | 87 | - | 1.1 | C-S | Mic | CRC | 4 | 63 |
| Al-Qabati, 2012 | 2011–2012 | Yemen | 206 | - | 18 | C-S | Mic | Mixed | 4 | 66 |
| Jiménez-Cordoso, 2013 | 2010–2011 | Mexico | 77 | - | 2.6 | C-S | Mol | HM | 6 | 62 |
| Durak, 2013 | UC | Turkey | 337 | - | 14.8 | C-S | Mic | Mixed | 4 | 50 |
| El-Mahallawy, 2013 | 2011–2012 | Egypt | 89 | 100 | 14.6 | 16 | C-C | Mic and ELISA | Mixed | 6 | 53 |
| Berenji, 2013 | 2008–2009 | Iran | 89 | - | 18 | C-S | Mic | HM | 5 | 37 |
| Bora, 2016 | UC | India | 15 | - | 20 | C-S | Mic | Mixed | 5 | 58 |
| Silva, 2016 | 2011–2012 | Brazil | 70 | - | 8.6 | C-S | Mic and ELISA | Mixed | 6 | 56 |
| Abdul Hussein, 2017 | 2015–2016 | Iraq | 106 | - | 18.9 | C-S | Mic | Mixed | 7 | 60 |
| Berahmat, 2017 | 2015–2016 | Iran | 132 | 132 | 3 | 1.5 | C-C | Mic | Mixed | 7 | 36 |
| Mohammadi, 2017 | 2015–2016 | Iran | 100 | - | 2 | C-S | Mic | Mixed | 5 | 39 |
| Esteghamati, 2018 | 2016–2017 | Iran | 85 | - | 2.4 | C-S | Mic | Mixed | 5 | 38 |
| Jeske, 2018 | UC | Brazil | 73 | - | 16.4 | C-S | Mic | Mixed | 6 | 55 |
| Toychiev, 2018 | 2015–2017 | Uzbekistan | 200 | 200 | 10 | 16 | C-C | Mic and ELISA | CRC | 7 | 65 |
| Taghipour, 2018 | 2017–2018 | Iran | 10 | - | 10 | C-S | Mic | Mixed | 5 | 47 |
| Salehi, 2018 | 2016–2017 | Iran | 150 | - | 0.7 | C-S | Mic | Mixed | 4 | 46 |
| Izodi, 2019 | 2015–2016 | Iran | 87 | - | 3.5 | C-S | Mic | Mixed | 7 | 43 |
| El-Badry, 2019 | 2013–2015 | Egypt | 137 | - | 1.5 | C-S | Mol | Mixed | 5 | 52 |
| Ghoyounchi, 2019 | 2015–2016 | Iran | 132 | - | 3 | C-S | Mic | Mixed | 6 | 41 |
| Akgul, 2020 | 2016–2017 | Turkey | 57 | 90 | 26.3 | 7.8 | C-C | Mol | Mixed | 6 | 49 |
| Mahmoudi, 2020 | 2017–2018 | Iran | 362 | 399 | 0 | 2 | C-C | Mic | Mixed | 7 | 44 |
| Banihashemi, 2020 | 2018–2019 | Iran | 250 | - | 2 | C-S | Mol | Mixed | 5 | 35 |

*UC: unclear; Mic: microscopic method; Mol: molecular method; C-C: case–control study; C-S: cross-sectional study.*
Table 1. The estimated pooled prevalence of *G. duodenalis* infection in cancer patients.

| Study name                          | Event rate | Lower limit | Upper limit |
|-------------------------------------|------------|-------------|-------------|
| Rudrapatna, 1997                    | 0.031      | 0.022       | 0.044       |
| Menon, 1999                         | 0.060      | 0.019       | 0.170       |
| Togeh, 2000                         | 0.138      | 0.101       | 0.185       |
| Tasova, 2000                        | 0.068      | 0.041       | 0.112       |
| Gharavi, 2003                       | 0.170      | 0.117       | 0.241       |
| Robinson, 2006                       | 0.035      | 0.027       | 0.045       |
| Monsef, 2008                        | 0.058      | 0.032       | 0.102       |
| Idris, 2010                         | 0.100      | 0.014       | 0.467       |
| Hazrati-Tappeh, 2011                | 0.079      | 0.040       | 0.150       |
| El-Mahallawy, 2011                   | 0.052      | 0.031       | 0.086       |
| Sulzyc-Bielicka, 2012                | 0.011      | 0.001       | 0.077       |
| Al-Qobati, 2012                      | 0.180      | 0.133       | 0.239       |
| Jiménez-Cardoso, 2013                | 0.026      | 0.007       | 0.098       |
| Durak, 2013                          | 0.148      | 0.114       | 0.190       |
| El-Mahallawy, 2013                   | 0.146      | 0.087       | 0.235       |
| Berenji, 2013                        | 0.180      | 0.113       | 0.274       |
| Bora, 2016                           | 0.200      | 0.066       | 0.470       |
| Silva, 2016                          | 0.086      | 0.039       | 0.178       |
| Abdul Hussein, 2017                  | 0.189      | 0.125       | 0.275       |
| Berahmat, 2017                       | 0.030      | 0.011       | 0.078       |
| Mohammadi, 2017                      | 0.020      | 0.005       | 0.076       |
| Esteghamati, 2018                    | 0.024      | 0.006       | 0.090       |
| Jeske, 2018                          | 0.164      | 0.095       | 0.267       |
| Toychev, 2018                        | 0.100      | 0.065       | 0.150       |
| Taghipour, 2018                      | 0.100      | 0.014       | 0.467       |
| Salehi, 2018                         | 0.007      | 0.001       | 0.046       |
| Izadi, 2019                          | 0.035      | 0.011       | 0.102       |
| El-Badry, 2019                       | 0.015      | 0.004       | 0.057       |
| Ghoyounchi, 2019                     | 0.030      | 0.011       | 0.078       |
| Akgul, 2020                          | 0.263      | 0.165       | 0.392       |
| Banihashemi, 2020                    | 0.020      | 0.008       | 0.047       |
| Mahmoudi, 2020                       | 0.001      | 0.000       | 0.022       |
|                                 | 0.069      | 0.050       | 0.093       |

Figure 2. The estimated pooled prevalence of *G. duodenalis* infection in cancer patients.

Exposed to *G. duodenalis* infection than healthy controls, although this association was not statistically significant (Figure 3). Regarding case–control studies, the heterogeneity analysis showed that there was relatively high-level heterogeneity in our meta-analysis (Q=20.580, I²=65.9%, p=0.004).

**Sensitivity analysis**

The sensitivity analysis illustrated that by ignoring each of the eight studies with ORs, there was no significant change in the final OR and, again, immunodeficiency due to cancer was not a statistically significant risk factor for *G. duodenalis* infection (Supplementary File 2).

**Subgroup analysis of *G. duodenalis* infection in different examined groups**

The results of the subgroup analyses are shown in Table 3. The estimated pooled prevalence of giardiasis, on a country basis,
Table 1. Odds ratio and 95% CI for each study

| Study name          | Odds ratio | Lower limit | Upper limit | p-Value | Cases | Controls |
|---------------------|------------|-------------|-------------|---------|-------|----------|
| Tasova, 2000        | 2.844      | 1.005       | 8.049       | 0.049   | 14 / 206 | 5 / 200  |
| Gharavi, 2003       | 1.590      | 0.675       | 3.747       | 0.289   | 24 / 141 | 8 / 70   |
| El-Mahallawy, 2011  | 0.763      | 0.242       | 2.404       | 0.644   | 14 / 271 | 4 / 60   |
| El-Mahallawy, 2013  | 0.898      | 0.406       | 1.988       | 0.791   | 13 / 89  | 16 / 100 |
| Berahmat, 2017      | 2.031      | 0.366       | 11.285      | 0.418   | 4 / 132  | 2 / 132  |
| Toychiev, 2018      | 0.583      | 0.321       | 1.060       | 0.077   | 20 / 200 | 32 / 200 |
| Akgul, 2020         | 4.235      | 1.604       | 11.181      | 0.004   | 15 / 57  | 7 / 90   |
| Mahmoudi, 2020      | 0.064      | 0.004       | 1.105       | 0.059   | 0 / 362  | 8 / 399  |

Figure 3. A meta-analysis of the association of cancer patients and G. duodenalis infection using random effects analysis.

Discussion

A prevalence rate of 0.4–30% is estimated for Giardia infection in immunocompetent hosts, while there is no available information regarding the total prevalence and likely pathogenicity of G. duodenalis in immunocompromised people, especially in cancer patients. Therefore we conducted the present systematic review and meta-analysis to elucidate the prevalence and risk factors of G. duodenalis infection among cancer patients worldwide. Also, the association of immunodeficiency status with the parasitic infection was evaluated by estimation of a pooled OR derived from case-control studies.

A relatively moderate worldwide prevalence (6.9%) of Giardia infection in cancer patients was the principal finding of the present review. Moreover, cancer patients were shown to be 1.24-fold more susceptible and were at a higher risk of infection, which should alert physicians to the possible consequences.

Publication bias

There was no significant publication bias in the present systematic review and meta-analysis (p=0.221) (Figure 6).

Meta-regression

Our meta-regression results did not report a statistically significant association between the prevalence of G. duodenalis infection in cancer patients and quantitative variables such as publication year, sample size and HDI. Therefore the year of study (regression coefficient =−0.0135, p=0.578), sample size (regression coefficient =−0.0007, p=0.074) and HDI (regression coefficient =−1.6263, p=0.419) were not considered as a cause of variability in the results of Giardia infection rate in cancer patients (Figure 5).
Table 3. Subgroup analysis of the prevalence of G. duodenalis infection based on publication year, country income, continent, WHO region, country and cancer type

| Subgroup variable | Prevalence, % (95% CI) | Heterogeneity (Q) | I² (%) | p-Value |
|-------------------|------------------------|------------------|--------|---------|
| **Publication year** | | | | |
| ≤2000             | 6.60 (3.0 to 13.90)    | 40.206           | 92.5   | <0.001  |
| 2001–2005         | 17.0 (11.70 to 24.10)  | –                | –      | >0.999  |
| 2006–2010         | 5.10 (1.90 to 13.10)   | 3.441            | 41.9   | 0.179   |
| 2011–2015         | 9.40 (5.40 to 16.10)   | 35.443           | 80.3   | <0.001  |
| 2016–2020         | 5.80 (3.70 to 8.90)    | 94.629           | 84.1   | <0.001  |
| **Country income** | | | | |
| Low               | 8.10 (2.70 to 22.10)   | 65.345           | 98.5   | <0.001  |
| Lower-middle      | 6.70 (3.30 to 13.10)   | 39.931           | 87.5   | <0.001  |
| Upper-middle      | 7.10 (4.90 to 10.20)   | 118.307          | 81.4   | <0.001  |
| High              | 1.10 (0.10 to 7.70)    | –                | –      | >0.999  |
| **Continent**     | | | | |
| Africa            | 5.0 (2.20 to 11.10)    | 25.388           | 88.2   | <0.001  |
| Asia              | 6.60 (4.50 to 9.60)    | 152.255          | 86.9   | <0.001  |
| Europe            | 10.60 (4.60 to 22.50)  | 22.172           | 86.5   | <0.001  |
| North America     | 2.60 (0.70 to 9.80)    | –                | –      | >0.999  |
| South America     | 12.20 (3.90 to 32.10)  | 1.917            | 47.8   | 0.166   |
| **WHO region**    | | | | |
| AFR               | 3.50 (2.70 to 4.50)    | –                | –      | >0.999  |
| AMR               | 8.50 (3.20 to 20.30)   | 7.124            | 71.9   | 0.028   |
| EMR               | 6.30 (4.30 to 9.20)    | 118.138          | 84.8   | <0.001  |
| EUR               | 10.60 (5.30 to 20.00)  | 23.998           | 83.3   | <0.001  |
| SEAR              | 7.10 (2.50 to 18.40)   | 10.468           | 80.9   | 0.005   |
| WPR               | 6.0 (1.90 to 17.0)     | –                | –      | >0.999  |
| **Country**       | | | | |
| Brazil            | 12.20 (3.80 to 32.60)  | 1.917            | 47.8   | 0.166   |
| Egypt             | 5.80 (2.10 to 14.90)   | 13.872           | 85.6   | 0.001   |
| India             | 6.70 (1.90 to 20.70)   | 9.414            | 89.4   | 0.002   |
| Indonesia         | 10.0 (1.40 to 46.70)   | –                | –      | >0.999  |
| Iran              | 5.0 (3.0 to 8.10)      | 79.128           | 83.6   | <0.001  |
| Iraq              | 18.90 (12.50 to 27.50) | –                | –      | >0.999  |
| Malaysia          | 6.0 (1.90 to 17.0)     | –                | –      | >0.999  |
| Mexico            | 2.60 (0.70 to 9.80)    | –                | –      | >0.999  |
| Poland            | 1.10 (0.10 to 7.70)    | –                | –      | >0.999  |
| Turkey            | 14.20 (5.90 to 30.40)  | 15.380           | 87     | <0.001  |
| Uganda            | 3.50 (2.70 to 4.50)    | –                | –      | >0.999  |
| Uzbekistan        | 10.0 (6.50 to 15.0)    | –                | –      | >0.999  |
| Yemen             | 18.0 (13.30 to 23.90)  | –                | –      | >0.999  |
| **Cancer type**   | | | | |
| CRC               | 5.20 (1.30 to 19.0)    | 4.763            | 79     | 0.029   |
| HM                | 9.90 (4.20 to 21.70)   | 16.375           | 81.7   | 0.001   |
| Mixed             | 6.50 (4.50 to 9.30)    | 240.634          | 89.6   | <0.001  |

accurate inference and comparison of the results are problematic. In a similar study on Blastocystis, a zoonotic intestinal agent, a weighted frequency of 9% was obtained in cancer patients. This higher prevalence in such a susceptible group compared with Giardia infection may be justified by the fact that Blastocystis is recognized as the most common parasitic agent reported in human faecal samples. Also, Kalantari et al. reported that there is a positive association between Cryptosporidium infection and cancer (OR 3.3 [95% CI 2.18 to 4.98]), consistent with our findings. Their results revealed that Cryptosporidium is a highly opportunistic apicomplexan parasite and impaired immunity is a strong risk factor for this infection. However, our review and the report by Kalantari et al. were based on a limited number of investigations, hence more extensive studies are required to yield a more reasonable inference. Regarding publication year, no specific trend was observed for Giardia infection; accordingly, the
prevalence of infection was highest between 2001 and 2005, followed by a rapid decline until 2010. Also, the presence of a 4- to 5-y gap between the implementation and publication years complicates the true inference of the results.\(^\text{37,56,64}\)

The estimated pooled prevalence of *Giardia* infection varied among geographical regions, with the highest being reported from the EUR and Iraq, whereas the lowest prevalence was reported from the WHO African (AFR) region and Mexico. However, evaluation of the prevalence based on WHO regions is not so reliable, as countries in a particular region may demonstrate different parameters regarding geographical location or distance. In terms of continents, South America and North America showed the highest and lowest prevalence rates, respectively. However, most of the studies on *Giardia* prevalence in cancer patients were related to the Asian continent and there are very limited reports from other continents. The different weighted frequency of the infection among global regions results from the number of studies, geographical differences, treatment stage at the time of sampling and the sensitivity of diagnostic methods. In addition, the greater was a country’s income, the lower was the prevalence of *Giardia* infection; accordingly, the highest pooled prevalence rates were in low-income countries. Interestingly, the only high-income country included in our review was Poland,\(^\text{63}\) which does not appropriately represent the true prevalence of the infection in a given subgroup. At first glance, the weighted prevalence of infection in African nations was expected to be equal to that in low-income countries, while a closer look showed that since some Asian countries, for example, Yemen,\(^\text{66}\) are included in the low-income group, the prevalence of giardiasis in African nations varies from low-income ones. In addition, some African countries such as Egypt\(^\text{52–54}\) are not included among low-income nations, which causes a difference in the weighted prevalence.

Interestingly, the weighted prevalence of giardiasis was higher among patients suffering from HMs compared with CRC patients as well as those individuals with mixed cancers. The same locale for both CRC and *Giardia* may direct one’s mind to the higher prevalence of infection among CRC patients, but this information was not supported by obtained evidence in the present review. Generally culture and microscopic methods are considered as the gold standard diagnostic technique for giardiasis.\(^\text{18}\) However, increasing utilization of molecular tests demonstrates that the direct method of DNA extraction from stool samples is very sensitive for accurate diagnosis of this parasitic infection.\(^\text{72}\) Certainly the limited number of studies and different sensitivities and specificities of methods have caused bias,\(^\text{73–75}\) and the method-based prevalence was not provided in the present review due to the unreliability of data. There was no significant publication bias \((p=0.221)\) based on the included papers in the present review, indicating that published studies are a representative sample of the available evidence.

In total, the present systematic review and meta-analysis showed some strengths: evaluation of the pooled frequency of the *G. duodenalis* infection among 7024 cancer patients from 13 different countries on five continents, estimation of pooled random effects ORs of *Giardia* infection in cancer patients compared with control groups and subgroup analysis regarding publication year, continent, country, WHO region, country income and cancer type. However, the present review had some limitations: a lack of prevalence studies in several countries, the absence of sufficient molecular studies investigating the prevalence of *Giardia* infection, not including various risk factors such as age and sex in some studies, including some studies with very small sample sizes and a lack of adequate studies on the prevalence of *Giardia* infection in patients with various cancer types. The lack of studies obviously biased our results; for example, the global weighted OR reported here was only inferred from eight studies in four different countries. Furthermore, the pooled prevalence of the infection estimated in the present review (6.9%) was approximately
Figure 5. The meta-regression shows an absence of a statistically significant association between the prevalence of *G. duodenalis* infection in cancer patients and quantitative variables such as (A) publication year, (B) sample size and (C) HDI.
based on the microscopic method. This was not a surprising finding, since Giardia can be easily detected by its unique morphology in infected stool specimens. However, with the increasing use of molecular studies, more aspects of Giardia epidemiology in cancer patients can be identified. Inevitably, these limitations would have a substantial impact on the prevalence status of giardiasis in cancer patients that should not be ignored. With all these limitations, the present work tried to show a clear estimate of Giardia infection prevalence in cancer patients based on the current status of science, which may be elucidated in the near future by the implementation of extensive research.

Conclusions

To the best of our knowledge this is the first systematic review and meta-analysis showing a general overview of G. duodenalis infection prevalence and associated risk factors among cancer patients globally. The results indicated a mild prevalence in such at-risk patients, although based on the weighted OR, the immunodeficiency status of the examined hosts was not a statistically significant risk factor for Giardia infection. Our results demonstrated that the immunodeficiency status of cancer patients is a possible risk factor for acquiring Giardia infection, which requires strict preventive measures. Altogether, with the limited number of studies, it was not possible to accurately investigate the association between the prevalence of Giardia infection and a patient's immunodeficiency status. Achieving this goal will require more extensive cohort and case–control studies, particularly in neglected areas of the world.

Supplementary data

Supplementary data are available at International Health online.

Authors’ contributions: AA and SH conceived the study, designed the study protocol and carried out the meta-analysis. AA, FM, AS, AMC, RB and MO carried out the data extraction. AA wrote and revised the manuscript. All authors read and approved the final manuscript.

Acknowledgements: None.

Funding: None.

Competing interests: None declared.

Ethical approval: Not required.

Data availability: The data underlying this article are available in the article and in its online supplementary material.

References

1. Plata JD, Castañeda X. Parasites in cancer patients. Oncol Crit Care. 2020; : 1441–50.
2. Asghari A, Zare M, Hatam G, et al. Molecular identification and subtypes distribution of Blastocystis sp. isolated from children and adolescent with cancer in Iran: evaluation of possible risk factors and clinical features. Acta Parasitol. 2020;65:462–73.
3. Van Tong H, Brindley PJ, Meyer CG, et al. Parasite infection, carcinogenesis and human malignancy. EBioMedicine. 2017;15: 12–23.
4. Hooshyar H, Rostamkhani P, Arbabi M, et al. Giardia lamblia infection: review of current diagnostic strategies. Gastroenteral Hepatol Bed Bench. 2019;12(1):3–12.
5. Jian Y, Zhang X, Li X, et al. Occurrence of Cryptosporidium and Giardia in wild birds from Qinghai Lake on the Qinghai-Tibetan Plateau, China Parasitol Res. 2021;120:615–28.
6. Lone S, Lloyd D. Current trends in research into the waterborne parasite Giardia. Crit Rev Microbiol. 2002;28(2):123–47.
7. Lanata CF, Fischer-Walker CL, Olascoaga AC, et al. Global causes of diarrheal disease mortality in children <5 years of age: a systematic review. PLoS One. 2013;8(9):e72788.
8. Escobedo AA, Arencibia R, Vega RL, et al. A bibliometric study of international scientific productivity in giardiasis covering the period 1971–2010. J Infect Dev Ctries. 2015;9(1):76–86.
9. Esch KJ, Petersen CA. Transmission and epidemiology of zoonotic protozoal diseases of companion animals. Clin Microbiol Rev. 2013;26(1):58–85.

10. Kasaei R, Carmena D, Jelowdar A, et al. Molecular genotyping of *Giardia duodenalis* in children from Behbahan, southwestern Iran. Parasitol Res. 2018;117(5):1425–31.

11. Mirezaie E, Beiramvand M, Tavalla M, et al. Molecular genotyping of *Giardia duodenalis* in humans in the Andimeshk County, southwestern Iran. Acta Parasitol. 2019;64(2):376–83.

12. Li J, Wang H, Wang R, et al. *Giardia duodenalis* infections in humans and other animals in China. Front Microbiol. 2017;8:2004.

13. Al-Huchaimi SN, Al-Hassani MK, Khattar A, et al. The association between genotypes and clinical symptoms of *Giardia lamblia* in patients with symptomatic giardiasis. Int J Pharma Res. 2020;12(4):0228317.

14. Rafiei A, Baghlaninezhad R, Köster PC, et al. Multilocus genotyping of *Giardia duodenalis* in southwestern Iran. A community survey. PLoS One. 2020;15(2):e0228317.

15. Dixon BR. *Giardia duodenalis* in humans and animals – transmission and disease. Res Vet Sci. 2021;135:283–9.

16. Hussein EM, Ismail OA, Mokhtar AB, et al. Nested PCR targeting intergenic spacer (IGS) in genotyping of *Giardia duodenalis* isolated from symptomatic and asymptomatic infected Egyptian school children. Parasitol Res. 2017;116(2):763–71.

17. Certad G, Viscogliosi E, Chabé M, et al. Pathogenic mechanisms of *Cryptosporidium* and *Giardia*. Trends Parasitol. 2017;33(7):561–76.

18. de Mendonça Uchôa FF, Sudré AP, Campos SD, et al. Assessment of the diagnostic performance of four methods for the detection of *Giardia* duodenalis in fecal samples from human, canine and feline carriers. J Microbiol Methods. 2018;145:73–8.

19. Samie A, Tanih NF, Seisa I, et al. Prevalence and genetic characterization of *Giardia lamblia* in relation to diarrhea in Limpopo and Gauteng provinces, South Africa. Parasite Epidemiol Control 2020;9:e00140.

20. Koehler AV, Jex AR, Haidon SR, et al. *Giardia*/*giardiasis* – a perspective on diagnostic and analytical tools. Biotechnol Adv. 2014;32(2):280–9.

21. Bertrand I, Albertini L, Schwartzbrod J. Comparison of two target genes for detection and genotyping of *Giardia lamblia* in human feces by PCR and PCR-restriction fragment length polymorphism. J Clin Microbiol. 2005;43(12):5940–4.

22. Zahedi A, Field D, Ryan U. Molecular typing of *Giardia duodenalis* in humans in Queensland – first report of Assemblage E. Parasitology. 2017;144(9):1154–61.

23. Soliman RH, Fuentes I, Rubio JM. Identification of a novel Assemblage B subgenotype and a zoomorphic Assemblage C in human isolates of *Giardia intestinalis* in Egypt. Parasitol Int. 2011;60(4):507–11.

24. Pipiková J, Papajová I, Majňáthová V, et al. First report on *Giardia duodenalis* assembly B F in Slovakian children living in poor environmental conditions. J Microbiol Immunol Infect. 2020;53(1):148–56.

25. Dubourg A, Xia D, Wimpenny JP, et al. *Giardia* secretome highlights secreted tenascins as a key component of pathogenesis. GigaScience. 2018;7(3):giz003.

26. Fink MY, Singer SM. The intersection of immune responses, microbiota, and pathogenesis in giardiasis. Trends Parasitol. 2017;33(11):901–13.

27. Buret AG, Amat CB, Manko A, et al. *Giardia duodenalis*: new research developments in pathophysiology, pathogenesis, and virulence factors. Curr Trop Med Rep. 2015;2(3):110–8.
46. Salehi S, Elmí T, Meamar AR, et al. Investigating the prevalence of enteric opportunistic parasitic infections among cancer patients of a teaching hospital. Int J Hosp Res. 2018;7(1):12–22.

47. Taghipour A, Azimi T, Javanmard E, et al. Immunocompromised patients with pulmonary tuberculosis: a susceptible group to intestinal parasites. Gastroenterol Hepatol Bed Bench. 2018;11(Suppl 1):S134–9.

48. Togeh GR, Dogan M, Atambay M, et al. Evaluation of the intestinal parasitic infections in children patients with cancer. Türkiye Parazitol Derg. 2013;37(3):179–85.

49. Akgül O, Uysal HK, Oktem S, et al. PCR-based detection of intestinal protozoa in cancer and organ transplant recipient patients compared to a healthy control group. Int J Clin Exp Med. 2020;13(6):4434–40.

50. Durak F, Dogan M, Atambay M, et al. Performance of microscopy and ELISA for diagnosing Blastocystis hominis in Turkish patients with hematological malignancy. Acta Med Okayama. 2000;54(3):133–6.

51. El-Mahallawy H, El Basha NR, Zaki MM, et al. A comparative study on the intestinal parasites in children patients with cancer. Acta Med Okayama. 2000;54(3):133–6.

52. El-Badry AA, El Sayed SS, Hussein RR, et al. Intestinal parasitism in Malaysian children with cancer. J Trop Pediatr. 1999;45(4):241–2.

53. El-Mahallawy H, Zaki MM, El-Arousy M, et al. Diagnosis of intestinal parasitic infections in children patients with cancer. Türkiye Parazitol Derg. 2013;37(3):179–85.

54. Jiménez-Cardoso E, Eligio-Garcia L, Cano-Estrada A, et al. Frequency of emerging parasites in HIV/AIDS and oncological patients stool by coprological and molecular analysis. Adv Infect Dis. 2013;3:162–71.

55. Suliz-Bielia V, Kołodziejczyk L, Jaczewska S, et al. Prevalence of Cryptosporidium sp. in patients with colorectal cancer. Polish J Surg 2012;84(7):348–51.

56. Robinson AJ, Katongoole-Mbidde E. Gastrointestinal parasites in Ugandan cancer patients: a retrospective departmental review. Trop Doct. 2006;36(3):188–9.

57. Toychiev A, Abduljapparov S, Imamov A, et al. Intestinal helminths and protozoan infections in patients with colorectal cancer: prevalence and possible association with cancer pathogenesis. Parasitol Res. 2018;117(12):3715–23.

58. Al-Qobati SA, Al-Maktari MT, Al-Zoa AM, et al. Intestinal parasitosis among Yemeni patients with cancer, Sana’a, Yemen. J Egypt Soc Parasitol. 2012;42(3):727–34.

59. Khosrowshad V, Khazaee S, Amiri M, et al. Worldwide prevalence of emerging parasite Blastocystis in immunocompromised patients: a systematic review and meta-analysis. Microb Pathog. 2021;152:104615.

60. Asghari A, Sadraei J, Pirestani M, et al. First molecular identification and subtype distribution of Blastocystis sp. isolated from hooded crows (Corvus cornix) and pigeons (Columba livia) in Tehran Province, Iran. Comp Immunol Microbiol Infect Dis. 2019;62:25–30.

61. Asghari A, Hassanipour S, Hatam G. Comparative molecular prevalence and subtypes distribution of Blastocystis sp. a potentially zoonotic infection isolated from symptomatic and asymptomatic patients in Iran: a systematic review and meta-analysis. Acta Parasitol. 2021; doi:10.1007/s11686-021-00360-0.

62. Sheikh S, Asghari A, Sadraei J, et al. Blastocystis sp. subtype 9: as the first reported subtype in patients with schizophrenia in Iran. SN Compr Clin Med. 2020;2:633–9.

63. Kalantari N, Gorgani-Firouzjæe T, Ghaffari S, et al. Association between Cryptosporidium infection and cancer: a systematic review and meta-analysis. Parasitol Int. 2020;74:101979.

64. Adeyemo FE, Singh G, Reddy P, et al. Methods for the detection of Cryptosporidium and Giardia: from microscopy to nucleic acid based tools in clinical and environmental regimes. Acta Trop. 2018;184:15–28.

65. Egger M, Smith GD. Meta-analysis bias in location and selection of studies. BMJ. 1998;316(7124):61–6.

66. Juni P, Holenstein F, Sterne J, et al. Direction and impact of language bias in meta-analyses of controlled trials: empirical study. Int J Epidemiol. 2002;31(1):115–23.

67. Thornton A, Lee P. Publication bias in meta-analysis: its causes and consequences. J Clin Epidemiol. 2000;53(2):207–16.