Report

What is the relationship between UV B and global incidence rates of colorectal cancer?

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Abstract:
The purpose of this study is to examine the relationship between UV B and global incidence of colorectal cancer, while controlling for relevant covariates. Linear regression was used to assess the relationship between latitude and incidence rates of colon cancer in 173 countries. Multiple linear regression was employed to investigate the relationship between UVB dose and colorectal cancer rates while controlling for per capita intake of energy from animal sources, per capita health expenditure, pigmentation, and life expectancy. Data on all variables were available for 139 countries. Incidence of colon cancer was highest in countries distant from the equator (R^2 = 0.50, p < 0.0001). UV B dose (p < 0.0001) was independently, inversely associated with incidence rates of colorectal cancer after controlling for intake of energy from animal sources, per capita health expenditure, pigmentation, and life expectancy (R^2 for overall model = 0.76, p < 0.0001). Consistent with previous research, UVB was inversely associated with incidence of colon cancer. Further research on vitamin D and prevention of colon cancer in individuals should be conducted, including studies of higher serum 25-hydroxyvitamin D concentrations than have been studied to date.

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Full Text

Introduction

Colorectal cancer accounts for approximately 1,234,000 cancer cases each year and causes approximately 608,000 deaths each year[1] making it the fourth most common cause of cancer death.[1] In the United States, there are expected to be 103,000 cases and 50,000 deaths from colon and rectal cancer in 2011.[2] About 37,000 of these deaths are thought to have occurred in patients with an original diagnosis of colon cancer. There are several well-established risk factors for colon cancer, such as smoking,[3] drinking,[4] and red meat.[5] However, these risk factors cannot account for all of the excess risk at the population level.

A wide range of studies support the hypothesis that inadequate sunlight exposure and low serum vitamin D metabolite levels may be making a substantial contribution to morbidity and mortality from this disease.[6] Colon cancer incidence and mortality rates tend to be higher in areas with low winter sunlight levels, and lower in sunny areas.[7] Evidence from epidemiological studies has been mostly supportive. Fifteen case-control studies[8] and eight prospective studies[9] of serum 25(OH)D concentration or oral vitamin D intake found significant, inverse relationships between vitamin D and colorectal cancer. A meta-analysis of 60 observational studies on dietary intake of vitamin D revealed a 6% reduction in colorectal cancer risk, although this correlation was not statistically significant.[10] However, studies of dietary intake of vitamin D, which mostly rely on information obtained from questionnaires, are subject to greater imprecision in exposure assessment than studies of serum 25(OH)D, a biomarker that incorporates vitamin D from all sources.

Exposure of the skin to UV B (UVB) rays in sunlight is the source of 80% to 95% of circulating vitamin D and its metabolites in humans, so availability and intensity of sunlight are strong correlates of serum 25-hydroxyvitamin D [25(OH)D], the principal circulating vitamin D metabolite.[11] Observational studies have shown that serum 25(OH)D concentrations are lower in populations residing at latitudes more distant from the equator, where less UVB irradiance is present.[6] Exposure to UVB and supplemental vitamin D_3 intake increase serum 25(OH)D levels in a dose-dependent manner.[12]

Once vitamin D is photosynthesized in the skin by contact with UVB radiation, it is converted in the liver to the main circulating vitamin D metabolite, 25(OH)D.[13] Some of the circulating 25(OH)D is further metabolized by the enzyme 1-α-hydroxylase into 1,25 dihydroxyvitamin D [1,25$(OH)_2$D], the most biologically active vitamin D metabolite, although this metabolite is present in the circulation in approximately 1/1000th the concentration of 25(OH)D.[13] The principal site of 1,25$(OH)_2$D synthesis is the kidney, but production of the hormone occurs in a wide range of tissue including colonic epithelial tissue,[13,14] which has vitamin D receptors that are highly sensitive to 1,25$(OH)_2$D. Moreover, 1,25$(OH)_2$D has been shown to promote differentiation and apoptosis in colon cancer cell lines.

The primary aim of this ecological study was to examine the relationship between UVB, adjusted for cloudiness, and colorectal cancer incidence on global scale, while controlling for possible confounders. This is the first study, to the authors' knowledge, to examine the associations between latitude and UVB dose with global age-standardized colorectal cancer incidence rates, while controlling for covariates.

Results

Age-standardized incidence rates of colorectal cancer were higher at latitudes distant from the equator, with a few exceptions (R^2 = 0.50, p < 0.001) (**Fig. 1**). A dose-response analysis also indicates an inverse association between modeled serum 25(OH)D and incidence rates (**Fig. 2**). In the multiple linear regression model, UVB adjusted for cloud cover was inversely associated with age-standardized colorectal cancer incidence rates (p = 0.01) (**Table 1**), after controlling for covariates. In this analysis there was a positive association between per capita animal consumption and colorectal cancer incidence rates (p = 0.0302) confirming results from previous research on risk factors for colorectal cancer (**Table 1**). The overall model was statistically significant (R^2 = 0.76, p < 0.0001) (**Table 1**).

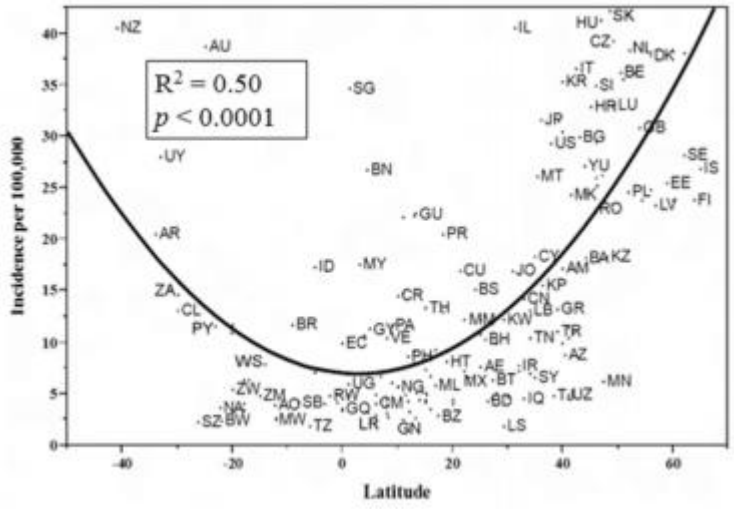

Figure 1. Annual age-adjusted incidence rates of colon cancer per 100,000 population by latitude, 173 countries, both sexes combined, 2008.

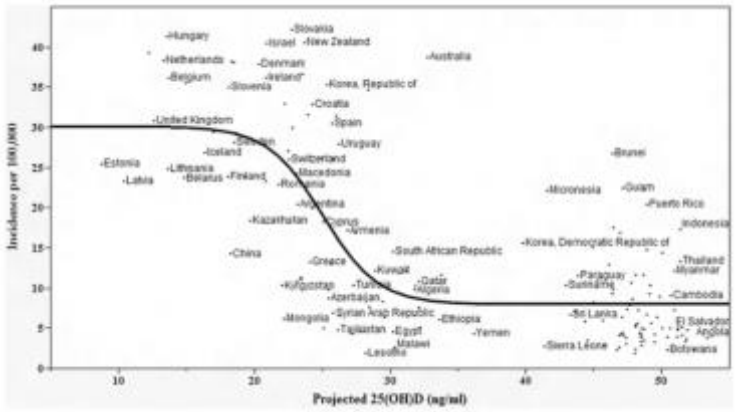

Figure 2. Dose-response relationship between modeled serum 25(OH)D and incidence rates of colon cancer per 100,000 population in 173 countries, 2008.

Table 1. **Solar UV B in association with age-adjusted incidence rates of colorectal cancer in 139 countries, controlling for covariates, 2008**

Covariate	Regression coefficient	Standard error	*t*	*p*
Solar UVB, Watts/m^2 [a]	-0.68426	0.24626	-2.78	0.0063
Intake of energy from animal sources [b]	0.00568	0.00259	2.19	0.0302
Per capita health expenditure [c]	0.00348	0.00102	3.40	0.0009
Pigmentation [d]	-2.72701	1.18248	-2.31	0.0226
Life expectancy [e]	0.05783	0.07422	0.78	0.4372
Intercept	16.67374	7.45034	2.24	0.0269

$R^2 = 0.76$; $p < 0.0001$. [a]Adjusted for cloud cover: Source: calculated using solar irradiance data from Columbia University and cloud cover from the NASA International Satellite Cloud Climatology Project (ISCCP). [b]UN Food and Agriculture Organization. [c]World Health Organization. [d]Jablonski et al.[15] [e]UN Department of Economic and Social Affairs

Discussion

To the authors' knowledge, this is the first analysis reporting the relationship between incidence rates of colorectal cancer and solar UVB dose while controlling for several covariates relevant to colorectal cancer risk. UVB varies inversely with latitude.[16] Countries located at latitudes distant from the equator, where the level of UVB is relatively low, had higher incidence rates than countries located at latitudes closer to the equator (**Fig. 1**). Colorectal cancer incidence rates may be higher than expected, given their latitudes, for Argentina, Australia, New Zealand, and Uruguay, which are all in the southern hemisphere. Part of the reason for this may be that the earth is farther from the sun in the Austral (southern hemisphere) winter than in the Boreal (northern hemisphere) winter, as Earth's orbit around the sun is mildly elliptic. This results in approximately 7% lower solar dose during winter in the southern hemisphere compared with the northern hemisphere.[17]

In a multiple linear regression model that included 139 countries, high levels of UVB were significantly, inversely associated with age-standardized incidence rates of colorectal cancer. This relationship may be due to reduced population levels of serum 25(OH)D, the principal circulating vitamin D metabolite, in countries distant from the equator, where UVB is lower.[6] In this analysis, intake of energy from animal sources was positively, significantly associated with colorectal cancer incidence, findings which are consistent with previous studies that have identified an association between colorectal cancer risk and consumption of red meat.[5] Although this covariate accounts for some of the variation in colorectal cancer incidence rates at the population level, it does not account for all the variation in risk. This suggests that another factor, possibly low vitamin D status, may account for the unexplained excess risk. Although it is possible that some of the association could be due to better surveillance in countries distant from the equator, where

incidence from colorectal cancer is highest, the inverse relationship between UVB dose and colorectal cancer incidence was independent of per capita health expenditure.

It is still not completely understood how vitamin D metabolites may prevent colorectal cancer. One possible explanation is that levels of $1,25(OH)_2D$ (the most biologically active vitamin D metabolite) present in colonic epithelial tissue may be increased by higher serum concentrations of 25(OH)D, which serves as substrate for extrarenal synthesis of $1,25(OH)_2D$. In one study of human colonic tumors, expression of the 1*a*-hydroxylase enzyme, which converts 25(OH)D into $1,25(OH)_2D$, was upregulated in cancerous tissue.[18] Although most synthesis of $1,25(OH)_2D$ occurs in the kidney and is tightly homeostatically regulated,[19] synthesis of $1,25(OH)_2D$ can occur in a wide range of tissues, including the epithelial tissues of the colon.[19] $1,25(OH)_2D$ has many anticarcinogenic properties such as promoting differentiation, inhibiting tumor cells from recruiting local vasculature[20] and inducing apoptosis of epithelial cells in tissue through the decrease of phospho-Akt and phospho-Erk, kinases responsible for the regulation of apoptosis, and through the upregulation of MEKK-1, a proapoptotic signaling molecule.[21]

A theoretical model has been proposed for the role of vitamin D deficiency in colorectal cancer risk, based on evidence from laboratory and observational studies consisting of the following steps: (1) loss of intercellular adhesion proteins due to the decoupling of epithelial cells; (2) initiation resulting from ionizing radiation, chemical carcinogens, infidelity of DNA reproduction, and, possibly, epigenetic factors; (3) natural selection of rapidly-reproducing clones within a tissue compartment; (4) overgrowth of tumor mass and basement membrane penetration; (5) metastasis to remote tissues; (6) the occurrence of an dormant state; and, finally, (7) transition to permanent dormancy, given the presence of vitamin D.[22] Recent studies have shown that the gene products of p53,[23] a human tumor suppressor oncogene, and p63,[24] the murine analog of p53, can induce vitamin D receptor synthesis, thereby controlling the effect of vitamin D on intercellular adhesion.

Strengths

There were several strengths to this study. It is the first study, to our knowledge, to analyze incidence rates of colorectal cancer by latitude and UVB dose at widely different latitudes in a large number of countries. The analysis uses multiple linear regression to account for several potential risk factors. This model accounted for 77% of the variation in age-standardized incidence rates for both sexes. Separate multiple linear regression models with the same independent variables were run for males ($R^2 = 0.72$; $p < 0.0001$) and females ($R^2 = 0.77$; $p < 0.0001$). These models account for a substantial amount of colorectal cancer incidence rates worldwide. For all models, the independent inverse association of incidence rates with UVB dose persisted after controlling for other variables. These variables, such as per capita health expenditures, pigmentation, life expectancy, and intake of energy from animal sources, were included in order to account for differences between countries on relevant factors also highly correlated with latitude. Furthermore, the proportion of global variation in incidence of colorectal cancer explained by latitude in this study is consistent with other observational studies on the relationship between UV B dose and risk of several cancers, including those of the colon ($R^2 = 0.68$; $p < 0.0001$),[25] breast (R^2 for the model = 0.55, $p < 0.0001$),[25] and ovary ($R^2 = 0.60$, $p < 0.0001$).[26]

Limitations

Although multiple regression was used to control for several confounders, complete data were available for only 139 countries. This may have potentially biased the results of the analysis if countries for which complete data were not available differed importantly from countries for which complete data were available with respect to prevalence of risk factors for colorectal cancer incidence. These exclusions were non-differential, being due to lack of data on all variables for these countries. The majority of the countries with incomplete data were economically poor countries in sub-Saharan Africa and Central Asia. Most of these countries are located close to the equator and experience high levels of UVB and low incidence rates of colorectal cancer. Therefore, under the vitamin D hypothesis, it is possible that the exclusion of these countries may have weakened an ecological association between UVB dose and colorectal cancer incidence. Also, since the excluded countries tended to have lower per capita health expenditure, a bias in favor of detecting the association may have been created.

Although they are the best available data sources, limitations have been described on the measurements for GLOBOCAN incidence rates,[1] WHO per capita health expenditures,[27] and ISCCP data on cloud cover.[28] This study could not account for all differences in diet, behavior, and culture across countries. For example, absorption of UVB by clothing could not be measured in the present study, yet it is possible that the association of UVB with incidence rates of colorectal 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 examine this possible interaction.

Findings from ecological data may not apply to individuals.[16] Ecologic studies such as the present analysis should be considered to be hypothesis-generating, rather than definitive. They may indicate variables which should be investigated in observational studies. However, studying a diverse geographic distribution of populations, as was done in this analysis, allows for a natural experiment on a very large scale. Natural experiments are valuable in that previously unrecognized environmental factors for a disease are identified.

Conclusion

In this analysis, UVB dose, the primary source of circulating 25(OH)D, was inversely associated with colorectal cancer incidence rates globally. The associations observed in this study should be further investigated in observational studies of individuals. New research on the relationship between pre-diagnostic serum 25(OH)D levels, especially at higher concentrations, and colorectal cancer risk in individuals would be especially informative.

Materials and Methods

Data Sources

A data set was created that contained information for each country on age-standardized incidence rates of colorectal cancer, latitude of the population centroid, UVB dose adjusted for cloudiness, per capita health care expenditure in international dollars, per capita energy intake from animal sources, pigmentation, and life expectancy. Data on all variables were available for 139 countries.

Age-standardized incidence rates of colorectal cancer were obtained for all countries using the International Agency for Research on Cancer (IARC) GLOBOCAN database.[1] GLOBOCAN uses national registries and registration of vital events to estimate annual age-standardized incidence rates per 100,000 population in 2008, the latest year for which complete data were available. Incidence rates were age-standardized to the world standard population, using the direct method with 5-y age intervals.

The total solar UVB irradiance at the top of the atmosphere on the winter solstice date was calculated using a standard algorithm.[29] The total noon solar irradiance at the top of the atmosphere for each country on the date of the winter solstice was calculated using the formula $A' = A * \cos(x + 23.5 \text{ degrees})$ in the northern hemisphere; and $A' = A * \cos(x - 23.5 \text{ degrees})$ in the southern hemisphere; where x = latitude of the population centroid of the country in degrees, A = total solar radiation at the equator in W/m^2 (i.e., the solar constant, 1366 W/m^2), and A' = total solar radiation in W/m^2 for the country on the date of the winter solstice.[29] Since UVB is approximately 0.4% of total solar irradiance, total solar irradiance was multiplied by 0.004 to obtain the estimated UVB irradiance at the top of the atmosphere. Latitude was determined for the population centroid of each country. Population centroids were calculated by the Columbia University Center for International Earth Science Information Network.[30]

The cloud cover estimate was based on data from the National Aeronautics and Space Administration (NASA) International Satellite Cloud Climatology Project (ISCCP) satellite[28] that provided cloud cover data for areas corresponding to the size of many countries, rather than population centroids. If there were multiple cloud cover percentages for a particular country, the percentage for the most populous region of the country was used. This differed to a minor degree from the procedure for UVB at the top of the atmosphere, which was estimated for the atmosphere above the population centroids. In order to account for the influence of cloud cover on transmission of UVB through the atmosphere, solar UVB at the top of the atmosphere was adjusted for mean cloud cover by multiplying UVB irradiance at the top of the atmosphere by the mean winter percentage of sky that was not covered by clouds for each country. UVB was adjusted for cloudiness by the following formula: UVB irradiance * (1- mean proportion of sky covered by clouds).

Data on life expectancy by country for those born in 2010 were provided by the UN Department of Economic and Social Affairs,[31] and data on pigmentation by country was available from published literature.[15] In order to control for disparities in access to and quality of healthcare among the different countries included in the analysis, data on per capita health expenditures in 2001 for each country were used in the regression model. This was expressed as the average number of international dollars spent by government on healthcare per citizen.[27] International dollars are the equivalent in purchasing power of US dollars. Per capita cigarette consumption was the mean number cigarettes smoked per person per year in 1980.[32] Including a time lag was not necessary for solar UVB irradiance at the top of the atmosphere, which does not vary appreciably over time.

Statistical Analysis

Age-standardized incidence rates for 173 countries were obtained from GLOBOCAN[1] and plotted by latitude of the population centroid. The best fit to the data points was obtained using a polynomial trend line. Multiple linear regression was employed in order to investigate the relationship between age-standardized incidence rates of colorectal cancer and UVB dose adjusted for cloudiness, per capita health care expenditure, pigmentation, and life expectancy. Data for all covariates were available for 139 of the 173 countries in the GLOBOCAN database, therefore the multiple linear regression model consisted of 139 countries. All analyses were performed using SAS Version 9.3 and JMP Version 10.0.0 (Cary NC: SAS Institute).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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