Original Paper

Neuro
epidemiology

Neuroepidemiology 2010;35:281–290
DOI: 10.1159/000314350

Received: June 28, 2009
Accepted: April 22, 2010
Published online: October 14, 2010

# Low Ultraviolet B and Increased Risk of Brain Cancer: An Ecological Study of 175 Countries

Sharif B. Mohr[a, b] Edward D. Gorham[a, b] Cedric F. Garland[a] William B. Grant[c] Frank C. Garland[a, b]

[a]Department of Family and Preventive Medicine 0620, University of California San Diego, La Jolla, Calif., [b]Naval Health Research Center, San Diego, Calif., and [c]Sunlight, Nutrition and Health Research Center, San Francisco, Calif., USA

**Key Words**
Brain neoplasms · Vitamin D · Ultraviolet rays · Alcohol · Cigarettes · Multiple regression · International comparisons

**Abstract**
***Background:*** The purpose of this study was to determine whether an inverse association exists between latitude, solar ultraviolet B (UVB) irradiance, modeled 25-hydroxyvitamin D [25(OH)D] levels and incidence rates of cancer of the brain. ***Methods:*** Associations of latitude and UVB irradiance with age-standardized incidence rates of cancer of the brain were analyzed for 175 countries while controlling for proportion of population overweight, energy from animal sources, fish consumption, cigarette and alcohol consumption and per capita health expenditures, using multiple regression. Serum 25(OH)D levels were modeled for each country, and their association with brain cancer also was determined. ***Results:*** The incidence rates of brain cancer were higher at higher latitudes ($R^2$ for males = 0.45, $p \leq 0.0001$; $R^2$ for females = 0.35, $p < 0.0001$). After adjustment for potential confounders, UVB irradiance ($p \leq 0.0001$) and modeled serum 25(OH)D were inversely associated with incidence rates. ***Conclusions:*** Countries with low solar UVB irradiance and estimated mean serum 25(OH)D levels generally had higher age-standardized incidence rates of brain cancer. Since this was an ecological study, further research would be worthwhile on the association of prediagnostic serum 25(OH)D with incidence rate in studies of cohorts of individuals.



## Introduction

Worldwide there are an estimated 189,485 cases and 141,650 deaths from primary brain cancer each year [1]. In the USA, 22,000 cases and 13,000 deaths were expected in 2010 [2]. However, very little is known about the etiology of primary brain cancer with the principal confirmed causes being ionizing radiation and a few uncommon genetic syndromes [3].

Greater exposure to solar ultraviolet B (UVB) in areas with high solar irradiance causes greater cutaneous photosynthesis of vitamin D in populations in these areas, resulting in higher levels of vitamin D metabolites, particularly 25-hydroxyvitamin D [25(OH)D] that are associated with lower incidence rates of certain cancers [4]. Populations living at higher latitudes, or having lower

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com


0251–5350/10/0354–0281$26.00/0

Accessible online at:
www.karger.com/ned

Cedric F. Garland, Dr. PH, FACE
Department of Family and Preventive Medicine, University of California San Diego
9500 Gilman Drive 0620
La Jolla, CA 92093-0620 (USA)
Tel. +1 619 553 9016, Fax +1 619 524 9888, E-Mail cgarland@ucsd.edu

prediagnostic serum 25(OH)D levels, have higher incidence rates of cancers of the breast [5–8], colon [9–12] and ovary [13], raising the possibility that vitamin D might also play a similar beneficial role in the etiology of cancer of other sites, such as the brain.

Tumors of the brain and nervous system are markedly different from tumors originating in other sites. However, it is possible that vitamin D may play a role in the prevention of brain cancer through its ability to help maintain the structural integrity of intercellular adhesion proteins. These adhesion proteins can be degraded by ionizing radiation, the principal known risk factor for brain cancer. In addition, vitamin $D_3$ (cholecalciferol) has been shown to induce death of human glioblastoma cells in vitro [14] and another study found that 25(OH)D can cause a significant reduction in growth of glioblastoma cells in vitro [15].

We chose several variables to include in the model as possible confounders based on previous research. It is well known that obesity is associated with lower levels of circulating serum 25(OH)D [16] as well as an increased risk for several cancers [17]. Intake of large quantities of energy of animal origin is thought to increase a growth hormone, insulin-like growth factor I (IGF-I), which is believed to increase the risk of cancer for other sites [18–20] and may possibly be relevant to the etiology of brain cancers.

Consumption of fish and fish oil are good sources of dietary vitamin D. They also exert a beneficial effect on age-related cognitive decline [21]. Cigarette smoking is a well-established risk factor for many cancers and some evidence exists that implicates parental drinking in increasing the risk of childhood brain cancer [22, 23], raising the possibility that alcohol use may play some role in the etiology of certain brain cancers. Per capita health expenditure was included in the analysis in order to account for international differences in quality of health care and the ability to detect cancers, which may be correlated with latitude since countries at higher latitudes tend to be wealthier than countries at lower latitudes.

Multiple linear regression was used to examine the associations of UVB irradiance adjusted for cloudiness with age-standardized incidence rates of cancer of the brain, while controlling for potential confounders such as proportion of the population overweight, intake of energy from animal sources, fish consumption, cigarette and alcohol consumption, and per capita health expenditures.

## Materials and Methods

*Data Sources*

Age-standardized incidence rates of brain cancer were obtained for 175 countries, along with latitude of the population centroid of each country, winter UVB irradiance adjusted for cloudiness, proportion of the population overweight, intake of energy from animal sources, intake of energy from fish sources, per capita alcohol and cigarette consumption, and per capita health expenditures. All 175 countries were used in the latitude analysis. Complete data on all other variables were available for 107 countries and were used in the multivariate analyses.

The sources for many of the variables have been described elsewhere [24]. Age-standardized incidence rates of brain and nervous center tumors (defined as ICD 10 codes C70-C72) were obtained using the International Agency for Research on Cancer GLOBOCAN database for 2002, the latest year for which data are available [1]. Per capita consumption of cigarettes, alcohol and energy from animal and fish sources were obtained from the United Nations Food and Agriculture Organization for 1980 [25]. Data on cloud cover were obtained from the National Aeronautics and Space Administration International Satellite Cloud Climatology Project earth-orbiting satellite [26].

Serum 25(OH)D values were modeled for 157 countries for which actual measurements of 25(OH)D from population-based samples were not available. We were able to obtain actual serum 25(OH)D measurements from 28 regions in 18 countries from previous research, and these actual measurements provided the basis for modeling estimated population 25(OH)D values. Estimated serum 25(OH)D was modeled using the measured levels of serum 25(OH)D during winter obtained from the 28 regions in 18 countries (Appendix 1) as the dependent variable, UVB irradiance as the independent variable and skin pigmentation levels in the areas where the studies were performed as a covariate. A multiple regression model based on known values of these variables provided regression coefficients for use in a separate multiple regression prediction equation that was applied to estimate mean winter serum 25(OH)D levels in countries where measurements were not available. The prediction equation included a scaling constant that was empirically determined. The measured 25(OH)D levels were used in the final calculations for the 18 countries, and the values modeled from the procedures described above were utilized for the remaining 157 countries.

*Statistical Analysis*

Age-standardized incidence rates from GLOBOCAN [1] were analyzed according to the latitude of the population centroid. The rates were age standardized to the age distribution of the 2000 world population [1]. The best fit to the data points was obtained using a polynomial trend line. A standard pharmacologic dose-response curve was plotted using a standard algorithm (Prism; GraphPad Software, San Diego, Calif., USA). Multiple linear regression was employed to examine the associations of UVB irradiance adjusted for cloudiness, while controlling for proportion of the population overweight, intake of energy from animal sources, fish consumption, cigarette and alcohol consumption, and per capita health expenditure in 107 countries. All analyses were performed using SAS version 9.1 and JMP version 5.1.2 ( SAS Institute, Cary, N.C., USA).

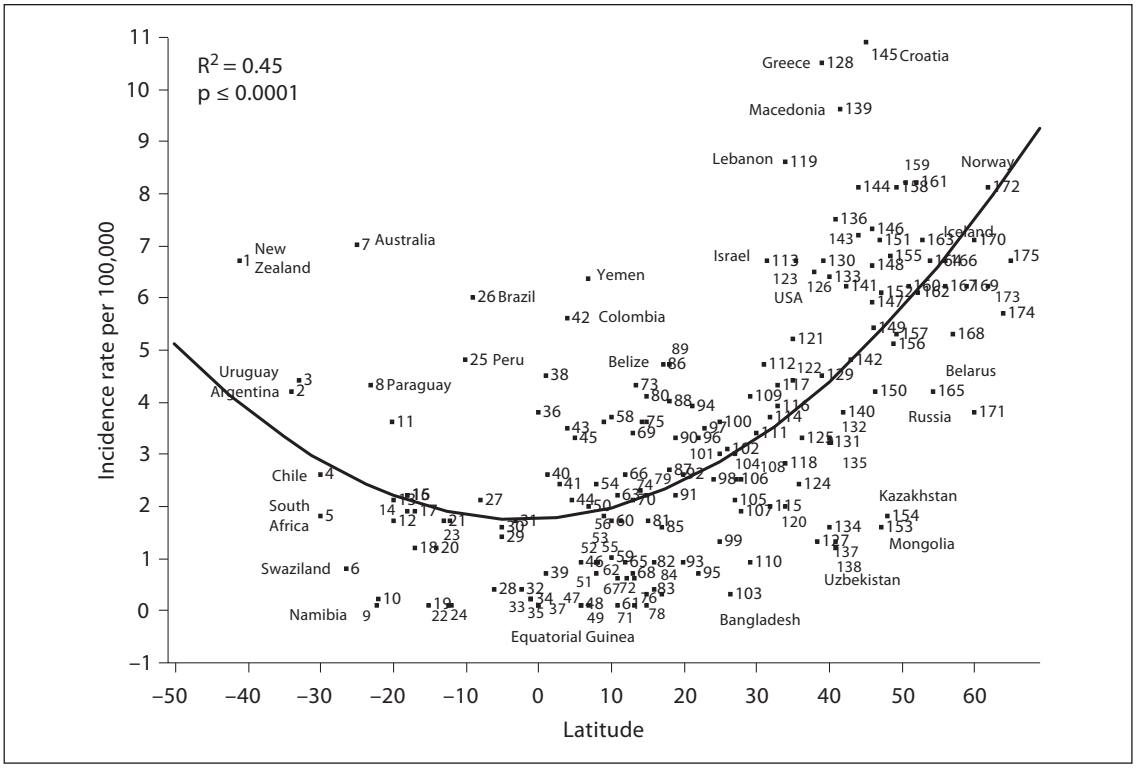


**Fig. 1.** Annual age-standardized incidence rates of cancer of the brain per 100,000 population, males, 175 countries, 2002. Source: data from GLOBOCAN [1].

**Country label numbers used in figures 1 and 2**

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 = | New Zealand | 27 = | Solomon Islands | | Republic | 75 = | Guatemala | 99 = | Qatar | 125 = | South Korea | 150 = | Moldava |
| 2 = | Argentina | 28 = | Tanzania | 50 = | Sri Lanka | 76 = | Chad | 100 = | Saudi Arabia | 126 = | USA | 151 = | Hungary |
| 3 = | Uruguay | 29 = | Indonesia | 51 = | Côte d'Ivoire | 77 = | Honduras | 101 = | United Arab Emirates | 127 = | Tajikistan | 152 = | Austria |
| 4 = | Chile | 30 = | Papua New Guinea | 52 = | Ghana | 78 = | Sudan | 102 = | Bahrain | 128 = | Greece | 153 = | Mongolia |
| 5 = | South African Republic | 31 = | Burundi | 53 = | Togo | 79 = | Thailand | 103 = | Bangladesh | 129 = | Turkey | 154 = | Kazakhstan |
| 6 = | Swaziland | 32 = | Rwanda | 54 = | Venezuela | 80 = | Yemen | 104 = | Egypt | 130 = | Portugal | 155 = | Slovakia |
| 7 = | Australia | 33 = | Congo Brazzaville | 55 = | Sierra Leone | 81 = | Eritrea | 105 = | Libya | 131 = | Armenia | 156 = | Ukraine |
| 8 = | Paraguay | 34 = | Gabon | 56 = | Ethiopia | 82 = | Cape Verde | 106 = | Bhutan | 132 = | North Korea | 157 = | Czech Republic |
| 9 = | Namibia | 35 = | Congo | 57 = | Panama | 83 = | Niger | 107 = | Algeria | 133 = | Spain | 158 = | Luxembourg |
| 10 = | Botswana | 36 = | Ecuador | 58= | Costa Rica | 84 = | Mali | 108 = | Nepal | 134 = | Turkmenistan | 159 = | Belgium |
| 11 = | Mauritius | 37 = | Equatorial Guinea | 59 = | Nigeria | 85 = | Vietnam | 109 = | Kuwait | 135 = | Azerbaijan | 160 = | Germany |
| 12 = | Madagascar | 38 = | Kenya | 60 = | Somalia | 86 = | Belize | 110 = | Lesotho | 136 = | Albania | 161 = | Poland |
| 13 = | Zimbabwe | 39 = | Uganda | 61 = | Guinea | 87 = | Lao People's Democratic Republic | 111 = | Pakistan | 137 = | Kyrgyzstan | 162 = | Netherlands |
| 14 = | Fiji | 40 = | Singapore | 62 = | Micronesia | 88 = | Jamaica | 112 = | Jordan | 138 = | Uzbekistan | 163 = | Ireland |
| 15 = | Mozambique | 41 = | Malaysia | 63 = | Trinidad and Tobago | 89 = | Puerto Rico | 113 = | Israel | 139 = | Macedonia | 164 = | UK |
| 16 = | Vanuatu | 42 = | Colombia | 64 = | Djibouti | 90 = | Dominican Republic | 114 = | Iran | 140 = | Georgia | 165 = | Belarus |
| 17 = | Bolivia | 43 = | Suriname | 65 = | Guinea-Bissau | 91 = | Haiti | 115 = | Morocco | 141 = | Italy | 166 = | Denmark |
| 18 = | Polynesia | 44 = | Brunei | 66 = | Philippines | 92 = | India | 116 = | China | 142 = | Bulgaria | 167 = | Lithuania |
| 19 = | Zambia | 45 = | Guyana | 67 = | Burkina Faso | 93 = | Mauritania | 117 = | Iraq | 143 = | Serbia and Montenegro | 168 = | Latvia |
| 20 = | Samoa | 46 = | Benin | 68 = | Cambodia | 94 = | Cuba | 118 = | Afghanistan | 144 = | Bosnia-Herzegovina | 169 = | Estonia |
| 21 = | Melanesia | 47 = | Cameroon | 69 = | Nicaragua | 95 = | Myanmar | 119 = | Lebanon | 145 = | Croatia | 170 = | Canada |
| 22 = | Angola | 48 = | Liberia | 70 = | Barbados | 96 = | Oman | 120 = | Tunisia | 146 = | France | 171 = | Russian Federation |
| 23 = | Comoros | 49 = | Central African Republic | 71 = | Gambia | 97 = | Mexico | 121 = | Cyprus | 147 = | Romania | 172 = | Norway |
| 24 = | Malawi | 50 = | Sri Lanka | 72 = | Guam | 98 = | Bahamas | 122 = | Syria | 148 = | Switzerland | 173 = | Sweden |
| 25 = | Peru | 51 = | Côte d'Ivoire | 73 = | El Salvador | 99 = | Qatar | 123 = | Malta | 149 = | Slovenia | 174 = | Finland |
| 26 = | Brazil | 52 = | Ghana | 74 = | Senegal | 100 = | Saudi Arabia | 124 = | Japan | | | 175 = | Iceland |

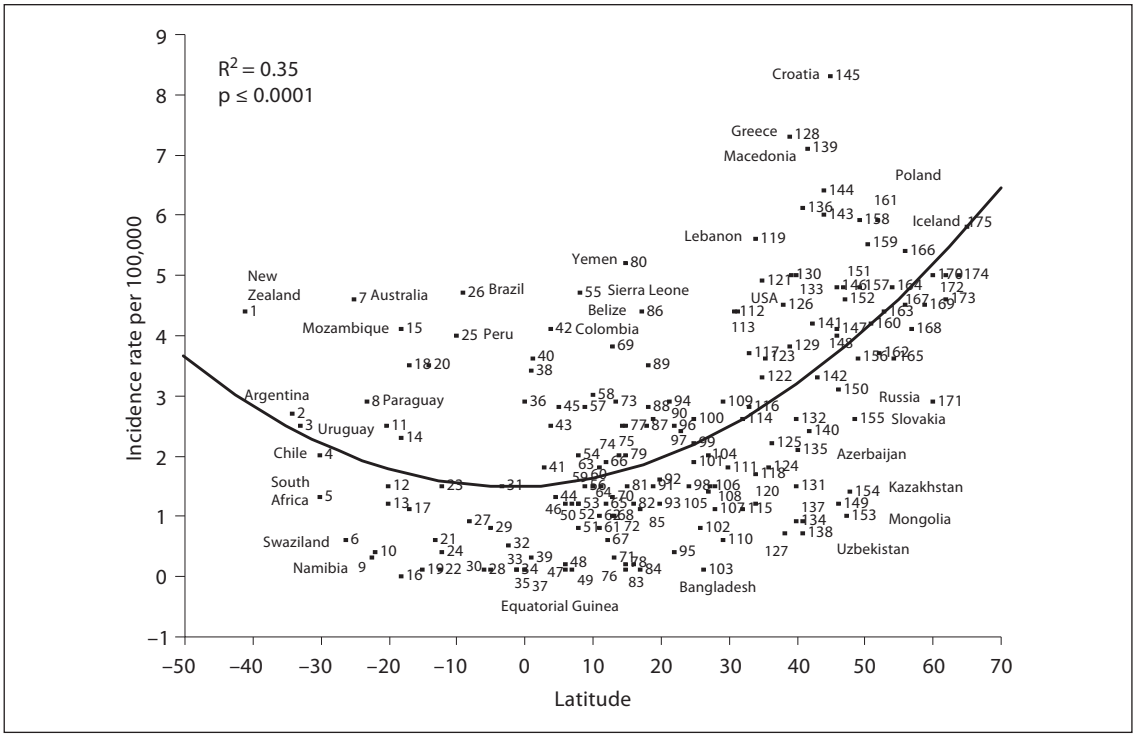


**Fig. 2.** Annual age-standardized incidence rates of cancer of the brain per 100,000 population, females, 175 countries. Source: data from GLOBOCAN [1]. Country label numbers are the same as in figure 1.

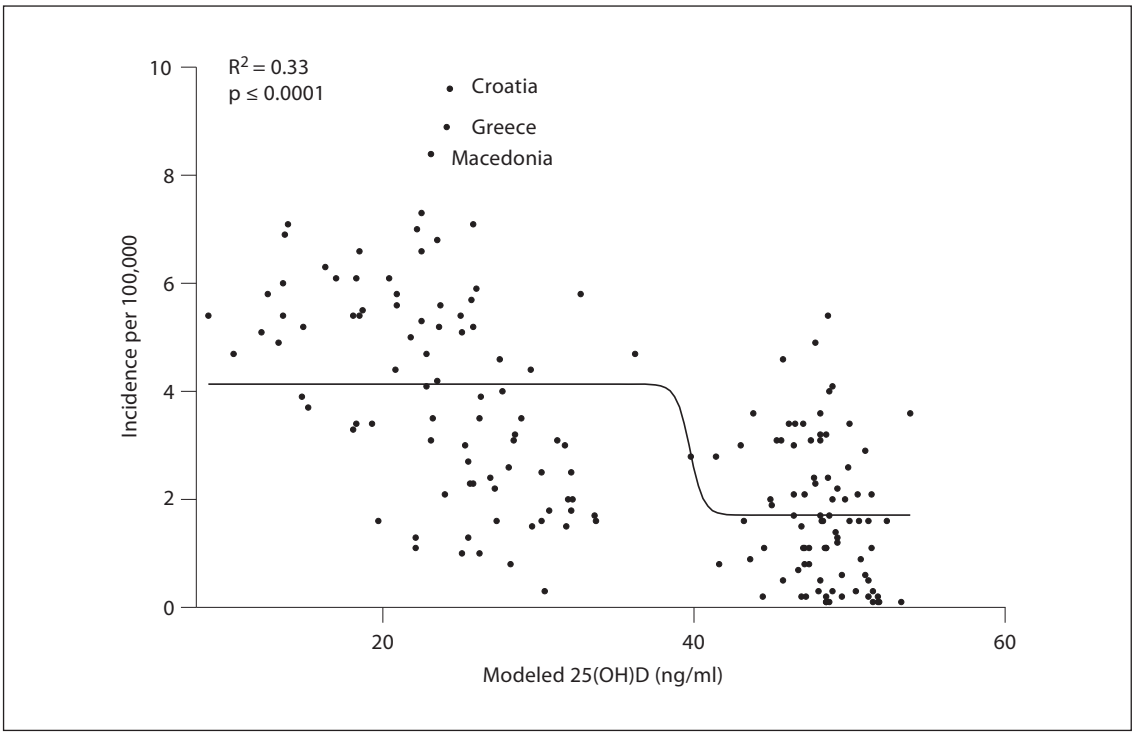


**Fig. 3.** Dose-response relationship between modeled serum 25(OH)D and incidence rates of brain cancer per 100,000 population in 175 countries, 2002. Source: data from GLOBOCAN [1]. Three outliers are labeled.

**Table 1.** Solar UVB irradiance and other covariates in association with brain cancer incidence rates, 107 countries, males, 2002

| Variable | Regression coefficient | Standard error | t | p |
|---|---|---|---|---|
| Solar UVB irradiance[a] | –0.2219 | 0.0541 | –4.11 | <0.0001 |
| Fish consumption[b] | –0.0082 | 0.0034 | –2.37 | 0.02 |
| Proportion of population overweight[c] | 0.3681 | 0.0181 | 2.03 | 0.04 |
| Intake of energy from animal sources[b] | 0.0019 | 0.0007 | 2.61 | 0.01 |
| Alcohol intake[b] | –0.0019 | 0.0024 | –0.81 | 0.42 |
| Cigarette consumption[c] | 0.0002 | 0.0002 | 1.01 | 0.32 |
| Per capita health expenditure[c, d] | 0.0004 | 0.0002 | 1.47 | 0.14 |
| Intercept | 4.1131 | 0.7596 | 5.41 | <0.0001 |

$R^2 = 0.74$, $p < 0.0001$. [a] Watts/square meter at vernal equinox, adjusted for cloudiness. [b] Source: United Nations Food and Agriculture Organization. [c] Source: World Health Organization. [d] All currencies were adjusted by the World Health Organization to USD.

**Table 2.** Solar UVB irradiance and other covariates in association with brain cancer incidence rates, 107 countries, females, 2002

| Variable | Regression coefficient | Standard error | t | p |
|---|---|---|---|---|
| Solar UVB irradiance[a] | –0.2143 | 0.0466 | –4.60 | <0.0001 |
| Fish consumption[b] | –0.0034 | 0.0029 | –1.16 | 0.25 |
| Proportion of population overweight[c] | 0.0117 | 0.0085 | 1.37 | 0.17 |
| Intake of energy from animal sources[b] | 0.0009 | 0.0006 | 1.49 | 0.14 |
| Alcohol intake[b] | –0.0018 | 0.0021 | –0.88 | 0.38 |
| Cigarette consumption[c] | 0.0002 | 0.0002 | 1.05 | 0.29 |
| Per capita health expenditure[c, d] | 0.0002 | 0.0002 | 0.94 | 0.35 |
| Intercept | 3.8424 | 0.6615 | 5.81 | <0.0001 |

$R^2 = 0.63$, $p < 0.0001$. [a] Watts/square meter at vernal equinox, adjusted for cloudiness. [b] Source: United Nations Food and Agriculture Organization. [c] Source: World Health Organization. [d] All currencies were adjusted by the World Health Organization to USD.

## Results

The incidence rates of brain cancer were higher at higher latitudes, with a roughly parabolic relationship (fig. 1, 2). According to multivariate analysis in males, UVB irradiance was independently inversely associated with incidence rates ($p < 0.0001$). In addition, the proportion of the population overweight ($p = 0.04$) and intake of energy from animal sources ($p = 0.01$) were positively associated with incidence rates, while intake of energy from fish was inversely associated ($p = 0.02$) (table 1).

According to a multivariate analysis in females, UVB irradiance ($p < 0.0001$) was independently inversely associated with incidence, similar to the association in males (table 2). No other covariates were related to incidence in females. Serum 25(OH)D was also inversely associated with incidence rates, according to a dose-response analysis performed for both sexes combined, based on modeled and measured serum levels of 25(OH)D (fig. 3).

## Discussion

The etiology of brain cancer is still poorly understood. This is the first report of the inverse association of incidence rates of solar UVB irradiance with cancer of the brain, to our knowledge. The incidence rates of cancer of the brain were higher in countries located at latitudes distant from the equator, where UVB irradiance is low, than in countries closer to the equator, where it is high. In the multivariate model, UVB irradiance was inversely associated with brain cancer incidence rates in both sexes even after controlling for other factors. UVB irradiance varies inversely with latitude [27], and photosynthesis in the skin resulting from it is the source of approximately 95% of circulating vitamin D and its metabolites in humans [28]. Previous studies have shown that 25(OH)D [14] and its precursor, vitamin $D_3$ [15], can inhibit growth or destroy human glioblastoma cells in vitro.

Several mechanisms are involved in vitamin D anticarcinogenesis [30, 51]. A 7-phase sequence has been proposed under the acronym DINOMIT that includes decoupling (D) of epithelial cells due to loss of intercellular adhesion proteins, initiation (I) due to chemical carcinogens, ionizing radiation, infidelity of DNA reproduction and, possibly, epigenetic factors [30, 51]. This is followed by natural selection (N) of rapidly-reproducing clones within a tissue compartment, overgrowth (O) of the tumor mass and penetration of the basement membrane and, eventually, metastasis (M) to remote tissues. It has been hypothesized that with vitamin D adequacy, an involutional (I) or dormant state may occur. If this does not occur, death may ensue. If it does occur, there may be a transition (T) to permanent dormancy as long as vitamin D adequacy is maintained [29, 30]. Other mechanisms may also be involved, since vitamin D metabolites induce differentiation of cancer cells, including lung cancer cells [31] in tissue culture, and arrest growth by mitotic arrest in the interphase (G0/G1) phase of the mitotic cycle. $1,25(OH)_2D$ enhances apoptosis of epithelial cells in tissue culture by decreasing phospho-Erk (and phospho-Akt) kinases that regulate apoptosis, and pathways upregulating MEKK-1, a proapoptotic signaling molecule [32]. Recent studies of the human tumor suppressor oncogene, p53 [33], and its murine analog, p63 [34], have shown that their gene products induce synthesis of vitamin D receptor, a molecule that may mediate the actions of vitamin D on intercellular adhesion.

Vitamin D metabolites are lipid soluble, and it has been established that $1,25(OH)_2$-vitamin D readily crosses the blood-brain barrier [35]. About 2,400 μg of $1,25(OH)_2D$ are present in the parenchyma of the human brain [35]. The normal range of serum $1,25(OH)_2$-vitamin D is 18–64 pg/ml [36].

Cancers of the brain have diverse pathological features, but the majority (approximately 60%, including gliomas and glioblastomas) have histological features that are suggestive of glial cell origin [37]. Recent evidence suggests that these tumors arise mainly, or perhaps exclusively, from glial stem cells [38], although it has not been definitely ruled out that some might arise directly from glia [39]. Glia are derived during embryogenesis from the ectodermal layer [40]. Under normal conditions, the number of glial cells in the human brain is approximately equal to the number of neurons [41]. Unlike neurons within the mature central nervous system, several types of glial cells undergo mitosis [39].

Intercellular tight junctions bind glial cells tightly to one another [42], with the exception of microglia, which are mobile [43]. The tight junctions of glial cells and associated myelin sheaths help provide a high-resistance barrier that insulates axons and allows rapid transmission of nerve impulses [44]. When tight junctions are weak or absent, the speed of transmission of impulses is reduced [44]. Tight junctions are upregulated by vitamin D metabolites in several tissues, including colonocytes [45], keratinocytes [46] and renal cells [47], but it has not been established that tight junctions of glial cells are regulated by vitamin D. However, regulation of tight junctions is an established physiological role of vitamin D metabolites in multiple tissues. Therefore, it is likely that vitamin D upregulates tight junctions between glial cells.

Several factors influence the risk of cancer of the brain, including history of some infections [48], exposure to ionizing radiation [49] and genetic predisposition [50]. However, a subset of tumors that may be due to vitamin D inadequacy might be explained, in part, by a multiphase process that may begin with loss of intercellular adherence and contact inhibition of glial cell proliferation [4], potentially resulting from vitamin D inadequacy. Weakening of tight junctions and loss of contact inhibition is the first of several proposed phases in evolution within a tissue compartment to early precursors of cancer [4, 51].

Contact inhibition is a well-established anticancer mechanism that arrests mitosis when cells in a tissue compartment (or tissue culture) reach high density [52]. In the absence of contact inhibition, which occurs due to

many reasons including vitamin D inadequacy, inappropriate proliferation may occur and is a first step toward a population of cells that may be regarded as potential cancer precursors [4].

In this analysis, per capita energy from fish consumption was significantly inversely associated with incidence rates in men. It is unclear what role, if any, fish consumption plays in preventing brain cancer. However, previous research has identified a beneficial effect of fish consumption on age-related cognitive decline [21]. On the other hand, some types of fish and fish oil are sources of vitamin D. Although some evidence exists that implicates parental drinking in increasing the risk of childhood brain cancer [22, 23], per capita alcohol consumption was not related to incidence rates of brain cancer in this study.

We also found that consumption of energy from animal sources was significantly associated with higher risk of brain cancers in men but not in women. High intake of energy from animal sources, primarily red meat, may increase the risk for several other cancers by raising the levels of IGF-I [18–20]. However, it is unclear what role IGF-I may play in the etiology of brain cancer and how that relationship may be modified by sex. This should be explored further in future observational studies of individuals. It is also possible that consumption of energy from animal sources is primarily a marker for socioeconomic status, despite the inclusion of per capita health expenditure in the multivariable model.

Per capita health expenditure was not positively associated with brain cancer incidence rates in either sex. As stated before, this variable was included in the analysis in order to account for international differences in quality of health care and the ability to detect cancers, which may be correlated with latitude, since countries at higher latitudes tend to be wealthier than countries at lower latitudes. However, it is possible that the effect of per capita health expenditure in this model may have been weakened by the inclusion of intake of energy with animal protein, which is also related to socioeconomic status. Nevertheless, UVB irradiance was significantly inversely associated with brain cancer risk despite the inclusion of these variables.

The high incidence of brain cancer in Macedonia, Croatia and Greece remains unexplained. However, it seems possible that the traditional agrarian practices in those countries, combined with a high ovine population, might account for some of the excess [53, 54]. Since rural areas of these countries use traditional methods for raising, maintaining and slaughtering livestock, there is inevitable contact of members of the population with sheep and lambs, in which *Toxoplasma gondii* infection is very widely endemic in the region.

Schuman et al. demonstrated that patients with brain cancer (especially gliomas, the most common type) were substantially more likely to have antibodies in the serum to *T. gondii* [48]. A later study confirmed the association, although it reported that the effect was confined to meningiomas [55]. A large observational study found that sheep handlers had an odds ratio of 2.7 (95% confidence interval = 1.4–5.3) for brain cancer [56].

Other possibilities may include the presence of health care systems especially well suited to detecting cases of brain cancer, use of industrial pesticides that are banned in the USA, but may still be used in the Balkans, or employment in regional chemical and refining industries. More research would be worthwhile to determine the reasons for the high incidence rates in these countries, compared to most other countries at similar latitudes.

*Strengths*

This study had several strengths. No other studies have analyzed incidence rates by latitude and UVB irradiance in a large number of countries located at widely different latitudes, to our knowledge. It accounts for several potential risk factors using multiple linear regressions. The regression model accounted for 74% of the variation in age-standardized incidence rates of brain cancer in men and 63% in women. The independent inverse association of UVB irradiance with incidence rates of brain cancer persisted after controlling for these factors.

The percentage of variation in incidence rates of cancer of the brain among countries that was accounted for by the regression model that included UVB irradiance and covariates was similar to that of cancers for which a role of vitamin D has been reported in observational studies of individuals, including those of the breast ($R^2$ for the model = 0.55, $p < 0.0001$) [57], colon ($R^2 = 0.68$, $p < 0.0001$) [57] and ovary ($R^2 = 0.60$, $p < 0.0001$) [58].

*Limitations*

A major limitation of this study is the lack of distinction between types of brain and nervous system tumors. The 2 most common types of brain cancer are gliomas and meningiomas. These tumors are vastly different from each other and should avoid being grouped together in the same category whenever possible. However, in the only source from which global incidence rates of brain cancer are publicly available, the International

Agency for Research on Cancer GLOBOCAN database, no distinction is made between the different types of brain and nervous system tumors. All diagnoses falling under ICD 10 codes C70-C72 are grouped into the same category. Therefore, it is impossible to tell for which tumors UVB and vitamin D status may be possible factors in preventing.

Another limitation was the lack of a comprehensive database with information by country on exposure to ionizing radiation or prevalence of genetic factors that increase risk. Furthermore, this study could not account for differences in culture, behaviors and diet that vary across countries and latitudes which may modify the risk of brain cancer. For example, absorption of UVB irradiance by clothing could not be measured in the present study, yet it is possible that the association of UVB with incidence rates of bladder cancer could have been influenced by the type of clothing worn. Since there was no systematic source of information available on clothing characteristics according to country, it was not possible to eliminate this possible interaction.

The data for several of the potential confounders were from 1980. This was done in order to allow for the 20- to 30-year latency period necessary for most cancers to develop after exposure [59]. Nevertheless, it is possible that significant shifts in these and other lifestyle habits that occurred over this time period as a result of economic development and globalization could have had a strong impact on the risk of brain cancer. However, there was no way to directly assess this in the current model given the data available to the investigators.

Studies such as the present one should be considered as hypothesis generating, rather than definitive. This was a study of aggregate populations rather than individual subjects. Findings that apply to aggregates may not always apply equally to individuals [60]. For example, all individuals living in areas of high UVB irradiance may not have high exposure to UVB. This can result from urbanization and industrialization. On the other hand, regional solar UVB irradiance tends to affect a broad range of individuals, and the association was present despite the possible misclassification of exposure. While nondifferential classification of exposure is possible in ecological studies, it generally obscures associations, rather than creating them [61].

Ecological studies are potentially the source of variables to be investigated using other methods. Still, the diverse geographic distribution of populations in areas with widely different levels of solar UVB irradiance provides a natural experiment on a large scale. Natural experiments can be of value in identifying potentially relevant etiological factors. For example, ecological comparisons of areas with high fluoride levels in drinking water with areas with low levels showed that higher fluorine content was associated with lower incidence of dental caries [62].

Despite their value for identifying new ideas for research, ecological studies usually cannot account for all possible confounders such as exposure to ionizing radiation by country or differences in ability to diagnose cancer of the brain. To our knowledge, no comprehensive database on exposure to ionizing radiation by country exists, and as a result this could not be included in the analysis. The covariate for per capita health care expenditures may control for international variation in diagnostic capabilities to some extent. No covariate was available besides this to control for diagnostic differences. Many of these limitations could be addressed by observational studies of individuals. Such studies should be performed to more definitively examine hypotheses generated from natural experiments such as the present study.

## Conclusion

Further investigation is warranted to confirm the associations observed in this study with observational trials of individuals. New research on the association of the prediagnostic serum 25(OH)D levels of individuals with their risk of brain cancer might be particularly informative.


## Acknowledgements

This research was supported by a Congressional allocation to the Penn State Cancer Institute of the Hershey Medical Center, Hershey, Pa., USA, through the Department of the Navy, Bureau of Medicine and Surgery, under work unit No. 60126 at the Naval Health Research Center (San Diego, Calif., USA). The views expressed in this report are those of the authors and do not represent an official position of the Department of the Navy, Department of Defense or the US Government.

**Appendix 1.** Mean population 25(OH)D levels from 28 published studies

| Author | Year | Journal | Location | Mean 25(OH)D, ng/ml |
|---|---|---|---|---|
| Mazess et al. | 1985 | Am J Clin Nutr | Alaska, USA | 16.6 |
| Oliveri et al. | 1990 | Medicina | Buenos Aires, Argentina | 19.0 |
| Xue et al. | 1991 | Zhonghua Yu | Beijing, China | 17.7 |
| Chailuikit et al. | 1996 | J Med Assoc Thai | Thailand | 67.4 |
| Chapuy et al. | 1997 | Osteoporos Int | France | 17.9 |
| Aloia al. | 1998 | J Lab Clin Med | New York, USA | 27.5 |
| Harris et al. | 1998 | Am J Clin Nutr | Boston, USA | 25.0 |
| Bettica et al. | 1999 | Osteoporos Int | Italy | 18.7 |
| Guillemant et al. | 1999 | Osteoporos Int | Paris, France | 8.6 |
| Kristal-Boneh et al. | 1999 | Eur J Epidemiol | Israel | 25.4 |
| Goswami et al. | 2000 | Am J Clin Nutr | New Delhi, India | 19.6 |
| Brot et al. | 2001 | Br J Nutr | Denmark | 26.2 |
| Mishal et al. | 2001 | Osteoporos Int | Amman, Jordan | 14.4 |
| Nakamura et al. | 2001 | Nutrition | Japan | 14.1 |
| Vieth et al. | 2001 | Eur J Clin Nutr | Toronto, Canada | 24.1 |
| Looker et al. | 2002 | Bone | USA | 26.2 |
| Nesby-O'Dell et al. | 2002 | Am J Clin Nutr | USA | 32.9 |
| Rucker et al. | 2002 | CMAJ | Calgary, Canada | 23.8 |
| Tangpricha et al. | 2002 | Am J Med | USA | 29.1 |
| Fassi et al. | 2003 | Medicina | Buenos Aires, Argentina | 22.0 |
| Arya et al. | 2004 | Osteoporos Int | Lucknow, India | 12.3 |
| Hashemipour et al. | 2004 | BMC Public Health | Tehran, Iran | 8.6 |
| MacFarlane et al. | 2004 | J Steroid Biochem Mol Biol | Brussels, Belgium | 13.8 |
| Premaor et al. | 2004 | Endocrine | Porto Alegre, Brazil | 12.0 |
| Rejnmark et al. | 2004 | Calcif Tissue Int | Greenland | 12.1 |
| Tangpricha et al. | 2004 | Endocr Pract | USA | 28.3 |
| Meddeb et al. | 2005 | Osteoporos Int | Tunis, Tunisia | 22.0 |
| Rockell et al. | 2005 | J Nutr | Dunedin, New Zealand | 22.0 |

## References


1 Ferlay J, Bray F, Pisani P, Parkin D: GLOBOCAN 2002: cancer incidence, mortality and prevalence worldwide. IARC Cancerbase No 5, version 2.0. http://www-dep.iarc.fr/. (accessed 2008).

2 American Cancer Society: Cancer facts and figures. 2010. http://www.cancer.org/acs/groups/content/@nho/documents/.../acspc-024113.pdf (accessed 2010).

3 Davis FS: Epidemiology of brain tumors. Expert Rev Anticancer Ther 2007;7(suppl 12):S3–S6.

4 Garland CF, Gorham ED, Mohr SB, Garland FC: Vitamin D for cancer prevention: global perspective. Ann Epidemiol 2009;19:468–483.

5 Abbas S, Linseisen J, Slanger T, Kropp S, Mutschelknauss EJ, Flesch-Janys D, et al: Serum 25-hydroxyvitamin D and risk of postmenopausal breast cancer – results of a large case-control study. Carcinogenesis 2008;29:93–99.

6 Bertone-Johnson ER, Chen WY, Holick MF, Hollis BW, Colditz GA, Willett WC, et al: Plasma 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D and risk of breast cancer. Cancer Epidemiol Biomarkers Prev 2005;14:1991–1997.

7 Garland CF, Gorham ED, Mohr SB, Grant WB, Giovannucci EL, Lipkin M, et al: Vitamin D and prevention of breast cancer: pooled analysis. J Steroid Biochem Mol Biol 2007;103:708–711.

8 Lowe LC, Guy M, Mansi JL, Peckitt C, Bliss J, Wilson RG, et al: Plasma 25-hydroxy vitamin D concentrations, vitamin D receptor genotype and breast cancer risk in a UK Caucasian population. Eur J Cancer 2005;41:1164–1169.

9 Feskanich D, Ma J, Fuchs CS, Kirkner GJ, Hankinson SE, Hollis BW, et al: Plasma vitamin D metabolites and risk of colorectal cancer in women. Cancer Epidemiol Biomarkers Prev 2004;13:1502–1508.

10 Garland CF, Comstock GW, Garland FC, Helsing KJ, Shaw EK, Gorham ED: Serum 25-hydroxyvitamin D and colon cancer: eight-year prospective study. Lancet 1989;2:1176–1178.

11 Gorham ED, Garland CF, Garland FC, Grant WB, Mohr SB, Lipkin M, et al: Optimal vitamin D status for colorectal cancer prevention: a quantitative meta-analysis. Am J Prev Med 2007;32:210–216.

12 Tangrea J, Helzlsouer K, Pietinen P, Taylor P, Hollis B, Virtamo J, et al: Serum levels of vitamin D metabolites and the subsequent risk of colon and rectal cancer in Finnish men. Cancer Causes Control 1997;8:615–625.

13 Tworoger SS, Lee IM, Buring JE, Rosner B, Hollis BW, Hankinson SE: Plasma 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D and risk of incident ovarian cancer. Cancer Epidemiol Biomarkers Prev 2007;16:783–788.

14 Magrassi L, Butti G, Pezzotta S, Infuso L, Milanesi G: Effects of vitamin D and retinoic acid on human glioblastoma cell lines. Acta Neurochir (Wien) 1995;133:184–190.

15 Magrassi L, Adorni L, Montorfano G, Rapelli S, Butti G, Berra B, et al: Vitamin D metabolites activate the sphingomyelin pathway and induce death of glioblastoma cells. Acta Neurochir (Wien) 1998;140:707–713; discussion 13–14.

16 Harris SS, Dawson-Hughes B: Reduced sun exposure does not explain the inverse association of 25-hydroxyvitamin D with percent body fat in older adults. J Clin Endocrinol Metab 2007;92:3155–3157.
17 Hursting SD, Smith SM, Lashinger LM, Harvey AE, Perkins SN: Calories and carcinogenesis: lessons learned from 30 years of calorie restriction research. Carcinogenesis 2010;31:81–89.
18 Giovannucci E, Pollak MN, Platz EA, Willett WC, Stampfer MJ, Majeed N, et al: A prospective study of plasma insulin-like growth factor-1 and binding protein-3 and risk of colorectal neoplasia in women. Cancer Epidemiol Biomarkers Prev 2000;9:345–349.
19 Giovannucci E: Insulin, insulin-like growth factors and colon cancer: a review of the evidence. J Nutr 2001;131(suppl 11):3109S–3120S.
20 Giovannucci E: Nutrition, insulin, insulin-like growth factors and cancer. Horm Metab Res 2003;35:694–704.
21 Morris MC, Evans DA, Tangney CC, Bienias JL, Wilson RS: Fish consumption and cognitive decline with age in a large community study. Arch Neurol 2005;62:1849–1853.
22 Hu J, Mao Y, Ugnat AM: Parental cigarette smoking, hard liquor consumption and the risk of childhood brain tumors – a case-control study in northeast China. Acta Oncol 2000;39:979–984.
23 Infante-Rivard C, El-Zein M: Parental alcohol consumption and childhood cancers: a review. J Toxicol Environ Health B Crit Rev 2007;10:101–129.
24 Mohr SB, Garland CF, Gorham ED, Grant WB, Garland FC: Is ultraviolet B irradiance inversely associated with incidence rates of endometrial cancer: an ecological study of 107 countries. Prev Med 2007;45:327–331.
25 United Nations Food and Agriculture Organization: FAOSTAT Food and Agriculture database. http://www.fao.org/geonetwork/srv/en/main.search (accessed 2008).
26 National Aeronautics and Space Administration: International Satellite Cloud Climatology Project database.http://isccpgiss-nasagov/products/browsed2html (accessed 2008).
27 Frederick J, Lubin D: The budget of biologically active ultraviolet radiation in the earth-atmosphere system. J Geophys Res 1988;93:3825–3832.
28 Adams JS, Clemens TL, Parrish JA, Holick MF: Vitamin-D synthesis and metabolism after ultraviolet irradiation of normal and vitamin-D-deficient subjects. N Engl J Med 1982;306:722–725.
29 Gorham ED, Mohr SB, Garland CF, Garland FC: Vitamin D for cancer prevention and survival. Clin Rev Bone Mineral Metab 2009;7:159–175.
30 Garland C, Gorham E, Garland F: Vitamin D for cancer prevention: global perspective. Ann Epidemiol 2009;19:468–483.
31 Trump DL, Muindi J, Fakih M, Yu WD, Johnson CS: Vitamin D compounds: clinical development as cancer therapy and prevention agents. Anticancer Res 2006;26:2551–2556.
32 Johnson CS, Muindi JR, Hershberger PA, Trump DL: The antitumor efficacy of calcitriol: preclinical studies. Anticancer Res 2006;26:2543–2549.
33 Maruyama R, Aoki F, Toyota M, Sasaki Y, Akashi H, Mita H, et al: Comparative genome analysis identifies the vitamin D receptor gene as a direct target of p53-mediated transcriptional activation. Cancer Res 2006;66:4574–4583.
34 Kommagani R, Caserta TM, Kadakia MP: Identification of vitamin D receptor as a target of p63. Oncogene 2006;25:3745–3751.
35 Gascon-Barre M, Huet PM: Apparent [3H]1,25-dihydroxyvitamin D3 uptake by canine and rodent brain. Am J Physiol 1983;244:E266–E271.
36 Kratz A, Lewandrowski KB: Case records of the Massachusetts General Hospital: weekly clinicopathological exercises: normal reference laboratory values. N Engl J Med 1998;339:1063–1072.
37 Sarkar C, Jain A, Suri V: Current concepts in the pathology and genetics of gliomas. Indian J Cancer 2009;46:108–119.
38 Jacques TS, Swales A, Brzozowski MJ, Henriquez NV, Linehan JM, Mirzadeh Z, et al: Combinations of genetic mutations in the adult neural stem cell compartment determine brain tumour phenotypes. EMBO J 2010;29:222–235.
39 Kelly JJ, Stechishin O, Chojnacki A, Lun X, Sun B, Senger DL, et al: Proliferation of human glioblastoma stem cells occurs independently of exogenous mitogens. Stem Cells 2009;27:1722–1733.
40 Denham M, Dottori M: Signals involved in neural differentiation of human embryonic stem cells. Neurosignals 2009;17:234–241.
41 Azevedo FA, Carvalho LR, Grinberg LT, Farfel JM, Ferretti RE, Leite RE, et al: Equal numbers of neuronal and nonneuronal cells make the human brain an isometrically scaled-up primate brain. J Comp Neurol 2009;513:532–541.
42 Peters A: Plasma membrane contacts in the central nervous system. J Anat 1962;96:237–248.
43 Gehrmann J, Matsumoto Y, Kreutzberg GW: Microglia: intrinsic immuneffector cell of the brain. Brain Res Brain Res Rev 1995;20:269–287.
44 Devaux J, Gow A: Tight junctions potentiate the insulative properties of small CNS myelinated axons. J Cell Biol 2008;183:909–921.
45 Kong J, Zhang Z, Musch MW, Ning G, Sun J, Hart J, et al: Novel role of the vitamin D receptor in maintaining the integrity of the intestinal mucosal barrier. Am J Physiol Gastrointest Liver Physiol 2008;294:G208–G216.
46 Gniadecki R, Gajkowska B, Hansen M: 1,25-dihydroxyvitamin D3 stimulates the assembly of adherens junctions in keratinocytes: involvement of protein kinase C. Endocrinology 1997;138:2241–2248.
47 Fujioka T, Suzuki Y, Okamoto T, Matsushita N, Hasegawa M, Omori S: Prevention of renal cell carcinoma by active vitamin D3. World J Surg 2000;24:1205–1210.
48 Schuman LM, Choi NW, Gullen WH: Relationship of central nervous system neoplasms to *Toxoplasma gondii* infection. Am J Public Health Nations Health 1967;57:848–856.
49 Prasad G, Haas-Kogan DA: Radiation-induced gliomas. Expert Rev Neurother 2009;9:1511–1517.
50 Gu J, Liu Y, Kyritsis AP, Bondy ML: Molecular epidemiology of primary brain tumors. Neurotherapeutics 2009;6:427–435.
51 Gorham ED, Garland CF, Garland FC: Vitamin D for cancer prevention; in Holick MF (ed): Vitamin D: Physiology, Molecular Biology, and Clinical Applications, ed 2. New York, Springer-Humana, 2010.
52 Seluanov A, Hine C, Azpurua J, Feigenson M, Bozzella M, Mao Z, et al: Hypersensitivity to contact inhibition provides a clue to cancer resistance of naked mole-rat. Proc Natl Acad Sci USA 2009;106:19352–19357.
53 United Nations Food and Agriculture Organization: World Census of Agriculture. http://www.fao.org/es/ESS/census/wcares/ (accessed 2008).
54 United Nations Food and Agriculture Organization: Sheep and goat husbandry in the former Yugoslav Republic of Macedonia. http://www.fao.org/regional/europe/PUB/RTS50/159.htm (accessed 2008).
55 Ryan P, Hurley SF, Johnson AM, Salzberg M, Lee MW, North JB, et al: Tumours of the brain and presence of antibodies to *Toxoplasma gondii*. Int J Epidemiol 1993;22:412–419.
56 Preston-Martin S, Lewis S, Winkelmann R, Borman B, Auld J, Pearce N: Descriptive epidemiology of primary cancer of the brain, cranial nerves, and cranial meninges in New Zealand, 1948–88. Cancer Causes Control 1993;4:529–538.
57 Mohr S, Garland C, Gorham E, Grant W, Highfill R, Garland F: Mapping vitamin D deficiency, breast cancer, and colorectal cancer. Proc ESRI Int User Conf, Redlands, 2005, p 1468.
58 Garland CF, Mohr SB, Gorham ED, Grant WB, Garland FC: Role of ultraviolet B irradiance and vitamin D in prevention of ovarian cancer. Am J Prev Med 2006;31:512–514.
59 Armenian HK: Incubation periods of cancer: old and new. J Chronic Dis 1987;40(suppl 2):9S–15S.
60 Robinson WS: Ecological correlations and the behavior of individuals. Am Sociol Rev 1950;15:351–357.
61 Szklo M, Nieto J: Epidemiology: Beyond the Basics. Gaithersburg, Aspen Publishers, 2000, pp 141–145.
62 Dean HT, Arnold FA Jr, Jay P, Knutson JW: Studies on mass control of dental caries through fluoridation of the public water supply. Public Health Rep 1950;65:1403–1408.