Ultraviolet B Irradiance and Incidence Rates of Bladder Cancer in 174 Countries

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Background: Although nearly half of bladder cancer cases are due to smoking, the cause of nearly half is unexplained.

Purpose: This study aims to determine whether an inverse association exists between ultraviolet B (UVB) irradiance and incidence rates of bladder cancer worldwide.

Methods: This study used an ecologic approach. Age-adjusted incidence rates of bladder cancer from 2002 were obtained for all 174 countries in GLOBOCAN, a database of the International Agency for Research on Cancer. The relationship of latitude and estimated serum 25-hydroxyvitamin D [25(OH)D] with incidence rates was determined. The independent contributions to incidence rates of bladder cancer of UVB, per capita cigarette consumption in 1980, and per capita health expenditure for 2001 were assessed using multiple regression. The analyses were performed in July 2008.

Results: Bladder cancer incidence rates were higher in countries at higher latitudes than those nearer to the equator ($r=-0.66$, 95% CI$=-0.74$, -0.57, $p<0.01$). Ultraviolet B irradiance was independently inversely associated with incidence rates of bladder cancer after controlling for per capita cigarette consumption ($\beta=-0.28$, 95% CI$=-0.51$, -0.05; R^2 for model$=0.38$, $p<0.0001$). Further, UVB irradiance was also inversely associated with incidence rates after controlling for per capita health expenditure ($\beta=-0.23$, 95% CI$=-0.36$, -0.01; R^2 for model$=0.49$, $p<0.0001$) in a separate regression model.

Conclusions: Further investigation is needed to confirm the associations identified in this study using observational studies of individuals. The focus of this research should include the association of serum 25(OH)D levels with risk of bladder cancer.
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Objective

Approximately 40% of bladder cancer cases are attributable to cigarette smoking.[1] Smoking cigarettes has an estimated relative risk of bladder cancer ranging from 2 to 6, depending on the overall duration of smoking and the number of cigarettes usually smoked per day.[2]

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Occupational exposures may account for 5%–25% of cases, leaving 35%–55% unexplained.[3] Approximately 357,000 cases and 145,000 deaths from bladder cancer occur globally each year,[4] including 69,000 cases and 14,000 deaths from the disease in the U.S. in 2008,[5] where it is the fifth most common cancer.

There are several established risk factors for bladder cancer. For example, individuals in occupations involving exposure to aniline dyes, aromatic amines, rubber, or cable manufacturing have an increased risk of bladder cancer, mainly from exposure to chemical carcinogens commonly encountered in those industries, including β-naphthylamine and polycyclic aromatic hydrocarbons.[3]

A study by Grant[6] of bladder cancer death rates by state in the U.S. was the first, to our knowledge, to identify an inverse association between ultraviolet B (UVB) irradiance and bladder cancer mortality rates. Death rates in the U.S. from several other types of cancer are inversely associated with UVB irradiance, including colorectal, breast, and ovarian cancers.[6–8] Other studies have found that individuals having lower prediagnostic serum 25-hydroxyvitamin D [25(OH)D] levels had substantially higher incidence rates of several cancers, including those of the breast,[9–12] colon,[13–16] and ovary.[17]

Solar photosynthesis in the skin is the source of 95% of circulating vitamin D and its metabolites.[18] Residence in regions with high levels of UVB irradiance is associated with greater duration of the period of cutaneous photosynthesis of vitamin D[19–21] and higher serum 25(OH)D levels.[20–22] Serum 25(OH)D levels decrease by 3 ng/mL for every 10 degrees of latitude from the equator.[23]

An inverse association between UVB irradiance and age-standardized incidence rates of bladder cancer has not, to our knowledge, been previously reported. This analysis examines the relationship between solar UVB irradiance, the principal source of serum 25(OH)D, and risk of bladder cancer in 111 countries. Despite a search for risk factors other than smoking and occupation,[24,25] the cause of most bladder cancer cases remains unexplained. This study raises the possibility that UVB exposure, and perhaps higher serum 25(OH)D levels, may be related to a lower risk of bladder cancer.

Methods

Data Sources

A data set was created that contained information for each country available in GLOBOCAN on age-standardized incidence rates of bladder cancer, latitude of the population centroid, UVB irradiance adjusted for cloudiness, modeled 25(OH)D, per capita health expenditure, and per capita cigarette consumption. The most-recent age-standardized incidence rates of bladder cancer were obtained from the International Agency for Research on Cancer GLOBOCAN database, which is for the year 2002.[4] The incidence rates were standardized using the direct method to the 2000 world standard population.

The total noon solar UVB irradiance at the top of the atmosphere during the month of the winter solstice (December in the northern hemisphere and June in the southern) was calculated for each country, using a standard computational algorithm.[26] Specifically, the solar irradiance on the date of the winter solstice was calculated using the standard formulas $A' = A \times \cos(x + 23.5 \text{ degrees})$ for countries in the northern hemisphere and $A' = A \times \cos(x - 23.5 \text{ degrees})$ in the southern hemisphere, where x = latitude of the population centroid of the country in degrees; A = total solar radiation at the equator in Watt (W)/meter $(m)^2$ (specifically, the solar constant, 1366 W/m^2); and A' = total solar irradiance in W/m^2 for the particular country on the date of the winter solstice.[26] Because UVB irradiance is approximately 0.4% of total solar irradiance,[26] total solar irradiance was multiplied by 0.004 to obtain estimated UVB irradiance at the top of the atmosphere. Then, UVB irradiance was corrected for percentage cloud cover using the following formula: UVB irradiance $\times$ (1 – percentage cloud cover). Cloud-cover data were obtained from the NASA International Cloud Climatology Project (ISCCP) satellite for the month of the winter solstice in each hemisphere.[27] Latitude was determined for the population centroid of each country, the point around which the population is equal in all directions. Population centroids were calculated by the Columbia University Center for International Earth Science Information Network.[28]

Data on per capita cigarette consumption for 1980 were obtained from the WHO.[29] Data from the year 1980 were chosen because this year would have been the median year of exposure of the patients to smoking, assuming an incubation period of 20 years.[30] Per capita health expenditures in U.S. dollars for each country were provided by the WHO for 2001.[31] Complete data on all variables described were available for 111 countries and were used in the regression analyses.

Statistical Analysis

This study used an ecologic approach. Age-standardized incidence rates for 174 countries were obtained from GLOBOCAN[4] and plotted by the latitude of the population centroid. The best fit to the data points was obtained using a polynomial trend line. Multiple linear regression was used to examine the associations of winter UVB irradiance adjusted for cloud cover with age-standardized incidence rates, while controlling for per capita health expenditure.

Because of the high collinearity between per capita cigarette consumption and per capita health expenditure, two separate regression models were used. The first model analyzed the relationship between UVB irradiance and incidence rates of bladder cancer while controlling for per capita cigarette consumption. The second model examined the relationship between UVB irradiance and incidence rates of bladder cancer while controlling for per capita health expenditures. Standardized regression (β) coefficients were calculated, with 95% CIs. The analyses were performed in July 2008 using SAS, version 9.1, and JMP, version 5.1.2.

Results

Incidence rates of bladder cancer were substantially higher at higher latitudes ($r = -0.66$, 95% CI $= -0.74$, -0.57, $p < 0.01$; Figure 1). In the first regression model, UVB irradiance adjusted for cloudiness ($\beta = -0.28$, 95% CI $= -0.51$, -0.05, $p = 0.02$) was independently inversely associated with incidence rates. Per capita cigarette consumption was positively associated (β=0.44, 95% CI=0.25, 0.63, p=0.0002); the coefficient of determination, R^2, for the model was 0.38, p<0.0001 (Table 1). In the second regres sion model, UVB irradiance adjusted for cloudiness (β=−0.23, 95% CI=−0.36, −0.10) also was independently inversely associated with incidence. Per capita health expenditure (β=0.54, 95% CI=0.41, 0.67) was positively associated with incidence rates; the coefficient of determination, R^2, for the model that included per capita health expenditures was 0.49, p<0.0001 (Table 2).

Discussion

Smoking is the principal established cause of bladder cancer,[1] and per capita cigarette consumption was the variable most strongly associated with bladder cancer incidence rates in this study. Incidence rates were higher in countries located at latitudes distant from the equator, where the level of UVB irradiance is low, than in countries closer to the equator, where it is high. Further, UVB irradiance was independently inversely associated with incidence rates, even after controlling for smoking or per capita health expenditures (Tables 1 and 2). Ultraviolet B irradiance varies inversely with latitude and is the principal source of circulating 25(OH)D,[18] almost all of which is a result of solar photosynthesis. In addition, 25(OH)D has been shown to be inversely associated with cancers of the breast,[9–12] colon,[13–16] and ovary.[17] Although 45%–65% of bladder cancers can be at-

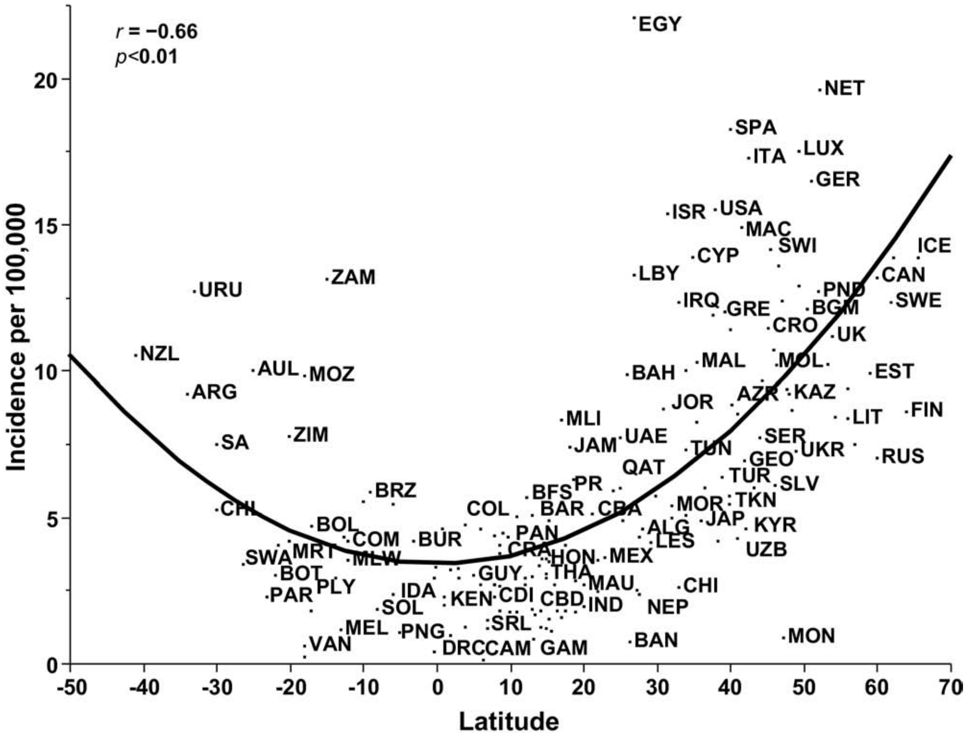

Figure 1. Age-adjusted incidence rates of bladder cancer per 100,000 population
Source: Data from GLOBOCAN (3)
ALG, Algeria; ARG, Argentina; AUL, Australia; AZR, Azerbaijan; BAN, Bangladesh; BFS, Burkina Faso; BGM, Belgium; BOL, Bolivia; BOT, Botswana; BRZ, Brazil; BUR, Burundi; CAM, Cameroon; CAN, Canada; CBA, Cuba; CBD, Cambodia; CDI, Cote d'Ivoire; CHI, China; CHL, Chile; COL, Colombia; COM, Comoros; CRA, Costa Rica; CRO, Croatia; CYP, Cyprus; DRC, Congo; EGY, Egypt; EST, Estonia; FIN, Finland; FRA, France; GAM, Gambia; GEO, Georgia; GER, Germany; GIB, Guinea-Bissau; GRE, Greece; GUY, Guyana; HON, Honduras; ICE, Iceland; IDA, Indonesia; IND, India; IRQ, Iraq; ISR, Israel; ITA, Italy; JAM, Jamaica; JAP, Japan; JOR, Jordan; KAZ, Kazakhstan; KEN, Kenya; KYR, Kyrgyzstan; LBY, Libya; LES, Lesotho; LIB, Liberia; LIT, Lithuania; LUX, Luxembourg; MAC, Macedonia; MAL, Malta; MAU, Mauritania; MEL, Melanesia; MEX, Mexico; MLI, Mali; MLW, Malawi; MOL, Moldova; MON, Mongolia; MOR, Morocco; MOZ, Mozambique; MRT, Mauritius; NEP, Nepal; NET, Netherlands; NZL, New Zealand; PAN, Panama; PAR, Paraguay; PLY, Polynesia; PND, Poland; PNG, Papua New Guinea; PR, Puerto Rico; QAT, Qatar; RUS, Russian Federation; SAF, South African Republic; SER, Serbia and Montenegro; SLV, Slovenia; SOL, Solomon Islands; SPA, Spain; SRL, Sri Lanka; SWA, Swaziland; SWE, Sweden; SWI, Switzerland; SYR, Syria; THA, Thailand; TKN, Turkmenistan; TUN, Tunisia; TUR, Turkey; UAE, United Arab Emirates; UK, United Kingdom; UKR, Ukraine; URU, Uruguay; USA, United States; UZB, Uzbekistan; VIE, Viet Nam; ZAM, Zambia; ZIM, Zimbabwe
Points shown, but not labeled: Afghanistan, Albania, Angola, Armenia, Austria, Bahrain, Barbados, Belarus, Benin, Bahamas, Bhutan, Belize, Bosnia Herzegovina, Brunei, Bulgaria, Central African Republic, Cape Verde, Congo Brazzaville, Chad, Czech Republic, Denmark, Djibouti, Dominican Republic, Ecuador, El Salvador, Equatorial Guinea, Eritrea, Ethiopia, Fiji, Gabon, Ghana, Guatemala, Guam, Guinea, Haiti, Hungary, Ireland, Iran, Kuwait, Laos, Latvia, Lebanon, Micronesia, Malaysia, Myanmar, Namibia, Nigeria, Nicaragua, Niger, Korea Democratic Republic, Norway, Oman, Pakistan, Peru, Philippines, Portugal, Romania, Rwanda, Samoa, Saudi Arabia, Senegal, Singapore, Korea, Republic of, Slovakia, Sierra Leone, Somalia, Sudan, Suriname, Tajikistan, Tanzania, Togo, Trinidad and Tobago, Uganda, Vanuatu, Venezuela, Yemen

Table 1. Ultraviolet B irradiance in association with bladder cancer incidence rates, controlling for cigarette consumption (111 countries, 2002)

Variable	Regression coefficient	SE	Standardized coefficient (β)	SE	*t*	*p*-value
Ultraviolet B irradiance[a]	−0.3320	0.1352	−0.2834	0.1154	−2.45	0.02
Per capita cigarette consumption[b]	0.0019	0.0005	0.4434	0.1141	3.89	0.0002
Intercept	6.5176	1.8606	0.0653	0.0819	3.51	0.0007

Note: R^2=0.38, $p<0.0001$
Source: GLOBOCAN[2]
[a]Adjusted for cloudiness
[b]Source: WHO[29,31]

tributed to smoking and occupational exposures,[1,3] it is possible that differences in vitamin D status may account for some of the remaining unexplained 35%–55%. Further, cigarette smoking may have an adverse effect on vitamin D metabolism.[32] Benzo[*a*]pyrene (BaP), a polycyclic aromatic hydrocarbon produced by cigarette combustion, stimulates catabolism of 1,25$(OH)_2$D, the most biologically active vitamin D metabolite.[33]

Per capita health expenditure was positively associated with bladder cancer incidence rates in the second regression model. This variable was included in the analysis in order to account for international differences in the ability to detect cancers. This may be correlated with latitude, because countries at higher latitudes tend to be wealthier than countries at lower latitudes.[34] However, UVB irradiance adjusted for cloudiness was still significantly inversely associated with bladder cancer incidence despite inclusion of this variable.

Several countries had very high incidence rates despite receiving relatively high levels of solar UVB irradiance, most notably Egypt, Mozambique, and Zambia. Although it receives abundant sunlight and UVB irradiance, Egypt has the highest incidence of bladder cancer in the world (Figure 1).[4] However, *Schistosoma hematobium* is highly prevalent in Egypt,[35] and chronic infection with it has been shown to substantially increase risk of bladder cancer.[36] Egypt also has a high prevalence of smoking,[37] which may further contribute to the high incidence of bladder cancer there. Mozambique and Zambia also have high endemic burdens of chronic infection with *S. hematobium*.[38,39]

The rates in New Zealand, Australia, Uruguay, and Argentina, all in the southern hemisphere, may be higher than expected for their latitudes, in part, because of the greater distance of the earth from the sun in the Austral (southern hemisphere) winter than in the Boreal (northern hemisphere) winter. The orbit of the earth around the sun is mildly elliptic, and solar irradiance is approximately 7% lower during winter in the southern compared to winter in the northern hemisphere.[40]

A factor that might contribute to higher bladder cancer risk in Uruguay is consumption of yerba mate tea, a popular beverage in Uruguay; a case–control study[41] reported that consumption of mate tea was associated with a twofold excess risk. However, consumption of mate tea is also positively associated with cigarette smoking.[41] Considering that cigarette smoking was positively associated with risk of bladder cancer in the present study and previous research,[1] the association between mate tea consumption and bladder cancer could be due to confounding by smoking. The extremely high incidence rates of bladder cancer in a few European countries may be due in part to the extremely high prevalence of cigarette smoking in those countries in the decades following World War II. For example, it has been reported from surveys[42,43] that 90% of the adult population of the Netherlands smoked cigarettes in 1950.

Strengths

This study was the first, to our knowledge, to analyze incidence rates for countries at widely different latitudes. The proportion of international variation that could be accounted for by latitude, or the coefficient of determination, was 43% ($p<0.01$). This is substantial, although slightly lower than the proportions previously observed for

Table 2. Ultraviolet B irradiance in association with bladder cancer incidence rates, controlling for per capita health expenditure (111 countries, 2002)

Variable	Regression coefficient	SE	Standardized coefficient (β)	SE	*t*	*p*-value
Ultraviolet B irradiance[a]	−0.2695	0.0779	−0.2311	0.0665	−3.46	0.0007
Per capita health expenditure[b]	0.0029	0.0004	0.5419	0.0671	8.11	<0.0001
Intercept	6.9538	0.8897	0.0121	0.0554	7.82	<0.0001

Note: R^2=0.49, $p<0.0001$
Source: GLOBOCAN[2]
[a]Adjusted for cloudiness
[b]Source: WHO[29,31]

cancer of the breast (R^2=0.55, p<0.0001);[44] ovary (R^2=0.49 p<0.0001);[45] and colon (R^2=0.61, p<0.0001).[46] These cancers are now known to be associated with lower levels of serum 25(OH)D in individuals.[12,17,47] Another strength of this study is that the analysis provided a quantitative assessment of the independent association of UVB irradiance with age-standardized incidence rates, while controlling for per capita cigarette smoking, the main established risk factor for bladder cancer.[1]

Limitations

This was a study of aggregate populations rather than individual subjects. Findings that apply to aggregates may not always apply to individuals. Random misclassification in studies of aggregate measures usually makes it more difficult to detect real associations, making measures of association seem closer to the null than they are. In extreme cases, theoretic examples may produce bias away from the null.[48–52] The possibility that characteristics that apply to a group may not apply to the individuals in it should be considered when evaluating this or any analysis based on groups.

There are several other potential sources of bias that should be evaluated when considering results of ecologic studies.[48–52] For example, it is possible that the association of UVB irradiance with incidence of bladder cancer is confounded by other factors, such as differences among countries regarding both the presence of certain industries and tobacco use.

The possibility of confounding was investigated by performing multiple regression analyses using a model that included the possible confounders on which data were available (i.e., a proxy index of cigarette smoking and per capita health expenditure). Multiple regression was used to control for the independent contributions of each covariate. Because data were not available by country on exposure to aromatic amines, dyes, rubber, or cable manufacture, these factors could not be used as covariates. A further limitation is that the proxy variable for smoking, per capita cigarette consumption, did not take into account differences in inhalation, percentage of each cigarette that is smoked, or other potential confounders that may vary according to country.

Because of incomplete data on per capita cigarette consumption, 63 of the 174 countries reporting to GLOBOCAN had to be excluded from the analysis. The excluded countries tended to have a lower per capita health expenditure than the countries included in the analysis. Countries with a higher per capita health expenditure probably have better diagnostic capabilities that would increase the ability to detect the effect of UVB on risk of bladder cancer. If countries with lower diagnostic capability were included, it may have been more difficult to detect an effect of UVB irradiance, as a result of misclassification error. These factors may have created a bias in favor of detection of the association. Therefore, it is possible that better diagnostic capability in countries located at latitudes distant from the equator may have accounted for some of the association.

Limitations on the measurements have been described for GLOBOCAN incidence rates,[4] WHO cigarette consumption,[29] and WHO per capita health expenditures.[31] The limitations of the ISCCP data on cloud cover have been previously described[27] in considerable detail. Although each data source has various limitations that are described, these are the best available data sources for the covariates.

Further, this study could not account for differences in culture, behavior, and diet across countries and latitudes, which may modify the risk of bladder 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 types of clothing worn in different areas. Because there was no systematic source of information available on clothing characteristics according to country, it was not possible to eliminate this possible interaction.

Ecologic studies should be considered to be hypothesis-generating, rather than definitive. They may indicate the variables that should be investigated in observational studies. On the other hand, the diverse geographic distribution of populations in areas with different levels of UVB irradiance provides a natural experiment on a large scale. Natural experiments may be of value in identifying previously unrecognized environmental factors for a disease. For example, ecologic comparisons of areas with high fluoride levels in drinking water to areas with low fluoride levels showed that higher concentrations of fluoride were associated with lower incidence rates of dental caries.[53] Factors identified in ecologic studies can be further examined in observational studies.

In this analysis, UVB irradiance, the principal source of circulating 25(OH)D,[18] was associated with incidence rates of bladder cancer worldwide. Further epidemiologic studies of the effect of serum 25(OH)D levels on bladder cancer risk in individuals would be worthwhile. If vitamin D deficiency is a risk factor for bladder cancer, which this study suggests is a possibility, the deficiency could be addressed with simple measures, such as vitamin D_3 supplementation.

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