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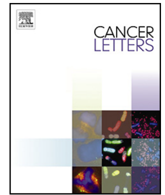

Original Articles

# *Toxoplasma gondii* infection in cancer patients: Prevalence, risk factors, genotypes and association with clinical diagnosis

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ABSTRACT

Prevalence of human infection with *Toxoplasma gondii* has been increasing in China due to the increasing number of cats. However, little is known of the epidemiology of *T. gondii* infection in different cancer patient groups. Thus, a case–control study of 900 cancer patients and 900 controls was conducted to detect anti-*T. gondii* antibodies by ELISA in China. Genomic DNA was extracted from the diseased tissues of 510 patients and the *T. gondii* B1 gene was amplified using a semi-nested PCR. DNA samples giving positive B1 amplification were then genetically characterized using multi-locus PCR-RFLP. The prevalence of anti-*T. gondii* IgG in cancer patients (35.56%) was significantly higher than that in controls (17.44%). The highest *T. gondii* seroprevalence was detected in lung cancer patients (60.94%), followed by cervical cancer patients (50%), brain cancer patients (42.31%) and endometrial cancer patients (41.67%). Exposure with soil and consumption of raw/undercooked meat were significantly associated with *T. gondii* infection in cancer patients. Three *T. gondii* genotypes (ToxoDB#9, ToxoDB#10 and Type I variant) were identified. In conclusion, *T. gondii* infection is a severe problem in cancer patients and it is imperative that improved integrated measures should be conducted to prevent and control *T. gondii* infection in cancer patients.
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## Introduction

Cancer is a leading cause of death worldwide, accounting for approximately 7.6 million deaths (13% of all deaths) in 2008 [1]. Deaths from cancer worldwide are projected to continue to rise, with an estimated 11 million deaths in 2030 [2]. Cancer often arouses fear due to ignorance and misunderstanding. If people modified their lifestyle or avoided key risk factors (such as smoking and other uses of or exposures to tobacco), over thirty percent of cancer cases could be prevented [3,4]. Moreover, nearly one third of cancer cases could be decreased if diagnosis and treatment have been carried out at an early stage [3]. A lot of infection-related cancers are preventable [3]. Infection with some pathogens, such as certain viruses, bacteria, and parasites, is one of the most important and preventable causes of cancer worldwide. Nearly a fifth of cancers worldwide are incurred by infectious agents [4–6]. Cancers induced by infections usually have a higher mortality rate than other cancers [4].

The most frequent protozoan causing opportunistic infections in immunocompromised individuals is *Toxoplasma gondii*, which is an obligate intracellular protozoan that infects up to one-third of the world's population [7]. Humans acquire *T. gondii* infection by ingesting the undercooked meat of intermediate hosts containing tissue cysts, especially pork and lamb, or by the ingestion of water or food contaminated by oocysts from the definitive hosts [7,8]. Toxoplasmosis can present with various signs and symptoms. In immunocompetent individuals, infection is generally self-limiting because an efficient immune control limits the dissemination of the rapidly multiplying tachyzoite stage [8]. However, the parasite still remains viable in the form of tissue cysts throughout the whole life of the host. During this stage, the humoral and cellular immune systems, including T-lymphocytes and macrophages, play a crucial role in controlling the tissue cysts [9,10]. Immunocompromised individuals, especially those with deficiency in cellular immunity, have a greater possibility of recurrence of chronic infection. Patients with cancer, transplant recipients under immune depressive therapy or hemodialysis patients with chronic renal failure have cellular immunity deficiency, and this makes them susceptible to infection [11–13].

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The distribution of *T. gondii* genotypes varies in different geographic regions [14,15]. Using multi-locus-PCR-RFLP and microsatellite typing, a large proportion of isolates from humans and animals in North America and Europe have been classified into three clonal lineage types (I, II, III) [16–18]. Although the differences among the three dominant lineages are no more than 1% at the genomic level, striking differences have been found in the virulence phenotypes in mice, with archetypal I strains being uniformly lethal in mice; instead, archetypal II and III strains are significantly less virulent [19]. Human toxoplasmosis is mainly caused by Type II lineage. Type I and atypical strains are found in severe toxoplasmic retinochoroiditis in patients and acute disseminated toxoplasmosis in patients who are immunocompromised [18]. Moreover, patients with ocular toxoplasmosis and animals are often infected by Type III strains [17,20]. In infected patients, genotype-specific antibody responses can be induced by these three clonal lineage types [21].

According to clinical and epidemiological evidences, many reports highlighted a potential association between *T. gondii* infection and cancer [1,2,4]. Cancer has been a major challenge for public health in China. It ranks first among all causes of death in urban areas, and second in rural areas. However, toxoplasmosis in patients who are immunocompromised by virtue of underlying neoplastic disease has received relatively little attention in China [22]. Thus, through a case–control study, we try to explore the association between *T. gondii* seroprevalence and types of cancer, and risk factors of *T. gondii* infection in cancer patients. Moreover, we firstly identified *T. gondii* genotypes in cancer patients by PCR-RFLP, aiming to attract public attention to *T. gondii* infection in cancer patients.

## Materials and methods

### *Study design*

Through a case–control study, we studied *T. gondii* seroprevalence and identified risk factors and possible contamination routes of *T. gondii* infection in cancer patients and control subjects in Qingdao and Weihai, China from July 2012 to February 2014. Moreover, the diseased tissue and clinical diagnosis of cancer patients were obtained, aiming to genetically characterize *T. gondii* isolates from cancer patients and explore the association between *T. gondii* infection and clinical diagnosis.

### *Cancer patients*

Nine hundred cancer patients who were presented to the Affiliated Hospital of Medical College, Qingdao University, Wendeng Municipal Hospital and Weihaiwei People's Hospital were included in the study. All cancer patients resided in Qingdao and Weihai, China (Table 1).

### *Control subjects*

Control subjects, numbered 900 and matched with cancer patients by age, gender and residence, were included in the study. Serum samples were randomly obtained from the general population of Qingdao and Weihai, China (Table 1).

### *Sample collection and transportation*

Approximately 5 ml of venous blood samples was drawn from participants who gave their consent to participate in this study. Blood samples were left overnight at room temperature to allow clotting and centrifuged at 3000 rpm for 10 minutes. The sera were collected in Eppendorf tubes and stored at 4 °C for 24–72 hours. Five hundred and ten diseased tissues (including brain, liver, lung, breast, and so on) were collected from cancer patients and kept at −20 °C. Both sera and tissues were transported in an ice box to State Key Laboratory of Veterinary Etiological Biology, Lanzhou Veterinary Research Institute, Chinese Academy of Agricultural Sciences, Lanzhou, Gansu Province where they were kept at −20 °C until tested.

### *Socio-demographic, clinical and behavioral data*

Socio-demographic data including age, sex, birth place and residence were obtained from all participants. Clinical data explored in patients were mainly the type of cancer; and behavioral data including animal contacts, presence of cats and dogs at home, consumption of raw/undercooked meat, consumption of raw vegetables and fruits, source of drinking water and exposure to soil from the participants were obtained. These variables were selected based on literature. Data were obtained from the patients/guardians, medical examination records, and informants. Patients were invited to provide veridical information and they were informed that data were used in a confidential manner.

### *Serological assay*

Sera were analyzed for the presence of IgG and IgM antibodies against *T. gondii* using the commercially available enzyme immunoassay kits (Demeditec Diagnostics GmbH, Germany) according to the manufacturer's instructions. Positive and negative serum controls were included in every plate. To avoid bias of results, the serology test was done double blinded. Samples from cancer patients and control group were randomly mixed, and the person performing the test did not know the source of samples in advance.

### *DNA extraction and genetic characterization of* T. gondii *isolates*

The diseased tissues of cancer patients were used for DNA extraction. Genomic DNA was extracted from these tissues using TIANamp Genomic DNA kit (TianGen™, Beijing, China) according to manufacturer's recommendations. In brief, 30 mg of the tissues was treated with sodium dodecyl sulfate/proteinase K at 56 °C for 5 h digestion in a thermostat water bath. DNA samples were prepared after purification by silica gel column chromatography and eluted into a 50 µl elution buffer. Then, a semi-nested PCR targeting the *T. gondii* B1 gene was performed to detect possible infection with *T. gondii* [23]. DNA samples giving positive B1 amplification were then used for genetic characterization. Genotyping was conducted using 11 genetic markers for PCR-RFLP (i.e., SAG1, SAG2, alter.SAG2, SAG3, BTUB, GRA6, c22-8, L358, c29-2, PK1, and Apico) according to previously reported protocol [24–26]. Nine reference

**Table 1**
Socio-demographic characteristics of the study populations and seroprevalence of *Toxoplasma gondii* infection.

| Characteristic | Cancer patients (N = 900) | | | | Control subjects (N = 900) | | | | Cancer patients *vs* control subjects *P*-value |
|---|---|---|---|---|---|---|---|---|---|
| | Prevalence of *T. gondii* infection | | | | Prevalence of *T. gondii* infection | | | | |
| | No. tested | No. positive | % | *P*-value | No. tested | No. positive | % | *P*-value | |
| Age group (years) | | | | | | | | | |
| 30 or less | 132 | 46 | 34.85 | | 96 | 12 | 12.50 | | <0.001 |
| 31–40 | 165 | 57 | 34.55 | 0.957 | 171 | 41 | 23.98 | 0.024 | 0.033 |
| 41–50 | 223 | 88 | 39.46 | 0.386 | 232 | 51 | 21.98 | 0.047 | <0.001 |
| 51–60 | 146 | 55 | 37.67 | 0.625 | 207 | 41 | 19.81 | 0.119 | <0.001 |
| 61–70 | 133 | 57 | 42.86 | 0.181 | 100 | 14 | 14.00 | 0.757 | <0.001 |
| >70 | 102 | 39 | 38.24 | 0.593 | 94 | 18 | 19.15 | 0.209 | 0.003 |
| Gender | | | | | | | | | |
| Male | 355 | 127 | 35.77 | | 359 | 76 | 21.35 | | <0.001 |
| Female | 545 | 215 | 39.45 | 0.267 | 541 | 101 | 18.67 | 0.355 | <0.001 |
| Residence place | | | | | | | | | |
| Qingdao | 420 | 164 | 39.05 | | 500 | 94 | 18.80 | | <0.001 |
| Weihai | 480 | 178 | 37.08 | 0.545 | 400 | 83 | 20.75 | 0.465 | <0.001 |
| Residence area | | | | | | | | | |
| Urban | 459 | 168 | 36.60 | | 440 | 92 | 20.91 | | <0.001 |
| Suburban or rural | 441 | 174 | 39.46 | 0.378 | 460 | 85 | 18.48 | 0.359 | <0.001 |

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