**Are low ultraviolet B and high animal protein intake associated with risk of renal cancer?**

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SHORT REPORT

Are low ultraviolet B and high animal protein intake associated with risk of renal cancer?

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ABSTRACT

Incidence rates of kidney cancer are thought to be highest in places situated at high latitudes, and in populations with high intake of energy from animal sources. This suggests that low 25-hydroxyvitamin D status, due to lower levels of UVB irradiance, and energy from animal sources might be involved in etiology. The association of latitude with age-adjusted incidence rates was determined for all 175 countries in a UN cancer database, GLOBOCAN. The independent association of UVB irradiance, cloud cover, and intake of calories from animal sources with age-adjusted incidence rates was assessed using multiple regression in 139 countries that provided dietary data. Renal cancer incidence rates were highest in countries situated at the highest latitudes in men ($R^2 = 0.64, p < 0.01$) and women ($R^2 = 0.63, p < 0.01$). According to multivariate analysis in men, UVB irradiance was inversely associated with renal cancer incidence rates ($p < 0.0003$), while cloud cover ($p < 0.003$), and intake of calories from animal sources ($p < 0.001$) were independently positively associated ($R^2$ for model = 0.73, $p < 0.0001$). In women, UVB irradiance was inversely associated with incidence rates ($p = 0.04$), while total cloud cover ($p < 0.0008$) and calories from animal sources ($p < 0.0001$) were positively associated ($R^2 = 0.68, p < 0.0001$). Lower levels of UVB irradiance and higher intakes of calories from animal sources were independently associated with higher incidence rates of kidney cancer.

Keywords: Renal neoplasms, ultraviolet irradiance, vitamin D, diet, multiple regression.
In 2002, there were 208,500 cases and 101,900 deaths from kidney cancer worldwide\(^1\) including 36,200 new cases and 12,700 deaths in the US\(^2\). The kidney is the primary site of conversion of circulating 25-hydroxyvitamin D [25(OH)D] to 1,25-dihydroxyvitamin D [1,25(OH)\(_2\)D]\(^3\) by 25-hydroxyvitamin-D-1-alpha hydroxylase\(^4\). Renal tissue also contains vitamin D receptors\(^3\). Greater photosynthesis of vitamin D, and possibly higher levels of 25(OH)D, which is the substrate for 1,25(OH)2D may be involved in the association between low levels of ultraviolet B (UVB) irradiance and higher incidence rates of renal cancer.

Solar UVB irradiance was inversely associated with age-adjusted renal cancer mortality rates in the United States\(^5\) and survival\(^6\). To our knowledge, there has been no study of the association of UVB with renal cancer on a global basis.

Previous studies reported an association between regional sunlight and lower risk of cancers of the colon\(^5,7,8\), breast\(^5,8-11\), and ovary\(^5,8,12\). All of these tissues contain vitamin D receptors\(^13,14\) and are sites of extrarenal synthesis of 1,25(OH)\(_2\)D\(^13-17\). The high degree of enzymatic conversion of 25(OH)D to 1,25(OH)\(_2\)D in the kidney provides a setting in which UVB exposure and the resulting variation in serum 25(OH)D levels could increase the local concentration of 1,25(OH)\(_2\)D, which is thought to be the most effective vitamin D metabolite in anticarcinogenesis\(^18\).
Higher levels of UVB$^{19, 20}$ and lower percentages of cloud cover$^{19, 21}$ are associated with greater cutaneous synthesis of vitamin D, the precursor of all vitamin D metabolites. For example, in mid-November at 42 degrees latitude, the window of time in which vitamin D can be synthesized is 6 times longer on a clear day than on an overcast day (1 hours/day vs. 6 hours/day, respectively)$^{21}$.

Other epidemiological studies have suggested a role of diet$^{22-29}$, particularly energy from animal sources$^{22}$. Multiple regression was used to assess the independent contributions of UVB irradiance, percentage total cloud cover, and intake of calories from animal sources with age-adjusted incidence rates of renal cancer.

**METHODS**

**Data Sources**

A file was created that contained information for 175 countries on incidence of kidney cancer, latitude, solar UVB irradiance at the top of the atmosphere at the vernal equinox, and total cloud cover as a proportion of sky covered. Dietary data were entered into the file for 139 countries.

The International Agency for Research on Cancer (IARC) GLOBOCAN database$^{30}$ was used to obtain age-adjusted incidence rates of renal cancer in 175 countries. GLOBOCAN uses national registries and registration of vital events to estimate annual
age-adjusted incidence rates per 100,000 population. The latest year for which complete data were available was 2002.

Amount of solar UVB irradiance at the top of the atmosphere, by latitude at the vernal equinox, was calculated using a standard algorithm. Irradiance was derived using the formula \( A' = A / \cos \theta \) where \( \theta \) = distance of the country in degrees from the solar noon midwinter subsolar point. This point was defined as latitude + 23.5 degrees on the date of the winter solstice in the northern hemisphere, and as latitude + 23.5 degrees on the date of the winter solstice in the southern hemisphere. \( A' \) was defined as solar radiation for the country's latitude on the date of the winter solstice, in W/m², and \( A \) was defined as solar radiation at the equator on the date of the vernal equinox. Since UVB is 0.42% of total solar irradiance, total solar irradiance at the top of the atmosphere was multiplied by 0.0042 in order to estimate the UVB irradiance.

The International Satellite Cloud Climatology Project (ISCCP) satellite instrument package was used to obtain data on total cloud cover. Total cloud cover was measured as the mean proportion of the sky covered by clouds during the week of the winter solstice in each hemisphere. Data on intake of calories from animal sources were available for 139 countries from the Food and Agriculture Organization (FAO), a branch of the United Nations (UN).
Statistical analysis

The relationship between latitude and incidence rates for all 175 countries was examined, and found to be parabolic, with a vertex (low point) near the equator. The fit of the data points to the parabolic curve was determined using a polynomial regression model (JMP, v. 5.1.2, Cary NC: SAS Institute). Latitude was determined for the capital city of each country using an international atlas.

Multiple linear regression was used to assess the relationship of solar UVB irradiance at the top of the atmosphere in Watts/m², mean cloud cover reported as a proportion of sky obscured by clouds, and intake of calories from animal sources, with age-adjusted annual incidence rates of renal cancer. Based on previous findings in the literature, one-tailed tests were used with an alpha probability of 0.05. All analyses were performed using JMP 5.1.2 (Cary NC: SAS Institute). The 175 countries with incidence and UVB data and the 139 countries for which dietary data also were available are listed in Appendix Table 1. The association between percentage of cloud cover from the ISCCP satellite and UVB irradiance at ground level measured by the United States Department of Agriculture (USDA) spectrometer network is shown in Appendix Table 2. A preliminary analysis of all dietary components available from FAO determined that intake of energy from animal sources was the principal dietary component related to incidence rates of renal cancer (Appendix Table 3).
RESULTS

Renal carcinoma incidence increased with increasing latitude in both hemispheres and both sexes ($R^2 = 0.64, p<0.01$) (Figure 1), ($R^2 = 0.63, p<0.01$) (Figure 2). According to linear regression, UVB irradiance at the top of the atmosphere was inversely associated with incidence rates of renal cancer in males ($p=0.003$). Total cloud cover ($p < 0.003$), and intake of calories from animal sources ($p < 0.0001$) were positively associated ($R^2 = 0.73, p < 0.0001$) (Table 1).

Results were similar for females. UVB irradiance at the top of the atmosphere was inversely associated with age-adjusted incidence rates ($p<0.04$), while total cloud cover ($p=0.0008$), and intake of calories from animal sources ($p < 0.001$) were statistically significantly positively associated with female renal cancer incidence rates ($R^2 = 0.68, p<0.0001$)(Table 2).

DISCUSSION

Little is known about the etiology of kidney cancer aside from increased risk from tobacco consumption $^{34}$, obesity $^{34}$, and diet $^{22-29}$. Previous epidemiological studies have described an inverse association between vitamin D or sunlight and cancer rates. Laboratory studies have shown that 1,25(OH)$_2$D, the most active vitamin D metabolite, promotes differentiation and inhibits tumor growth $^{18}$. However, little has been done to investigate the possible association of vitamin D status with risk of cancer of the kidney $^3$. 
The primary source of vitamin D is conversion of 7-dehydrocholesterol to vitamin D by solar UVB irradiance \textsuperscript{35}. Renal cancer incidence rates in males and females were highest in countries at latitudes distant from the equator where UVB irradiance is lower than in countries closer to the equator.

The regions with the highest amount of solar irradiance tended to have the lowest incidence rates, a pattern that was present for both men and women. Because the pattern is present in both sexes, it is unlikely that the international differences are due mainly to occupational exposures, which usually vary according to gender.

The geographic pattern supports the hypothesis that increased vitamin D photosynthesis could be responsible for differences in incidence rates. The association of UVB irradiance with reduced risk of renal cancer also is consistent with a previous case-control study that found that high serum levels of 1,25(OH)\textsubscript{2}D were associated with lower risk of renal cancer \textsuperscript{36}. 1,25(OH)\textsubscript{2}D maintains the functionality of intercellular (gap) junctions, and prevents destruction of the integrity of gap junctions caused by promoters, such as N-nitrosodimethylamine and N-ethyl-N-hydroxyethylnitrosamine, in tissue culture \textsuperscript{36}.

According to satellite data from the National Aeronautics and Space Administration, countries that were located far from the equator tended to be substantially cloudier than countries located nearer the equator. A sensitivity analysis of ground level UVB and cloud cover in 25 USDA ground stations confirmed that cloud cover was negatively correlated with ground level UVB at the 305 nm wavelength ($R^2 = 0.42$,}
The influence of clouds stronger than that of variations in ozone absorption, so ozone was dropped from the model. Countries at high latitudes also have higher levels of anthropogenic aerosols which absorb UVB irradiance. This may contribute to lower levels of vitamin D photosynthesis in populations living in countries with high amounts of clouds and aerosols.

Intake of energy from animal sources has been linked with mortality and survival of renal cancer. It has been hypothesized this could be due to higher serum levels of the growth hormone, insulin-like growth factor I (IGF-I), which is associated with intake of calories from animal sources. IGF-1 is a potent mitogen in the renal epithelium. Renal carcinoma cells in tissue culture cells express IGF-I receptors, and are responsive to stimulation by IGF-I in the serum. IGF-I is thought to damage intercellular adherence and contact inhibition between adjacent cells as part of stimulation of mitosis in the kidney epithelium, and to allow migration of renal epithelial cells. This action is opposite to the action of 1,25(OH)2D, which stimulates the secretion of cadherins and other compounds that foster intercellular adherence and the integrity of gap junctions.

A role for the cyclooxygenase pathway, which is involved in biosynthesis of arachadonic acid from its precursors, also has been suggested for renal cancer. Only very small quantities of arachidonic acid are present in foods, however the arachidonic acid content of meat is greater than of vegetables. For reasons that are not well understood,
increased intake of meat is associated with increased the arachidonic acid content of serum phospholipids \textsuperscript{52}.

Obesity is one of few factors that have been linked to risk of renal cancer \textsuperscript{34}. There are at least two possible mechanisms. First, obese people have lower levels of 25-hydroxyvitamin D than people of ordinary habitus \textsuperscript{53-57}. Serum vitamin D\textsubscript{3} levels 24 hours after experimental exposure to UVB showed a 57\% lower increase in obese subjects than in nonobese controls \textsuperscript{56}. Second, intake of energy from animal sources is associated with substantially greater prevalence of obesity than intake from vegetable sources \textsuperscript{58}.

This study had several strengths. The regression model was able to explain 73\% of the variation in kidney cancer rates in men and 68\% in women by assessing the independent contributions of UVB irradiance, cloud cover, and intake of calories from animal sources to incidence rates. UVB irradiance was significantly negatively correlated with incidence. This is consistent with geographic patterns observed for cancers of the colon \textsuperscript{59}, breast \textsuperscript{59}, and ovary \textsuperscript{60}. Epidemiological evidence supports the role of vitamin D in the prevention of these cancers. Intake of calories from animal sources had the strongest positive correlation with incidence rates in both sexes. This is consistent with results of previous studies \textsuperscript{22-29}.

Limitations. GLOBOCAN enabled the analysis of the relationship between ultraviolet radiation and cancer rates on a global scale, and demonstrated its unique value as a tool
for hypothesis generating-studies. However this is a study of aggregates (countries) rather than individual subjects. Findings that apply to aggregates may not apply to individuals. 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 is often likely to affect a broad range of individuals, and the finding was present despite the possible misclassification of exposure. Non-differential misclassification of exposure generally obscures associations, rather than creating them 61. Also, intake of energy from animal sources is a marker of industrialization, and therefore might be only indirectly related to incidence rates.

Studies of this type should be considered as hypothesis-generating, rather than definitive. They are potentially the source of variables to be investigated with other methods. 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 are sometimes of value in identifying relevant factors for a disease 62.

Ecological studies cannot account for all possible confounders. For example this study did not control for differences in physical activity among the populations of different countries. Still, there is no evidence supporting an association of low physical activity with renal cancer 63, and effects of these or other factors are not mutually exclusive of favorable effects of UVB and vitamin D status.
Many of these limitations could be addressed by observational studies of individuals. Of course such studies should be done to more directly examine hypotheses generated from natural experiments. Further epidemiological studies of the effect of serum 25(OH)D and oral intake of vitamin D on risk of renal cell carcinoma are needed.

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64. United Nations Food and Agriculture Organization.
FIGURE LEGENDS

Figure 1. Renal cancer incidence rates, males, by latitude, 2002. Source: Data from GLOBOCAN 1

Figure 2. Renal cancer incidence rates, females, by latitude, 2002. Source: Data from GLOBOCAN 1
Table 1. Renal cancer incidence rates according to solar UVB irradiance, total cloud cover, and calories from animal sources, males, 2002

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$R^2 = 0.73, p < 0.0001$

*Watts/m² at vernal equinox

†Mean percent of sky covered with clouds, winter solstice.

Source: International Satellite Cloud Climatology Project ³².

‡Source: Food and Agriculture Organization ⁶⁴.
Table 2. Renal cancer incidence rates according to solar UVB irradiance, total cloud cover, and calories from animal sources, females, 2002

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\[ R^2 = 0.68, \ p < 0.0001 \]

*Watts/m² at vernal equinox

†Mean percent of sky covered with clouds, winter solstice.

Source: International Satellite Cloud Climatology Project\textsuperscript{32}.

‡Source: Food and Agriculture Organization\textsuperscript{64}.
Appendix Table 1. Countries in the study, with the three-letter codes used in figures.
Countries with asterisks provided dietary data.

Figure 1. Renal cancer incidence rates, males, by latitude, 2002. Source: Data from GLOBOCAN.
Figure 2. Renal cancer incidence rates, females, by latitude, 2002. Source: Data from GLOBOCAN