Hypothesis

Eye Cancer Incidence in U.S. States and Access to Fluoridated Water

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Running Title: Uveal Melanoma and Fluoridation

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ABSTRACT

Environmental risk factors for uveal melanomas (cancer of the iris, ciliary body and choroid) have not been identified. In order to search for these, we examined the correlation of age-adjusted eye cancer incidence rates, a surrogate for uveal melanoma rates, in U.S. states with group level geographic and demographic factors using multivariate linear regression. Incidence rates for eye cancer were inversely correlated with the percent of the population receiving fluoridated water; i.e., higher rates were found in states with lower prevalences of fluoridation (P = 0.01). Fluoride is known to inhibit the growth of microbial agents that cause choroiditis and choroidal lesions in animals. We speculate that fluoridation protects against choroidal melanoma by inhibiting microbial agents that cause choroiditis and/or choroidal lesions in humans.

Keywords: Uveal melanoma, fluoridation, etiology, choroiditis, epidemiology
INTRODUCTION

Melanomas of the uveal tract (iris, ciliary body, and choroid) are the most common primary intraocular cancer in adults. The vast majority of these affect the choroid, the pigmented, highly vascular layer of the eye between the sclera and the retina. (1) Uveal melanomas are rare, with a mean age-adjusted incidence of 5.1 per million in the U.S. per year, but are sight- and life-threatening. (2,3) The case-fatality rate for uveal melanoma is approximately 50%, with most deaths due to liver metastases. (4) An increased risk of metastasis is strongly associated with somatic mutations in the BAP1 gene located on chromosome 3. (5) Germline mutations in BAP1 cause hereditary predisposition to uveal melanoma in a subset of patients. (6)

Little is known about the causes of uveal melanoma. Pathologically, uveal melanomas are believed to originate from neoplastic transformation of benign nevi. (7) Host factors include light skin color, blue eye color, and an inability to tan. (8) Arc welding is an established occupational risk factor. (9)(10) Conversely, environmental risk factors for uveal melanoma have not been consistently identified. Unlike cutaneous melanoma, which is strongly associated with exposure to ultraviolet radiation, evidence for an etiologic role for ultraviolet radiation in uveal melanoma is weak. (10, 11)

Historically, insights into cancer etiology often have come from ecologic (correlation) studies. Indeed, recognition of the association between cutaneous melanoma and exposure to ultraviolet radiation began with the correlation of cutaneous melanoma rates with geographic latitude. (12) We sought to generate insight into the etiology of uveal melanoma by correlating eye cancer incidence rates in U.S. states with geographic and demographic features. We report that the incidence of eye cancer within the U.S. is correlated inversely with the availability of fluoridated water.
MATERIALS AND METHODS

Uveal melanoma does not have a unique code in the International Classification of Disease. However, because 90% of eye cancers in adults are ocular melanomas and the majority involve the uveal tract, adult eye cancer rates are commonly used as a surrogate for uveal melanoma rates. (13) Data on eye and orbit cancer by state for 2006-2010 (for all ages) were obtained from the North American Association of Central Cancer Registries (NAACCR). (14) Rates were age-adjusted to the 2000 U.S. Standard Population. Rates based on fewer than 10 cases were considered unstable and were censored. Because the incidence of uveal melanoma is rare among African Americans and is lower in Hispanic than in non-Hispanic whites, we used data for non-Hispanic whites only. (15)

Data on latitude and longitude at the center of each state were obtained from netstate, an internet cartography website. (16) Data on population density were obtained from the 2010 U.S. Census. (17) Because the diagnosis of uveal melanoma requires ophthalmologic expertise, we examined the correlation between eye cancer incidence and the density of ophthalmologists. We calculated ophthalmologist density per state using the number of ophthalmologists per state as the numerator (available via U.S. News Doctor Finder) (18) and the corresponding 2010 Census population as the denominator, multiplied by 100,000.

The state with the highest incidence of eye cancer, Oregon, has attracted public health attention due to the long-standing opposition of many Oregonians to water fluoridation. (19) The U.S. Public Health Service endorsed water fluoridation to prevent tooth decay in 1951. However, the decision to fluoridate or not is made by municipal governments. (20) In order to explore a possible relationship between fluoridation and eye cancer, we correlated eye cancer incidence rates with the percentage of the population of each state receiving fluoridated water in 2010. Fluoridation data were obtained from the Centers for Disease Control and Prevention...
The CDC tracks the number of persons receiving fluoridated water using a validated data system maintained in cooperation with the Association of State and Territorial Dental Directors. Data were analyzed by multivariable linear regression using Excel. Variables considered to be potential confounders (e.g., latitude) were specified a priori or were identified empirically. Any factor with a p value ≤ .10 was considered a potential confounder and was included in a final model. All statistical tests were two-tailed. P values ≤ .05 were considered significant.

RESULTS

Data on eye cancer that met NAACCR quality standards were available for 44/50 states. Data from Washington, D.C. was censored due to small numbers (N=9). Age-adjusted incidence rates for eye cancer in the U.S. among non-Hispanic whites in 2006-2010 ranged four-fold and were lowest in South Dakota (0.29 per 100,000, 95% C.I. = 0.15-0.51, based on 13 cases) and highest in Oregon (1.23 per 100,000, 95% C.I. = 1.10-1.43, based on 242 cases). The average ophthalmologist density per state was 5.7 per 100,000 and ranged from 3.4 per 100,000 in Wyoming to 9.3 per 100,000 in New York. Access to fluoridated water ranged from 2.2 % in Utah to > 95% in several states.

Incidence rates for eye cancer were not significantly correlated with longitude, population density or ophthalmologist density (see Table 1). Incidence rates were modestly inversely correlated with latitude (i.e., were higher in sunnier states, P = .09) and were significantly inversely correlated with the percentage of the population with access to fluoridated water (P = 0.01) (see Figure 1). Only geographic latitude met our a priori criteria for possible confounding (p = .09). A multivariate model that included access to fluoridation and geographic latitude was highly significant (r = 0.45, P = 0.002).
DISCUSSION

Using population-based data on the incidence of eye cancer for 44 states, we observed an apparent protective effect of fluoridation; i.e., states with greater access to fluoridated water had lower incidence rates for eye cancer. To our knowledge, this is the first report of an association between water fluoridation and eye cancer.

The lowest incidence rates for eye cancer were found in South Dakota and North Dakota (0.29 per 100,000, 95% C.I. = 0.15-0.51 and 0.41 per 100,000, 95% C.I. = 0.22-0.70, respectively). At least in part, this may reflect under-diagnosis in rural states. However, the correlation between eye cancer and access to fluoridated water was little influenced by these states, as censoring data for North and South Dakota did not meaningfully alter the correlation between access to fluoridation and eye cancer ($r = 0.38$ vs. $r = 0.37$, with and without the Dakotas, respectively). The state with the highest incidence of eye cancer was Oregon (1.23 per 100,000). It is noteworthy that a type of multifocal choroiditis occurs in Oregon. Watzke et al. described ten patients with choroiditis that was identical to presumed ocular histoplasmosis, a choroidal disease thought to result from systemic infection with the fungus, *Histoplasma capsulatum*, which is prevalent in the U.S. Ohio and Mississippi River valleys. (23) However, the Oregon patients were seronegative for *Histoplasma* and had not traveled to regions where this fungus is endemic. (24)

Eye cancer incidence rates were not significantly correlated with population density or with the density of ophthalmologists per state ($P = 0.70$ and 0.20, respectively). This suggests that detection bias is unlikely to play a major role in the variation in U.S. rates. We did not observe a significant correlation with either geographic longitude or latitude ($P = 0.17$ and 0.09). This finding is consistent with many reports, including a recent meta-analysis, which did not find a significant association between uveal melanoma and latitude at place of birth. (10)

Our study has several limitations, including its ecologic design and biases caused by migration and misclassification. It is well known that correlations observed at the group level may not be observed at the individual level. (25) Epidemiologic studies in individuals should obtain data on fluoride intake, including...
fluoride in diet, toothpastes and mouthwashes. Since we do not know the latency period of uveal melanoma or the time period during which fluoride exposure may be important, these results are vulnerable to biases due to migration. However, because individuals at risk for eye cancer likely migrate for reasons unrelated to their disease, the effect of migration is likely to be non-directional and would reduce the correlation between fluoridation and eye cancer.

The incidence rates for eye cancer from NAACCR were not stratified by age and include childhood cases. The major eye tumor of childhood, retinoblastoma, accounts for approximately 200 cases per year in whites in the U.S. As our analysis is based on > 10,000 cases, retinoblastomas would contribute ~ 10% of the total. Because incidence rates for retinoblastoma are stable and do not vary geographically, any misclassification caused by their inclusion would bias our results toward the null. Some misclassification by other tumor types is likely. However, a detailed quality control analysis of NAACCR morphology data from 1995-1999 indicated that 70% of “eye and orbit” cancers were melanomas.

Conversely, this study has several strengths, including the use of high quality, incidence rates at the level of the state and the novel use of validated data on access to fluoridated water. Fluoridation could illuminate several unexplained observations about eye cancer epidemiology. For example, eye cancer mortality rates (used as a surrogate for uveal melanoma incidence rates, as survival from uveal melanoma has not changed significantly in the past 50 years) in the U.S. were similar to eye cancer mortality rates in England and Wales in 1955. However, mortality rates in the U.S. (but not the U.K.) declined > 50% since then. These trends are consistent with geographic trends in fluoridation, as only 10% of the U.K. currently receives fluoridated water (vs. ~ 69% of the U.S. in 2006), and with temporal trends in the prevalence of fluoridation in the U.S., which increased after 1951.

It is possible that the inverse correlation between access to fluoridated water and eye cancer incidence reflects a protective role for fluoride. Because fluoride has potent antimicrobial effects, a protective role would be
understandable if uveal melanoma had a microbial origin. A viral etiology for uveal melanoma was suggested in 1979 but has received little support. (34) In their discussion of histoplasma-like choroiditis in Oregon, Watzke et al. noted that in immunocompetent individuals, many microbial agents, e.g., mycobacteria, could produce subclinical infections and choroidal lesions that heal spontaneously, leaving choroidal scars. This would explain the existence of “ocular histoplasmosis” in areas of the world where histoplasmosis is not endemic. We speculate that in some individuals, choroidal lesions undergo malignant transformation. Thus, a tumor of the retinal pigment epithelium resembling uveal melanoma arising from a chorioretinal scar was described by Shields et al. (35) A choroidal melanoma regressing into a chorioretinal scar and recurring as a choroidal melanoma was described by Lambert et al. (36) Alternately, chorioretinal lesions have been described in association with infiltrating lymphocytes. (37) Some infiltrating lymphocytes, e.g., tumor associated macrophages, have potent immunosuppressive and angiogenic properties and are strongly associated with ocular carcinogenesis. (38, 39)

We speculate that fluoridation protects against uveal melanoma by inhibiting microbial agents that cause choroiditis and/or choroidal scars. Fluoride blocks metabolic enzymes required for the growth of bacteria and fungi. (40, 41) Consequently, bacterial counts in fluoridated water are lower than in unfluoridated water. (42) Fluoride prevents dental caries by inhibiting the oral bacterium, *Streptococcus mutans*. (43) *S. mutans* and other bacteria potently induce choroiditis in experimental animals. For example, intra-carotid injection of *S. mutans* causes choroiditis and chorioretinal scars in dogs. (44) It would be valuable to use this model of choroiditis to examine the incidence of choroidal lesions in dogs given access to water with different levels of fluoride.

In summary, in this hypothesis-generating study, we observed that eye cancer incidence rates in U.S. states are inversely correlated with the availability of fluoridated water. If confirmed by analytic studies, this finding may be a productive clue to the enigmatic etiology of uveal melanoma. (45)
REFERENCES


14 CINA+ Online Cancer in North America [Internet] [cited 2014 June 1]. Available from: http://www.cancer-rates.info/naaccr/


### Table 1.

<table>
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<tr>
<th>Variable</th>
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<td>Longitude</td>
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<td>Population density</td>
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<td>Percent receiving fluoridated water</td>
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<tr>
<td>Percent receiving fluoridated water, model Including latitude</td>
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**Table 1.** Correlation between the age-adjusted incidence rates of eye cancer in whites 2006-2010 in U.S. states with geographic and demographic risk factors. N = 44 for all correlations. NAACCR data for eye cancer were not available for Arkansas, Ohio, Massachusetts, Minnesota, Nevada and Virginia.
FIGURE LEGENDS

Figure 1. Scatter plot of incidence rates for eye cancer and percent of the population with access to fluoridated water in 2010.
Figure 1
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