International Journal of Cancer

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

| | |
|---|---|
| Journal: | *International Journal of Cancer* |
| Manuscript ID: | IJC-06-0987 |
| Wiley - Manuscript type: | Short Report |
| Date Submitted by the Author: | 11-May-2006 |
| Complete List of Authors: | Mohr, Sharif; University of California at San Diego, Family and Preventive Medicine<br>Gorham, Edward; University of California at San Diego, Family and Preventive Medicine<br>Garland, Cedric; University of California at San Diego, Family and Preventive Medicine<br>Grant, William; SUNARC<br>Garland, Frank; University of California at San Diego, Family and Preventive Medicine |
| Key Words: | Renal neoplasms, ultraviolet irradiance, vitamin D, diet, multiple regression |
| | |

10 May 2006 11:10 AM

SHORT REPORT

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

Sharif B. Mohr, M.P.H. [1], Edward D. Gorham[1], M.P.H., Ph.D. [1], Cedric F. Garland, Dr.P.H. [1], William B. Grant, PhD[2], and Frank C. Garland, Ph.D.[1]

[1]Department of Family and Preventive Medicine 0631C, University of California San Diego, La Jolla CA

[2]Sunlight, Nutrition, and Health Research Center, San Francisco CA

Running head: Ultraviolet B, animal protein and renal cancer

Length: Abstract 238 words; Text: 2,148 words; Tables: 2; Figures: 2

Corresponding author: Cedric F. Garland, Dr.P.H. Telephone (619) 553-9016; Fax (619) 524-9888

E-mail: garlandc@nhrc.navy.mil

## 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 [31]. Irradiance was derived using the formula (A' = A/cos x) where x = 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 $W/m^2$, and A was defined as solar radiation at the equator on the date of the vernal equinox [31]. 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 [32]. 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 [32]. 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 [33].



Multiple linear regression was used to assess the relationship of solar UVB irradiance at the top of the atmosphere in Watts/$m^2$, 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 $1,25(OH)_2D$, 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 [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$(OH)_2$D were associated with lower risk of renal cancer [36]. 1,25$(OH)_2$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 [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 ($R^2 = 0.42$,

$p$=0.0004)(Appendix Table 2). 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. [37-39]. 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 [40] and survival [6] 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 [41-43]. IGF-1 is a potent mitogen in the renal epithelium [44]. Renal carcinoma cells in tissue culture cells express IGF-I receptors, and are responsive to stimulation by IGF-I in the serum [44]. 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 [45, 46]. This action is opposite to the action of 1,25(OH)$_2$D, which stimulates the secretion of cadherins and other compounds that foster intercellular adherence and the integrity of gap junctions [47, 48].

A role for the cyclooxygenase pathway, which is involved in biosynthesis of arachadonic acid from its precursors, also has been suggested for renal cancer [49, 50]. Only very small quantities of arachidonic acid are present in foods, however the arachidonic acid content of meat is greater than of vegetables [51]. For reasons that are not well understood, increased intake of meat is associated with increased the arachidonic acid content of serum phospholipids [52].

Obesity is one of few factors that have been linked to risk of renal cancer [34]. There are at least two possible mechanisms. First, obese people have lower levels of 25-hydroxyvitamin D than people of ordinary habitus [53-57]. Serum vitamin $D_3$ levels 24 hours after experimental exposure to UVB showed a 57% lower increase in obese subjects than in nonobese controls [56]. Second, intake of energy from animal sources is associated with substantially greater prevalence of obesity than intake from vegetable sources [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 [59], breast [59], and ovary [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 [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.

## ACKNOWLEDGEMENTS

This research was supported by a Congressional allocation to the Hollings Cancer Center of the Medical University of South Carolina, Charleston SC, through the Department of the Navy, Bureau of Medicine and Surgery, under Work Unit No. 60126. 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 U. S. Government.

## REFERENCES

1. International Agency for Research on Cancer. GLOBOCAN 2002 Database: http://www-depdb.iarc.fr/globocan/GLOBOframe.htm. *Accessed March* 2005.

2. American Cancer Society. Cancer facts and figures, 2005. Atlanta: American Cancer Society, 2005.

3. Haussler MR, Whitfield GK, Haussler CA, Hsieh JC, Thompson PD, Selznick SH, et al. The nuclear vitamin D receptor: biological and molecular regulatory properties revealed. *J Bone Miner Res* 1998;13(3):325-49. Available from

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9525333.

4. Galante L, Colston KW, Evans IM, Byfield PG, Matthews EW, MacIntyre I. The regulation of vitamin D metabolism. *Nature* 1973;244(5416):438-40. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=4582497.

5. Grant WB. Ecologic studies of solar UV-B radiation and cancer mortality rates. *Recent Results Cancer Res* 2003;164:371-7. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12899536.

6. Grant W. The likely role of vitamin D from solar ultraviolet-B irradiance in increasing cancer survival. *Anticancer Res* 2006;26(in press).

7. Garland C, Garland F. Do sunlight and vitamin D reduce the likelihood of colon cancer? *Int J Epidemiol* 1980;9:227-31.

8. Freedman D, Dosemeci M, McGlynn K. Sunlight and mortality from breast, ovarian, colon, prostate, and non-melanoma skin cancer: a composite death certificate based case-control study. *Occup Environ Med.* 2002;59(4):257-62.

9. Gorham E, Garland C, Garland F. Acid haze air pollution and breast and colon cancer in 20 Canadian cities. *Can J Publ Health* 1989;80:96-100.

10. Garland F, Garland C, Gorham E, Young J, Jr. Geographic variation in breast cancer mortality in the United States: a hypothesis involving exposure to solar radiation. *Prev Med* 1990;19:614-22.

11. Gorham ED, Garland FC, Garland CF. Sunlight and breast cancer incidence in the USSR. *Int J Epidemiol* 1990;19(4):820-4. Available from http://www.ncbi.nlm.nih.gov/htbin-post/Entrez/query?db=m&form=6&dopt=r&uid=2084008.

12. Lefkowitz ES, Garland CF. Sunlight, vitamin D, and ovarian cancer mortality rates in US women. *Int J Epidemiol* 1994;23(6):1133-6. Available from http://www.ncbi.nlm.nih.gov/htbin-post/Entrez/query?db=m&form=6&dopt=r&uid=0007721513.

13. Cross HS, Bareis P, Hofer H, Bischof MG, Bajna E, Kriwanek S, et al. 25-Hydroxyvitamin D(3)-1alpha-hydroxylase and vitamin D receptor gene expression in human colonic mucosa is elevated during early cancerogenesis. *Steroids* 2001;66(3-5):287-92. Available from http://www.ncbi.nlm.nih.gov/htbin-post/Entrez/query?db=m&form=6&dopt=r&uid=11179736.

14. Friedrich M, Rafi L, Mitschele T, Tilgen W, Schmidt W, Reichrath J. Analysis of the vitamin D system in cervical carcinomas, breast cancer and ovarian cancer. *Recent Results Cancer Res* 2003;164:239-46. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12899526.

15. Bareis P, Bises G, Bischof MG, Cross HS, Peterlik M. 25-hydroxy-vitamin d metabolism in human colon cancer cells during tumor progression. *Biochem Biophys Res Commun* 2001;285(4):1012-7. Available from http://www.ncbi.nlm.nih.gov/htbin-post/Entrez/query?db=m&form=6&dopt=r&uid=11467853.

16. Tangpricha V, Flanagan JN, Whitlatch LW, Tseng CC, Chen TC, Holt PR, et al. 25-hydroxyvitamin D-1alpha-hydroxylase in normal and malignant colon tissue. *Lancet* 2001;357(9269):1673-4. Available from http://www.ncbi.nlm.nih.gov/htbin-post/Entrez/query?db=m&form=6&dopt=r&uid=11425375.

17. Zehnder D, Bland R, Williams MC, McNinch RW, Howie AJ, Stewart PM, et al. Extrarenal expression of 25-hydroxyvitamin d(3)-1 alpha-hydroxylase. *J Clin Endocrinol Metab* 2001;86(2):888-94. Available from http://www.ncbi.nlm.nih.gov/htbin-post/Entrez/query?db=m&form=6&dopt=r&uid=11158062 http://jcem.endojournals.org/cgi/content/full/86/2/888 http://jcem.endojournals.org/cgi/content/abstract/86/2/888.

18. Banerjee P, Chatterjee M. Antiproliferative role of vitamin D and its analogs--a brief overview. *Mol Cell Biochem* 2003;253(1-2):247-54. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14619976.

19. Webb AR, Kline L, Holick MF. Influence of season and latitude on the cutaneous synthesis of vitamin D3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D3 synthesis in human skin. *J Clin Endocrinol Metab* 1988;67(2):373-8. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=2839537.

20. Matsuoka LY, Wortsman J, Haddad JG, Hollis BW. In vivo threshold for cutaneous synthesis of vitamin D3. *J Lab Clin Med* 1989;114(3):301-5. Available from

http://www.ncbi.nlm.nih.gov/htbin-post/Entrez/query?db=m&form=6&dopt=r&uid=2549141.

21. Engelsen O, Brustad M, Aksnes L, Lund E. Daily duration of vitamin D synthesis in human skin with relation to latitude, total ozone, altitude, ground cover, aerosols and cloud thickness. *Photochem Photobiol* 2005;81(6):1287-90. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16354110.

22. Armstrong B, Doll R. Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. *Int J Cancer* 1975;15(4):617-31. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=1140864.

23. Handa K, Kreiger N. Diet patterns and the risk of renal cell carcinoma. *Public Health Nutr* 2002;5(6):757-67. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12570884.

24. Hu J, Mao Y, White K. Diet and vitamin or mineral supplements and risk of renal cell carcinoma in Canada. *Cancer Causes Control* 2003;14(8):705-14. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14674734.

25. Nicodemus KK, Sweeney C, Folsom AR. Evaluation of dietary, medical and lifestyle risk factors for incident kidney cancer in postmenopausal women. *Int J Cancer*

2004;108(1):115-21. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14618625.

26. Rashidkhani B, Lindblad P, Wolk A. Fruits, vegetables and risk of renal cell carcinoma: a prospective study of Swedish women. *Int J Cancer* 2005;113(3):451-5. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15455348.

27. Rashidkhani B, Akesson A, Lindblad P, Wolk A. Major dietary patterns and risk of renal cell carcinoma in a prospective cohort of Swedish women. *J Nutr* 2005;135(7):1757-62. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15987861.

28. van Dijk BA, Schouten LJ, Kiemeney LA, Goldbohm RA, van den Brandt PA. Relation of height, body mass, energy intake, and physical activity to risk of renal cell carcinoma: results from the Netherlands Cohort Study. *Am J Epidemiol* 2004;160(12):1159-67. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15583368.

29. van Dijk BA, Schouten LJ, Kiemeney LA, Goldbohm RA, van den Brandt PA. Vegetable and fruit consumption and risk of renal cell carcinoma: results from the Netherlands cohort study. *Int J Cancer* 2005;117(4):648-54. Available from

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15929109.

30. Ferlay J, Bray F, Pisani P, Parkin D. GLOBOCAN 2002: Cancer Incidence, Mortality and Prevalence Worldwide: IARC CancerBase No. 5. version 2.0, vol. 2006 Lyon: IARC Press, 2004.

31. Columbia University. The Earth's Radiation Budget, Part I. http://www.ldeo.columbia.edu/edu/dees/ees/climate/labs/radiation1/. *Accessed March* 2005.

32. National Aeronautics and Space Administration. International Satellite Cloud Climatology Project database: http://isccp.giss.nasa.gov/products/browsed2.html. *Accessed March* 2005.

33. Rand McNally. The International Atlas. Chicago: Andrew McNally III, 1969.

34. Dhote R, Thiounn N, Debre B, Vidal-Trecan G. Risk factors for adult renal cell carcinoma. *Urol Clin North Am* 2004;31(2):237-47. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15123404.

35. 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(12):722-5. Available from http://www.ncbi.nlm.nih.gov/htbin-post/Entrez/query?db=m&form=6&dopt=r&uid=7038486.

36. Fujioka T, Suzuki Y, Okamoto T, Mastushita N, Hasegawa M, Omori S. Prevention of renal cell carcinoma by active vitamin D3. *World J Surg*

2000;24(10):1205-10. Available from http://www.ncbi.nlm.nih.gov/htbin-post/Entrez/query?db=m&form=6&dopt=r&uid=11071463.

37. Chameides WL, Yu H, Liu SC, Bergin M, Zhou X, Mearns L, et al. Case study of the effects of atmospheric aerosols and regional haze on agriculture: an opportunity to enhance crop yields in China through emission controls? *Proc Natl Acad Sci U S A* 1999;96(24):13626-33. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10570123.

38. Novakov T, Ramanathan V, Hansen J, Kirchstetter T, Sato M, Sinton J, et al. Large historical changes of fossil-fuel black carbon aerosols. *Geophys Res Lett* 2003;30(6):1324.

39. Chung C, Ramanathan V, Kim D, Podgomy I. Global anthropogenic aerosol direct forcing derived from satellite and ground-based observations. *J Geophys Res* 2005;110(D24207):1-17.

40. Grant W, Garland C. The association of solar ultraviolet B with reducing risk of cancer: multifactorial ecological analysis of geographic variation in age-adjusted cancer mortality rates. *Anticancer Res (in press)* 2006.

41. Allen NE, Appleby PN, Davey GK, Kaaks R, Rinaldi S, Key TJ. The associations of diet with serum insulin-like growth factor I and its main binding proteins in 292 women meat-eaters, vegetarians, and vegans. *Cancer Epidemiol Biomarkers Prev* 2002;11(11):1441-8. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12433724.

42. Voskuil DW, Vrieling A, van't Veer LJ, Kampman E, Rookus MA. The insulin-like growth factor system in cancer prevention: potential of dietary intervention strategies. *Cancer Epidemiol Biomarkers Prev* 2005;14(1):195-203. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16041870.

43. 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(4):345-9. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10794477.

44. Cheung CW, Vesey DA, Nicol DL, Johnson DW. The roles of IGF-I and IGFBP-3 in the regulation of proximal tubule, and renal cell carcinoma cell proliferation. *Kidney Int* 2004;65(4):1272-9. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15086466.

45. Weston CE, Feibelman MB, Wu K, Simon EE. Effects of EGF and IGF-1 on proliferation of cultured human proximal tubule cells after oxidant stress. *Ren Fail* 2004;26(1):13-20. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15083916.

46. Zhang X, Lin M, van Golen KL, Yoshioka K, Itoh K, Yee D. Multiple signaling pathways are activated during insulin-like growth factor-I (IGF-I) stimulated

breast cancer cell migration. *Breast Cancer Res Treat* 2005;93(2):159-68. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16187236.

47. Palmer HG, Gonzalez-Sancho JM, Espada J, Berciano MT, Puig I, Baulida J, et al. Vitamin D(3) promotes the differentiation of colon carcinoma cells by the induction of E-cadherin and the inhibition of beta-catenin signaling. *J Cell Biol* 2001;154(2):369-87. Available from http://www.ncbi.nlm.nih.gov/htbin-post/Entrez/query?db=m&form=6&dopt=r&uid=11470825.

48. 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(6):2241-8. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9165007.

49. Miyata Y, Koga S, Kanda S, Nishikido M, Hayashi T, Kanetake H. Expression of cyclooxygenase-2 in renal cell carcinoma: correlation with tumor cell proliferation, apoptosis, angiogenesis, expression of matrix metalloproteinase-2, and survival. *Clin Cancer Res* 2003;9(5):1741-9. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12738729.

50. Tuna B, Yorukoglu K, Gurel D, Mungan U, Kirkali Z. Significance of COX-2 expression in human renal cell carcinoma. *Urology* 2004;64(6):1116-20. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15596182.

51. Taber L, Chiu CH, Whelan J. Assessment of the arachidonic acid content in foods commonly consumed in the American diet. *Lipids* 1998;33(12):1151-7. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9930399.

52. Anderson RA, Jr., Oswald C, Willis BR, Zaneveld LJ. Relationship between semen characteristics and fertility in electroejaculated mice. *J Reprod Fertil* 1983;68(1):1-7. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=6842442.

53. Compston JE, Vedi S, Ledger JE, Webb A, Gazet JC, Pilkington TR. Vitamin D status and bone histomorphometry in gross obesity. *Am J Clin Nutr* 1981;34(11):2359-63. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7304477.

54. Buffington C, Walker B, Cowan GS, Jr., Scruggs D. Vitamin D Deficiency in the Morbidly Obese. *Obes Surg* 1993;3(4):421-24. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10757956.

55. Liel Y, Ulmer E, Shary J, Hollis BW, Bell NH. Low circulating vitamin D in obesity. *Calcif Tissue Int* 1988;43(4):199-201. Available from http://www.ncbi.nlm.nih.gov/htbin-post/Entrez/query?db=m&form=6&dopt=r&uid=3145124.

56. Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. *Am J Clin Nutr* 2000;72(3):690-3. Available from http://www.ncbi.nlm.nih.gov/htbin-post/Entrez/query?db=m&form=6&dopt=r&uid=10966885.

57. Snijder MB, van Dam RM, Visser M, Deeg DJ, Dekker JM, Bouter LM, et al. Adiposity in relation to vitamin D status and parathyroid hormone levels: a population-based study in older men and women. *J Clin Endocrinol Metab* 2005;90(7):4119-23. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15855256.

58. Newby PK, Tucker KL, Wolk A. Risk of overweight and obesity among semivegetarian, lactovegetarian, and vegan women. *Am J Clin Nutr* 2005;81(6):1267-74. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15941875.

59. Mohr S, Garland C, Gorham E, Grant W, Highfill R, Garland F. Mapping vitamin D deficiency, breast cancer, and colorectal cancer. *Proceedings of the ESRI International User Conference 2005* 2005:1468 (in press).

60. Garland C, Mohr S, Gorham E, Grant W, Garland F. Ultraviolet B irradiance, vitamin D status, and incidence of ovarian cancer in 175 countries. *(In preparation)* 2005.

61. Szklo M, Nieto J. Epidemiology: Beyond the Basics. Gaithersburg, MD: Aspen Publishers, Inc., 2000.

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(43):1403-8. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14781280.

63. Dhote R, Pellicer-Coeuret M, Thiounn N, Debre B, Vidal-Trecan G. Risk factors for adult renal cell carcinoma: a systematic review and implications for prevention. *BJU Int* 2000;86(1):20-7. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10886077.

64. United Nations Food and Agriculture Organization. http://www.fao.org/geonetwork/srv/en/main.search. *Accessed May* 2005.

## 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

| Variable | Coefficient | Standard error | *t* | *p* |
|---|---|---|---|---|
| Solar UVB irradiance* | -0.4489 | 0.1219 | -3.68 | 0.0003 |
| Total cloud cover† | 4.3765 | 1.4439 | 3.03 | 0.003 |
| Intake of calories from animal sources‡ | 0.0049 | 0.0009 | 5.38 | <0.0001 |

$R^2 = 0.73$, $p < 0.0001$

*Watts/m$^2$ 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

| Variable | Coefficient | Standard error | *t* | *p* |
|---|---|---|---|---|
| Solar UVB irradiance* | -0.1105 | 0.0608 | -1.82 | 0.04 |
| Total cloud cover† | 2.4730 | 0.7203 | 3.43 | 0.0008 |
| Intake of calories from animal sources‡ | 0.0002 | 0.0004 | 5.66 | <0.0001 |

$R^2 = 0.68$, $p < 0.0001$

*Watts/$m^2$ 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].

Appendix Table 1. Countries in the study, with the three-letter codes used in figures. Countries with asterisks provided dietary data.

AFG Afghanistan, ALB Albania*, ALG Algeria*, ANG Angola*, ARG Argentina*, ARM Armenia, AUL Australia*, AUS Austria*, AZR Azerbaijan, BAH Bahrain, BAN Bangladesh*, BAR Barbados*, BEL Belarus, BEN Benin*, BFS Burkina Faso*, BGM Belgium*, BHM Bahamas*, BHU Bhutan, BLZ Belize*, BOL Bolivia*, BOS Bosnia Herzegovena, BOT Botswana*, BRU Brunei*, BRZ Brazil*, BUL Bulgaria*, BUR Burundi*, CAM Cameroon*, CAN Canada*, CAR Central African Republic*, CAV Cape Verde*, CBA Cuba*, CBD Cambodia*, CDI Cote d'Ivoire*, CGB Congo Brazzaville*, CHD Chad*, CHI China*, CHL Chile*, COL Colombia*, COM Comoros*, CRA Costa Rica*, CRO Croatia, CYP Cyprus*, CZR Czech Republic*, DEN Denmark*, DJI Djibouti*, DR Dominican Republic*, DRC Congo*, ECU Ecuador*, EGY Egypt*, ELS El Salvador*, EQG Equatorial Guinea, ERI Eritrea, EST Estonia, ETH Ethiopia*, FIJ Fiji*, FIN Finland*, FRA France*, GAB Gabon*, GAM Gambia*, GEO Georgia, GER Germany*, GHA Ghana*, GIB Guinea-Bissau*, GRE Greece*, GTA Guatemala*, GUA Guam, GUI Guinea*, GUY Guyana*, HAI Haiti*, HON Honduras*, HUN Hungary*, ICE Iceland*, IDA Indonesia*, IND India*, IRE Ireland*, IRN Iran*, IRQ Iraq, ISR Israel*, ITA Italy*, JAM Jamaica*, JAP Japan*, JOR Jordan*, KAZ Kazakhstan, KEN Kenya*, KUW Kuwait*, KYR Kyrgyzstan, LAO Laos*, LAT Latvia, LBY Libya*, LEB Lebanon*, LES Lesotho*, LIB Liberia*, LIT Lithuania, LUX Luxembourg*, MAC Macedonia, MAD Madagascar*, MAL Malta*, MAU Mauritania*, MEL Melanesia, MEX Mexico*, MIC Micronesia, MLI Mali*, MLW Malawi*, MLY

Malaysia*, MOL Moldava, MON Mongolia*, MOR Morocco*, MOZ Mozambique*, MRT Mauritius*, MYA Myanmar*, NAM Namibia*, NEP Nepal*, NET Netherlands*, NGA Nigeria*, NIC Nicaragua*, NIG Niger*, NKO Korea Democratic Republic*, NOR Norway*, NZL New Zealand*, OMA Oman, PAK Pakistan*, PAN Panama*, PAR Paraguay*, PER Peru*, PHI Philippines*, PLY Polynesia, PND Poland*, PNG Papua New Guinea, POR Portugal*, PR Puerto Rico, QAT Qatar, ROM Romania*, RUS Russian Federation, RWA Rwanda*, SAF South African Republic*, SAM Samoa*, SAU Saudi Arabia*, SEN Senegal*, SER -Sebia and Montenegro, SNG Singapore*, SKO Korea Republic of, SLK Slovakia*, SLN Sierra Leone*, SLV Slovenia, SOL Solomon Islands*, SOM Somalia, SPA Spain*, SRL Sri Lanka*, SUD Sudan*, SUR Suriname*, SWA Swaziland*, SWE Sweden*, SWI Switzerland*, SYR Syria*, TAJ Tajikistan, TAN Tanzania*, THA Thailand*, TKN Turkmenistan, TOG Togo*, TRI Trinidad and Tobago*, TUN Tunisia*, TUR Turkey*, UAE United Arab Emirates*, UGA Uganda*, UK United Kingdom*, UKR Ukraine, URU Uruguay*, USA United States of America*, UZB Uzbekistan, VAN Vanuatu*, VEN Venezuela*, VIE Viet Nam*, YEM Yemen*, ZAM Zambia*, ZIM Zimbabwe*

Figure 1.

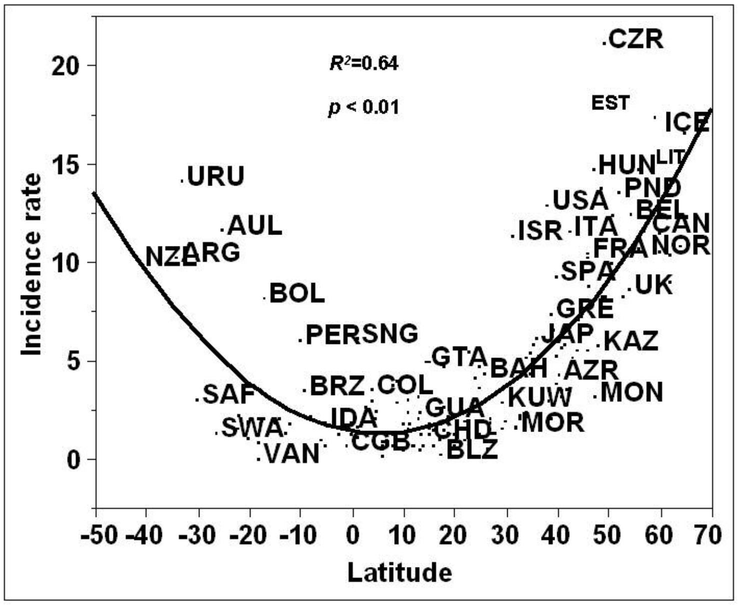


**Figure 1. Renal cancer incidence rates, males, by latitude, 2002. Source: Data from GLOBOCAN**

Figure 2.

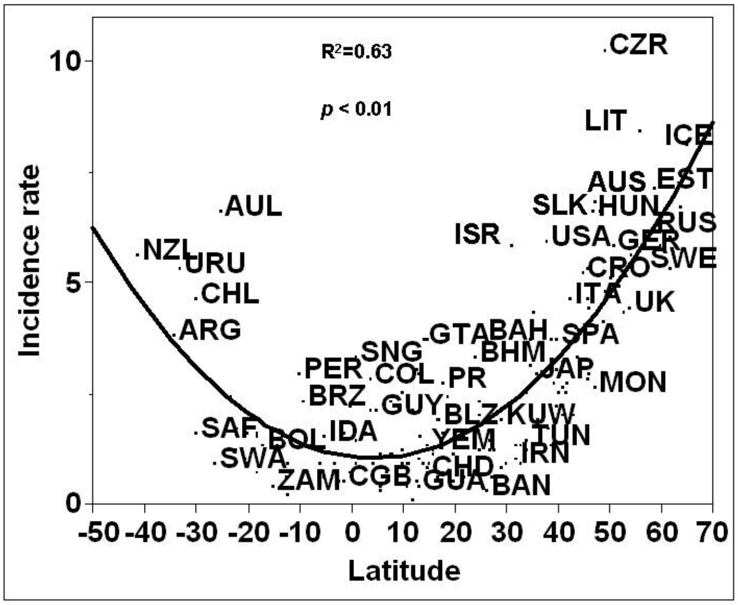


**Figure 2. Renal cancer incidence rates, females, by latitude, 2002. Source: Data from GLOBOCAN**