

Association Between Malaria Incidence and All Cancer Mortality in Fifty U.S. States and the District of Columbia

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Abstract. *Background: There is a relationship between malaria in the United States and brain tumor incidence, seen in data on malaria outbreaks in 2004 from the Centers for Disease Control and Prevention and reports of brain tumor incidence by state from 19 US states. Methods: In the present study, data from 50 US states and the District of Columbia on malaria outbreaks in 1994, compiled by the Centers for Disease Control and Prevention, was analyzed in relation to state by state all cancer mortality data, 1950-94, from the National Cancer Institute. Results: There was a significant association of malaria incidence with all cancer mortality in 50 US states and the District of Columbia. The association was independent of state population size, percentage black population by state, and median population age. Conclusion: The association between malaria and cancer mortality can be possibly explained by the well established ability of Plasmodium to induce suppression of the immune system. A second explanation may be that the anopheles mosquito, the vector of malaria, transmits an obscure virus that initially causes only a mild transitory illness but much later predisposes to cancer.*

There are few studies of the relationship of cancer to malaria, although Suresh *et al.* have reported analogies at the cellular level for the two diseases (1). Welsh *et al.* found no relationship of malaria seropositivity rates to primary liver cancer (2). Efferth *et al.* have shown that the anti-malarial artesunate is active against cancer (3). Epstein Barr Virus-related Burkitt's lymphoma is believed to require cofactors, such as malaria infection, for tumor development (4).

There is a relationship between malaria in the United States and brain tumor incidence, seen in data on malaria outbreaks in 2004 from the Centers for Disease Control

and Prevention (5) and reports of brain tumor incidence by state from 19 US states (6). The association of malaria with brain tumors was significant ($p < 0.001$), and independent of the effect of state population size ($p < 0.001$) (7).

In the present study, data from 50 US states and the District of Columbia on malaria outbreaks in 1994, compiled by the Centers for Disease Control and Prevention (8), was analyzed in relation to state by state all-cancer mortality data, 1950-1994, from the National Cancer Institute (9).

Methods

The following data sources were used:

- Malaria incidence: Centers for Disease Control and Prevention (8).
- State by state cancer mortality, 1950-1994: The National Cancer Institute Cancer Mortality Maps & Graphs Web Site (<http://www3.cancer.gov/atlasplus/index.html>)
- State Populations, percentage black population, and median population ages: US Census Bureau (www.census.gov)
- Encephalitis incidence: Centers for Disease Control and Prevention, Division of Vector Borne Infectious Diseases (<http://www.cdc.gov/ncidod/dvbid/index.html>)

Multivariate linear regression was performed with all cancer mortality as the dependent variable, 1994 malaria incidence, state population size, percentage black population by state and population median age as independent variables.

Results

There was a significant association ($p < 0.001$) of 1994 malaria incidence with all cancer mortality, 1950-1994, in 50 US states and the District of Columbia (Figure 1). Increased numbers of both malaria cases and cancer could be due solely to the fact that some states, such as New York, have much larger populations than other states, such as North Dakota. Moreover, age differences in the various state populations could confound the results, since cancer mortality increases with age (10). Because many Blacks carry the sickle cell trait, which makes them more resistant to malaria (11), the percentage black population of each state was included in the statistical analysis.

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Key Words: Mosquito, adenovirus, susceptibility, immune suppression.

There was a significant relationship of malaria cases to all cancer mortality ($p=0.035$) that was independent of state population size ($p<0.001$), population median age ($p=0.006$), and percentage black population ($p=0.514$).

There was no relationship of Eastern Equine Encephalitis, Western Equine Encephalitis, St Louis Encephalitis, or West Nile virus infection to cancer mortality.

Discussion

The association between malaria and all cancer mortality can be possibly explained by the well established ability of *Plasmodium* to induce suppression of the immune system leading to an increased susceptibility to many secondary infections. Individuals or experimental animals infected with malaria are much more susceptible to Salmonella, herpes zoster virus, hepatitis B virus, Epstein barr virus reactivation or infections with Moloney murine leukemia virus. Efficacy of certain vaccines against pneumococci is reduced during the malaria transmission season (12). The immune suppression induced in patients infected with *Plasmodium falciparum* is evident predominantly after the peak of infection. Several new studies link the suppression of adaptive immune response to heterologous antigens following *Plasmodium* infection and induction of regulatory T cells (13, 14).

A second possible explanation for the relationship between malaria and all cancer mortality may be that the anopheles mosquito, the vector of malaria, transmits an obscure virus that initially causes only a mild transitory illness but much later predisposes to cancer. Anopheles carries o'nyong-nyong virus, chikungunya virus (15) and multiple arboviruses, including that causing Japanese Encephalitis (16). Moreover, adenoviruses, which often cause upper respiratory tract infections and gastroenteritis, have considerable potential to induce malignant transformation in cell lines (17).

Since Eastern Equine Encephalitis, Western Equine Encephalitis, and St Louis Encephalitis were not related to cancer mortality, the *Aedes* mosquito, their vector, is probably not a carrier of the hypothesized cancer susceptibility virus. Likewise, because West Nile Virus was unrelated to cancer mortality, its main vector, the *Culex* mosquito, probably does not carry the hypothesized cancer virus. (Although *Anopheles* can carry West Nile Virus, *Anopheles* is not the dominant mode of transmission in the US (18)).

An immune system mechanism is also possible. The viruses listed above, in contrast to malaria, do not appear to induce persistent or sustained immunosuppression in infected hosts. Regulatory T-cells appear to protect the hosts infected by these viruses and return to pre-infection levels within a year after the infection (19, 20). Apparently, immune surveillance in these patients is not compromised.

One might argue that insecticide spraying was the actual factor responsible for the increase in all cancer mortality

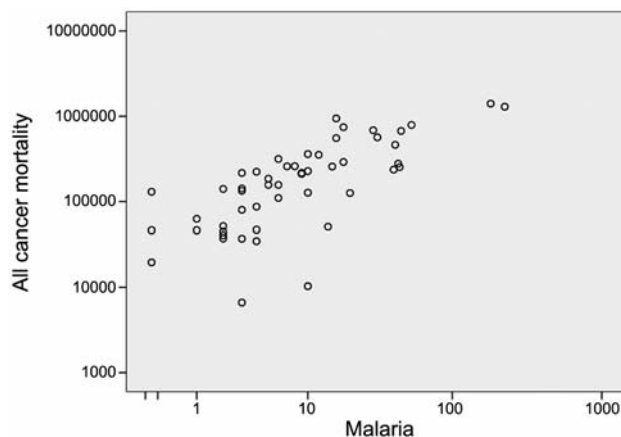


Figure 1. Number of US malaria cases in 1994, source Centers for Disease Control and Prevention vs. all cancer mortality, 1950-1994, in 50 US states and the District of Columbia, source National Cancer Institute. The correlation is significant ($r=0.917$, $p<0.001$).

associated with malaria, rather than mosquito transmission of a virus. But this argument is weakened by the fact that Eastern Equine Encephalitis, Western Equine Encephalitis, St Louis Encephalitis, and West Nile Virus infection were not related to all cancer mortality, although the same insecticides are used to control *Anopheles*, *Aedes*, and *Culex*.

If a mosquito-transmitted cancer virus could be identified, development of a cancer vaccine might be possible.

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Received January 5, 2010

Revised March 11, 2010

Accepted March 15, 2010