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Incidence of adult brain cancers is higher in countries where the protozoan parasite *Toxoplasma gondii* is common

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We explored associations between the common protozoan parasite *Toxoplasma gondii* and brain cancers in human populations. We predicted that *T. gondii* could increase the risk of brain cancer because it is a long-lived parasite that encysts in the brain, where it provokes inflammation and inhibits apoptosis. We used a medical geography approach based on the national incidence of brain cancers and seroprevalence of *T. gondii*. We corrected reports of incidence for national gross domestic product because wealth probably increases the ability to detect cancer. We also included gender, cell phone use and latitude as variables in our initial models. Prevalence of *T. gondii* explained 19 per cent of the residual variance in brain cancer incidence after controlling for the positive effects of gross domestic product and latitude among nations. Infection with *T. gondii* was associated with a 1.8-fold increase in the risk of brain cancers across the range of *T. gondii* prevalence in our dataset (4–67%). These results, though correlational, suggest that *T. gondii* should be investigated further as a possible oncogenic pathogen of humans.

Keywords: *Toxoplasma gondii*; brain cancer; medical geography

1. INTRODUCTION

Despite considerable research, the causes of brain cancers remain largely unknown. A few studies have found weak linkages between environmental factors and primary brain cell-derived tumours or lymphomas. In particular, brain cancers have been linked to ionizing radiations, though some have hypothesized associations with pesticides, solvents, electromagnetic fields (including cell phones) and nitrosamines in processed meats [1–4].

Persistent infections may promote cancer because long-term host defensive responses induce inflammation, which increases mutation rates [5]. In addition, intracellular pathogens may disrupt traditional cell barriers to cancer, allowing oncogenic mutations to accumulate through time [6]. Current evidence links Epstein–Barr virus, hepatitis B and C viruses, the bacterium *Helicobacter pylori*, human papilloma virus and the trematode *Schistosoma haematobium* to cancers of the lymph, liver, stomach, cervix and bladder, respectively [7]. Although several types of viruses (retroviruses, papovaviruses and adenovirus) cause brain tumours in experimental animals, few epidemiological studies have addressed the potential for pathogens to cause human brain cancers (see [2] for a review). Human cytomegalovirus is not currently causally implicated in human cancer, but emerging evidence suggests that infection and expression may be specifically associated with human malignancies, including malignant glioma [8].

Toxoplasma gondii is an apicomplexan parasite with a worldwide distribution. Cats are the final host and humans (and other warm-blooded vertebrates) are intermediate hosts. Following a period of asexual reproduction by tachyzoite forms (to which the host responds aggressively), the parasite enters a latent phase in a bradyzoite stage that persists for the host's lifetime in pseudocysts, macrophages and neurons of various tissues, notably in the brain [9]. About one-third of the world human population has antibodies to *T. gondii* [10]. Although conventional medicine considers latent toxoplasmosis asymptomatic, recent research has linked toxoplasmosis with a number of neurological pathologies [11,12]. In the latent phase, the cysts provoke the immune system (e.g. lymphocytes, plasma cells and macrophages), stimulating mild inflammation [13]. Also, they inhibit programmed cell death [14]. *Toxoplasma gondii* has been reported to cause gliomas in experimental animals [15,16]. One study by Schuman *et al.* [17] convincingly linked astrocytoma with antibodies to *T. gondii*. Ryan *et al.* [18] showed no association with adult glioma, but did report an association with meningioma.

An obvious test of the hypothesis that *T. gondii* promotes brain cancer would be to compare measures of *T. gondii* in cancer patients with controls. Schlehofer *et al.* [19] looked at the medical history of patients with brain tumours, finding that subjects with allergic conditions and a history of colds and flu had reduced risk of glioma. Unfortunately, this study had less than 2 per cent of cases where the individual had clinically reported toxoplasmosis, and the much more prevalent condition of latent toxoplasmosis was not assessed. Here, we approached the question using medical geography (see [20]). The variation in prevalence of subclinical infection with *T. gondii* from nation to nation provides an opportunity for a comparative study using data from human populations throughout the world.

2. MATERIAL AND METHODS

We asked whether the prevalence of *T. gondii* in a nation was positively associated with the incidence of brain cancers in that nation. Because a variety of other factors could influence brain cancer, brain cancer detection and *T. gondii*, we considered possible effects of gender, wealth and environment.

(a) Data sources

International statistics on brain cancers in men and women were obtained from the International Agency for Research on Cancer (IARC GLOBOCAN project, year 2008, <http://globocan.iarc.fr/>). These data concern only malignant tumours, those classified C70–72 in the *International Classification of Disease* (ICD, 10th revision, available at <http://apps.who.int/classifications/apps/icd/icd10online/>). We did not include mortality data in our analysis as this variable is influenced by access to therapies, a parameter that strongly varies between countries. Instead, we used *incidence data* (age-standardized rate) that derive from population-based cancer registries. Age-standardized international statistics on *T. gondii* seroprevalence were from Lafferty [21]. Data on the *per capita* gross domestic product (GDP) for each country are available at <https://www.cia.gov/library/publications/the-world-factbook/rankorder/2004rank.html>. We obtained data on cell phone use (year 2010) from the Population reference Bureau (<http://www.prb.org/Publications/Datasheets/2010/2010wpds.aspx>).

(b) Analyses

Some of the recent increases in the incidence of brain cancers appear to be related to increased ability to detect disease using new technology and greater awareness [22]. We were concerned that detection might also vary owing to wealthy nations having higher detection ability. For this reason, we controlled for national wealth in nations by regressing the incidence of brain cancers against *per capita* gross domestic product (GDP) and taking the residuals (for a GDP-corrected measure of incidence). Data on all variables and *T. gondii* prevalence were available for 37 countries.

We used general linear models for hypothesis testing. Preliminary analysis indicated no effect of gender, so the incidence of males and females was averaged. Cell phone use was a competing environmental factor that has been hypothesized to increase cancer risk [23], and we considered this and *T. gondii* as competing explanatory factors in an initial model. Finally, because latitude was correlated with the prevalence of *T. gondii* and the GDP-corrected incidence of brain cancers, we conducted a separate analysis in which we further corrected the incidence of brain cancers for a potential effect of latitude. Using residuals to correct for priority effects may lead to inflated degrees of freedom. For this reason, we conducted a sequential *F*-test that assessed the effect of *T. gondii* prevalence after the effects of GDP were considered in a single model. To meet assumptions of normality, GDP, incidence of brain cancer and prevalence were transformed with the natural log, and the logit transformation was applied to prevalence. Ideally, we would have used direct measures of detection and other measures of infectious diseases potentially associated with brain cancers, but these data were not available to us.

3. RESULTS AND DISCUSSION

Variation in the incidence of brain cancers among nations increased with GDP ($r^2 = 0.52$, $p < 0.0001$), consistent with the hypothesis that detection rates increase with wealth [21], and/or that brain tumour risk increases with increasing socioeconomic status. After accounting for GDP (natural log-transformed), cell phone use and gender were not significant factors (when analysed concurrently with *T. gondii*). The residual incidence of brain cancers after correcting for GDP increased significantly with the age-standardized, natural log-transformed prevalence of antibodies to *T. gondii* ($n = 37$ nations, $r^2 = 0.15$, $p = 0.019$). A similar significant effect of *T. gondii* occurred for the sequential *F*-test ($p = 0.016$). In other words, after controlling for detection effort, the only significant predictor of brain cancers was *T. gondii* prevalence.

Like all medical geography studies, our results are correlational and explainable by alternative hypotheses. In addition, analyses of data aggregated at the population level may not pertain to individual risk [24,25]. This leaves open the possibility that brain cancers and *T. gondii* are both affected by a third correlated factor. For the environmental factors that we

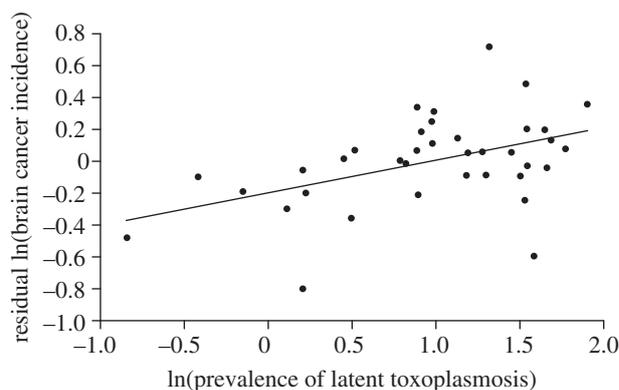


Figure 1. The correlation between the incidence of brain cancers in adults from 37 countries and the prevalence of *T. gondii* (proportion of infected people, natural log-transformed). The residuals of incidence control for GDP (as a proxy of detection) and a positive (and unexplained) influence of latitude on brain cancer incidence. We averaged the incidence of brain cancers between males and females before plotting.

considered (latitude, longitude and cell phone use), only latitude was substantially associated with both *T. gondii* and the GDP-corrected incidence of brain cancers. After statistically controlling for the association between latitude and the incidence of brain cancers, the latitude-corrected incidence of brain cancers had a stronger positive association with *T. gondii* ($r^2 = 0.21$, $p = 0.005$) than our initial analysis. In other words, prevalence of *T. gondii* explained a fifth of the residual variance of the incidence rate in brain cancers after controlling for the positive effects of GDP and latitude among nations (figure 1). Performing a similar analysis for the incidence of 46 cancers (and correcting for multiple comparisons) finds five significant associations with *T. gondii*: brain in men, brain in women, larynx in men, larynx in women and lung in men.

Although we do not currently have information at the level of infected and uninfected individuals, the slope of the relationship in figure 1 (intercept = 0.27 (± 0.10), slope = 0.20 (± 0.07)) suggests that across the range of prevalence in infection with *T. gondii* in our study (from 4 to 67%), there was a 1.8-fold increase in the incidence of brain cancers.

Other unmeasured variables could drive a spurious association with *T. gondii*. Furthermore, there are several types of brain cancers in our dataset, and these probably have diverse origins, suggesting that no one factor should be expected to explain a large amount of variation in the incidence of brain cancers among nations. Other infectious organisms might be carcinogenic (e.g. viruses, see [2]), but we did not have sufficient data to analyse these. Another limitation of this study is that we only had *T. gondii* data from a limited number of countries, so the conclusions would only be generalizable to other countries that are similar to those for which the prevalence values were available [26]. However, despite the limitations of a medical geography approach, we feel our results are sufficiently strong to propose that *T. gondii* potentially increases the risk of brain cancers in humans. Clearly, further research is necessary to determine the proximate links between *T. gondii* and different types of brain tumours and to investigate a mechanism of action.

Other correlational studies are possible. For instance, the National Cancer Institute has an archive of blood from brain cancer patients that could be screened for antigens to *T. gondii*. Establishing a link between *T. gondii* and brain cancers could open the door to potential means to reduce cancer risk. Another interesting research direction would be to explore whether *T. gondii* has oncogenic effects when in synergy with other infections. *Toxoplasma gondii* might contribute to brain cancers in concert with viruses that have been associated with brain cancers (see §1), much as *Plasmodium falciparum* contributes to Burkitt's lymphoma in synergy with Epstein–Barr virus (see [6] for a review).

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