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Protective effect of latent *Toxoplasma* infection against breast cancer risk: a comparative cross-sectional study in Iran

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ABSTRACT

Background and Objective: Some evidence suggested that *Toxoplasma gondii*, an obligate intracellular protozoan parasite, might have an inhibitory effect on cancers development.

Methods: We performed a matched case-control study of incident breast cancer (BC) cases versus healthy control subjects to evaluate the association between *Toxoplasma* infection and BC. We enrolled 161 newly diagnosed cases and 91 healthy controls, and anti-*Toxoplasma* serum antibodies were examined using ELISA kits. Chi-squared test was used to calculate the odds ratios (OR) and 95% confidence intervals (CIs).

Findings: Only one BC patient was seropositive for IgM while all healthy controls were seronegative. Moreover, the prevalence of anti-*Toxoplasma* IgG serum antibodies in the case and control groups was 70.8% (95% CI, 63.1–77.7%; 114/161) and 95.6% (95% CI, 89.1–98.7%; 87/91), respectively, indicating a significant protective association (OR, 0.11; 95% CI, 0.03–0.35%) for *Toxoplasma* infection in relation to BC development.

Conclusion: Latent *Toxoplasma* infection might have a protective role against the development of BC. More studies are needed to confirm our findings.

Keywords: *Toxoplasma* infection, Breast cancer, Association, ELISA

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Introduction

Global Burden of Disease Study, there were about 2 million incident cases of BC in 2017, responsible to 17.7 million disability-adjusted life-years, and 181,004 deaths (1). BC is recognized as a multifaceted disease and both genetic and environmental risk factors can contribute in its aetiology (2). Despite several investigations in past decades, the relationship between infectious pathogens and development of different type of cancers including BC is still a matter of major contention (3). While some viral pathogens (e.g. papillomaviruses, herpes viruses and retroviruses) appear to increase the risk of BC and other type of cancers (3), some experimental studies indicated that *Toxoplasma gondii*, an obligate intracellular protozoan parasite, might have inhibitory effect on cancers development (4, 5). Approximately two billion people of the world's population are exposed or latently infected by *T. gondii* (6, 7). Up to our knowledge, there is no observational study assessing the association between *Toxoplasma* infection and BC using newly diagnosed BC cases. Therefore we designed this study to better understand the association between *Toxoplasma* infection and BC, and performed a comparative cross-sectional study of incident BC cases versus healthy control subjects.

Methods

We performed a comparative cross-sectional study from December 2019 to January 2021 at the Rohani Hospital of the Babol University of Medical Sciences (BUMS) in north of Iran. The ethics review board of BUMS approved (date: 12/20/2019) the study (no. IR.MUBABOL.REC.1399.187). Eligible cases were females aged 18 years or older with newly diagnosed breast cancer. All patients were confirmed histologically and included in this study prior to the initiation of any kind of cancer therapy (chemotherapy, radiotherapy, or surgery). To ensure complete ascertainment of cases, we reviewed all medical records and laboratory pathology reports. The population-based controls were healthy age matched women referred to the health care centers for their routine health checkup. The subjects were excluded if they had any clinical symptoms related to toxoplasmosis such as lymphadenopathy and ocular symptoms and those who had not answered interview questions. Sera were collected from the all cases and controls and examined for anti-*Toxoplasma* immunoglobulin G and M (IgG and IgM) antibodies using commercial ELISA kits (ACON, San Diego, CA, USA) according to the manufacturer's instructions. The SPSS Statistics software (version 16; IBM, Armonk, NY, USA) was used for statistical analyses. The seroprevalence of *Toxoplasma* infection was presented as the relative percentage with an exact binomial 95% confidence interval (CI). Differences in demographic variables between cases and controls were calculated using the Chi-squared test and Fisher's exact test, when available. To estimate the association of *Toxoplasma* infection and breast cancer, we used unconditional logistic regression models to compute. Due to lack of some demographic data we were unable to apply adjusted models. A two-sided p value less than 0.05 was considered statistically significant.

Results

In total, 161 BC patients and 91 controls met the inclusion criteria to be included in this study. The participants in case and control groups had median age of 52.1±10.9 and 53.3±11.8, respectively. Only one patient in case group was positive for anti-*Toxoplasma* serum IgM antibodies while all subjects in control group were seronegative for IgM. Furthermore, the prevalence of anti-*Toxoplasma* IgG serum antibodies in the case and control groups was 70.8% (95% CI, 63.1–77.7%; 114/161) and 95.6% (95% CI, 89.1–98.7%; 87/91), respectively. In the univariate analysis we have found a significant lower

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(OR, 0.11; 95% CI, 0.03–0.35%; *P* value: < 0.001) prevalence of anti-*Toxoplasma* IgG serum antibodies in cases than control subjects, suggesting a protective association.

Discussion

This study found a strong inverse association suggesting that *Toxoplasma* infection might have a protective role in development of BC. In two previous primary studies by Kalantari et al. (8, 9), there was no a significant association between *Toxoplasma* infection and BC. Although it should be noted that very few of BC cases, 28 and 29 patients in first and second study, were enrolled in these studies (8, 9). Despite our findings, the pathophysiological mechanisms underlying the protective role of *Toxoplasma* infection to the development of BC is unclear, although some previous studies indicated that *Toxoplasma* infection might have either risk factor or anti-tumoral activity by generating a continual inflammation in host tissues and modulating the host's cell response (4, 5, 10-13).

Hafez et al. (11) indicated that vaccination with gamma radiation-attenuated *T. gondii* has the capacity to stimulate immunity and activate antitumor cells against ovarian invasion in Ehrlich ascites carcinoma (EAC)-bearing mice. Mohamadi et al. (12) showed that anti-*Toxoplasma* antibodies reacted markedly with the surface of mouse melanoma and breast cancer cells, but not normal mouse lymphocytes. They concluded that anti-*Toxoplasma* antibodies may be useful for selective drug delivery in BC treatment. Caner's study(10) indicated that "*Toxoplasma* infection could modulate certain signaling pathways of host, which h were also common to those perturbed in carcinogenesis. Parasite might also control the tumor growth due to its potent immunestimulant effects". Kim et al. (5) reported the anticancer effects of dense granule protein 16 (GRA16) of *T. gondii* in mouse xenograft models of GRA16-stable hepatocellular carcinoma (HCC). GRA16 increased the nuclear localization of phosphatase, tensin homolog (PTEN), and p53-dependent apoptosis by binding with herpes virus-associated ubiquitin-specific protease (HAUSP) in HCC cells. Seo et al. (4) reported that irinotecan and GRA16 co-treatment promotes the anticancer effects of irinotecan via NF-κB inhibition and cell cycle arrest induced by GRA16, subsequently increasing the chemotherapeutic effect of irinotecan to non-small-cell lung carcinoma cells via NF-κB inhibition. In another study Choo et al. (13) demonstrated that *Toxoplasma* lysate antigen (TLA) inhibits the proliferation and invasion of glioma cells in vitro and in vivo, and these antitumor effects of TLA are significantly enhanced by the addition of Quil-A.

Conclusion

In conclusion, findings from this study for the first time provide evidence suggesting that *Toxoplasma* infection/exposure might have a protective role against development of BC. To confirm these findings, it is essential that well designed case-control and cohort studies with strict control of confounders be performed.

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Declarations

Funding

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Competing interest

There is no conflict of interest.

Availability of data and material

Data may be available on reasonable request by contacting the corresponding author.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki and was approved (date: 12/20/2019) by the Ethical Board in Babol University of Medical Sciences (no. IR.MUBABOL.REC.1399.187).

Consent to participate

Informed consent was obtained from all individual participants parents included in the study.

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