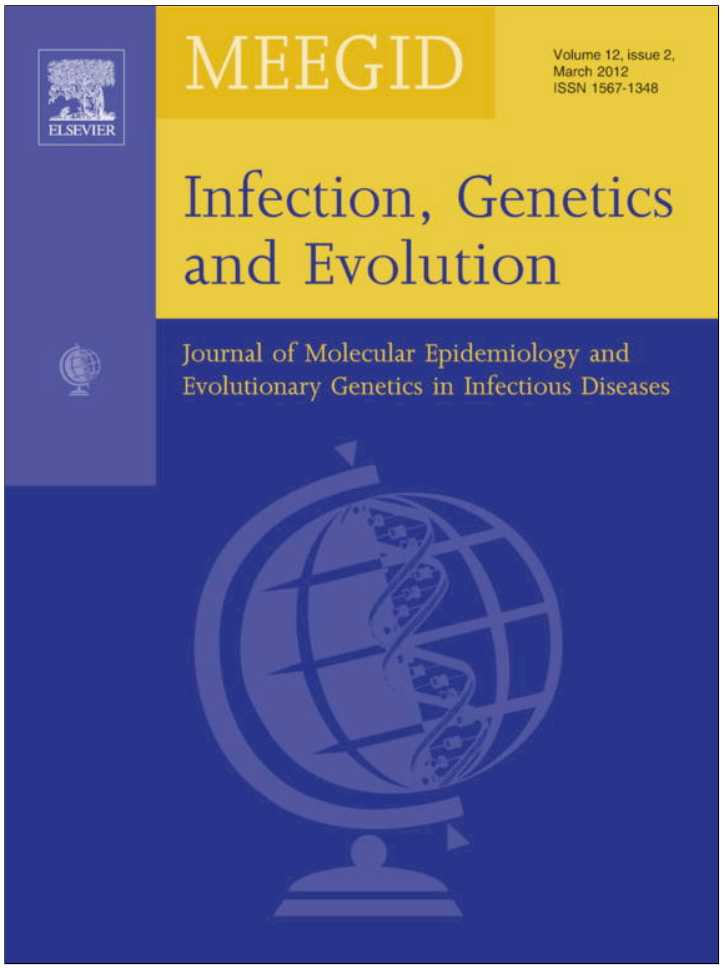

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Short communication

Brain cancer mortality rates increase with *Toxoplasma gondii* seroprevalence in France

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ABSTRACT

The incidence of adult brain cancer was previously shown to be higher in countries where the parasite *Toxoplasma gondii* is common, suggesting that this brain protozoan could potentially increase the risk of tumor formation. Using countries as replicates has, however, several potential confounding factors, particularly because detection rates vary with country wealth. Using an independent dataset entirely within France, we further establish the significance of the association between *T. gondii* and brain cancer and find additional demographic resolution. In adult age classes 55 years and older, regional mortality rates due to brain cancer correlated positively with the local seroprevalence of *T. gondii*. This effect was particularly strong for men. While this novel evidence of a significant statistical association between *T. gondii* infection and brain cancer does not demonstrate causation, these results suggest that investigations at the scale of the individual are merited.

1. Introduction

More than 237 000 central nervous system cancers are diagnosed each year worldwide and survival remains low even in the most developed countries (GLOBOCAN, 2008). Despite considerable research, the causes of these malignancies are largely unknown. Some studies have highlighted associations between brain tumors and environmental factors including ionizing radiation, diverse chemical products and electromagnetic fields (Fisher et al., 2007). In animals, infections by different viruses have experimentally led to brain tumors (Wrensch et al., 2002). Persistent infections may promote cancer by increasing mutation rates through the inflammation they induce. Moreover, intracellular pathogens may disrupt cell barriers to cancer. However, there are very few studies investigating the link between pathogens and brain cancer in humans. Recently, using a dataset including 37 countries, Thomas et al. (2012) detected a positive relationship between the national seroprevalence of the protozoan parasite *Toxoplasma gondii* and the national incidence of brain cancer.

T. gondii is an apicomplexan parasite that is transmitted to its final host, a felid, through the consumption of an intermediate host, which can be any warm-blooded vertebrate, including humans (Dubey, 1998). This parasite is very common and infects more than one-third of the world human population. Humans are infected by eating tissue cysts in contaminated meat or by contact with soil contaminated with oocysts from cat feces. Within Europe and North America, most strains isolated from humans and domestic/farm animals belong to three clonal types: genotypes I, II and III (Boothroyd, 2009). Type I strains are lethal and do not readily give rise to chronic infections in mice. An increased frequency of type I strains in severe congenital toxoplasmosis in humans suggests that this lineage may also be more pathogenic for humans than lineage II and III (e. g. Howe and Sibley, 1995). By contrast, type II and III strains are considerably less virulent and characterized by long-term infections (Su et al., 2002). In Europe, human infections are most commonly associated with Type II strains (Sibley et al., 2009). Latent *T. gondii* infections are traditionally considered benign by conventional medicine, but evidence is accumulating that the bradyzoite stages encysted in the brain during the latent phase are responsible for diverse neurological pathologies (see Flegr, 2010 for a recent review). *T. gondii* is sufficiently common in humans that it could lead to a large proportion of brain cancer cases (Thomas et al., 2012).

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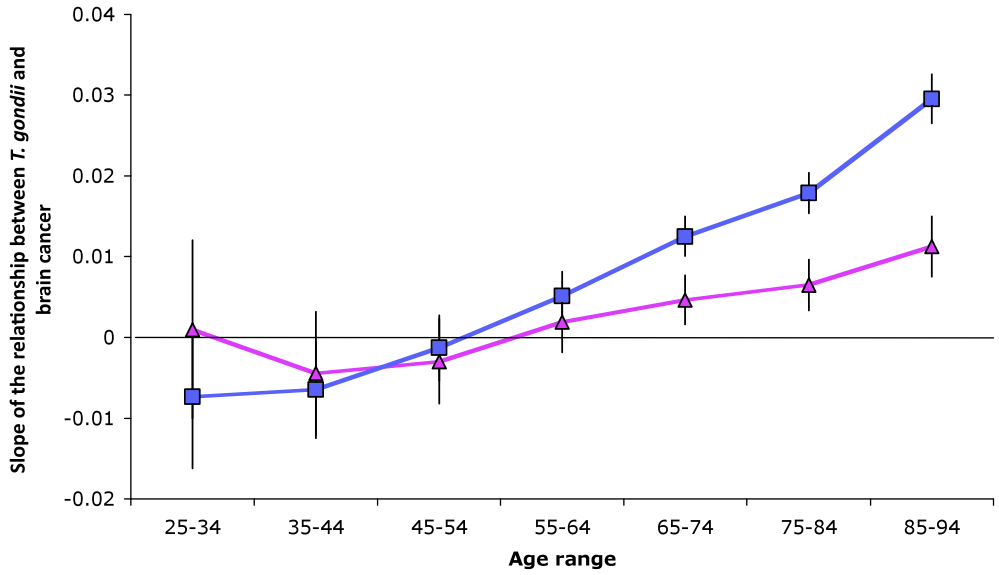

Fig. 1. Relationship between *Toxoplasma gondii* seroprevalence and mortality rates due to brain cancers. Slopes (+/− 95% confidence intervals) of the relationship between *Toxoplasma gondii* prevalence in a region in France (range 34–62) and mortality rates due to brain cancers in adults (per 1,00,000 individuals), separated by gender and age class (after controlling for year). Slopes > 0 indicate a positive relationship between regional brain cancer mortality and *T. gondii* prevalence for males (squares) and females (triangles).

2. Materials and methods

In France, mortality causes, including brain cancer, are available for each of the 22 administrative regions since 1979 (until 2007), and regional data on *T. gondii* seroprevalence is available for women of childbearing age for 1995 and 2003 (Berger et al., 2007). We asked whether the prevalence of *T. gondii* in a region was positively associated with the mortality due to brain cancer in that region.

National statistics on brain cancer mortalities in men and women for each of the 29 years (1979–2007) were obtained from an Inserm database available at http://www.cepidc.vesinet.inserm.fr/. These data do not include the incidence of brain cancer. They concern mortality from malignant primary encephalon tumors, those classified 191 (until 1999) and C71 (from 2000) in the International Classification of Disease (ICD, 9th and 10th revision, available at: http://apps.who.int/classifications/apps/icd/icd10online/). Because sample sizes were too small among the C71/191 sub-categories (0–9, depending on localization in the brain), data were pooled prior to analyses. Mortality data due to malignant C70 and C72 tumors were anecdotal over the entire period and were not analyzed. The 22 regions of metropolitan France served as replicates. Mortality data are crude rates for 100 000 inhabitants. Because the reliability of these estimations may depend on the number of inhabitants per region, rates were weighted for the analysis by the relative regional population size in 1995 (near the midpoint of the dataset) available at http://www.insee.fr/fr/bases-de-donnees/default.asp?page=recensements.htm. National statistics on *T. gondii* seroprevalence for the 22 regions were from two successive studies on pregnant women in 1995 ($n = 13\ 459$) and 2003 ($n = 15\ 108$) (Berger et al., 2007). We analyzed age-standardized seroprevalence, which were obtained through direct standardization using the total population sampled in 2003 as the reference (for both 1995 and 2003 data) and six age groups (<20, 20–24, 25–29, 30–34, 35–39, >39; see Berger et al., 2007 for details). For each region, the estimates for the 2 years were highly correlated ($r = 0.83$; $P < 0.0001$), though prevalence in 2003 was lower than in 1995 ($P < 0.0001$). At first, we used the mean seroprevalence value across the 2 years for each region. Consistent with other studies (e.g., Jones et al., 2003; Studeničová et al., 2006) we assumed that this mean for pregnant women adequately represents the infection status of men and women. We also analyzed the years separately, which led to similar results. In the statistical models, brain cancer mortality was the dependent variable and *T. gondii* seroprevalence, year of reported death, sex, and their interactions were predictors. It was not possible to directly test a *T. gondii* effect in a generalized linear model as residuals were not normally distributed. Hence, we used a generalized linear model with Poisson Distribution and a Log-link function. These results were consistent with general linear models and non-parametric analyses. Because there was a strong interaction between age class, gender, and *T. gondii* prevalence, we opted to analyze age classes and genders separately.

3. Results and discussion

T. gondii prevalence in pregnant women was lower in 2003 than in 1995 (probably due to changes in meat production that have led to less contamination with cysts) and brain cancer related mortalities increased over time (probably due to improvements in detection of brain cancer). Both *T. gondii* prevalences and brain cancer mortalities were highly variable across regions. As an example in 2003 prevalence varied from 29% to 56.3% and mortality varied from 3.15 to 5.44 deaths per 100 000 inhabitants (mean mortality rate for the whole population of a region). Brain cancer mortality was consistently higher for males than for females.

Once mortality data were corrected for year effects, a moderate but significant effect of *T. gondii* was detected for men from 55 years and older (*P*-values: 55–64 years = 0.0282, 65–74 to 85–94 years < 0.0001), for women from 65 years (*P*-values: 65 years = 0.0023, 75–84 and 85–94 years < 0.0001). This effect increased with age and was stronger for men than for women (Fig. 1). Both results are consistent with the fact that *T. gondii* exposure increases with age and has different neurological effects on men and women (Flegr, 2010). While this novel evidence of a significant statistical association between *T. gondii* infection and brain cancer does not indicate causation, it is consistent with a similar pattern at the global level for the incidence of brain cancer (Thomas et al., 2012). Although we cannot exclude the existence of confounding variables, these results, together with those by Thomas et al. (2012), suggest it would be worth investigating the prediction

that individuals with brain cancer are more likely to have been infected with *T. gondii*. Finding a causal link between *T. gondii* and brain cancer would radically change the way we consider *T. gondii* infections, and provide a means to reduce the risk of brain cancer, particularly in countries like France where the incidence of brain cancer and *T. gondii* are both high.

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