RESEARCH COMMUNICATION

Does Solar Ultraviolet Irradiation affect Cancer Mortality Rates in China?

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Abstract

Solar ultraviolet B (UVB) has been found to correlate with reduced risk for 14 types of cancer in three or more observational studies and another 14 in one-to-two observational studies. The beneficial role of UVB is thought to be mediated through vitamin D production. Few such studies have been conducted in Southeast Asia. Data on cancer mortality rates for 65 counties in China in 1978 and approximately 300 geographic, dietary, serum, occupation, and lifestyle factors from 1983–4 are available in Diet, Life-style and Mortality in China (Chen et al., Oxford University Press, 1990). The data for 39 counties away from the east coast of China were here used in multiple linear regression analyses. The indices of solar UV radiation (UVR), latitude and heat index, were correlated with reduced mortality rates for cervical, colorectal (females), esophageal, gastric, and lung (males) cancer. Latitude was inversely correlated with liver cancer (males) and nasopharyngeal carcinoma (NPC). Lung cancer, the index used for smoking, was correlated with all less lung (males), cervical, liver (males), and NPC. Several other factors were also correlated with some of the cancers. However, no other factors could explain the latitudinal variation for these seven cancers. Thus, it is concluded that solar UVB, through production of vitamin D, reduces the risk of some types of cancer in China. Liver cancer and NPC are linked to viruses, and UVR may increase the risk through immunosuppression. Further studies are warranted.

Keywords: Cancer - cervical/esophageal/liver/lung/nasopharyngeal - ecological study - ultraviolet - vitamin D

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Introduction

Solar ultraviolet B (UVB; 290–315 nm) irradiance through production of vitamin D has been found to be a risk reduction factor for more than 20 types of cancer, largely through ecologic studies (Grant, 2002b; Freedman et al., 2002; Grant, 2003; Boscoe and Schymura, 2006; Grant 2006a,b; Grant and Garland, 2006). Such studies were favorably reviewed recently (Garland et al., 2006; Grant, 2006c; Kricker and Armstrong, 2006; van der Rhee et al., 2006), and confirmed in some cases by other epidemiologic studies (Hughes et al., 2004; Smedby et al., 2005; Giovannucci et al., 2006; Skinner et al., 2006). In addition, the dose-response relations have been determined for prevention of breast (Garland et al., 2007) and colorectal (Gorham et al., 2007) cancer, and mechanisms whereby vitamin D reduces the risk of cancer are well known (van den Bemd and Chang, 2002; Lamprecht and Lipkin, 2003). Generally, these ecologic studies use some index of solar UVB dose based on geographic location such as latitude (Grant, 2003),3 measured solar UVB doses (Leffell and Brash, 1996), or an index of solar UVB based on some combination or latitude, ozone, aerosols, and clouds (Mohr et al., 2006; Garland et al., 2006). Although critics object that geographic location may be confounded by different personal exposure practices or indices of other cancer risk factors, a recent study using nonmelanoma skin cancer (NMSC) as the index of population solar UVB irradiance obtained results similar to those in the same study using latitude (Grant, 2007). Using a geographic index for UVB irradiance is thus reasonably well justified.

On the other hand, solar UVR can increase the risk of disease, most notably NMSC and melanoma. More recently, attention has also turned to the role of UV in both skin- and systemic-immunosuppression and effect on defenses against viruses related to cancer risk (Schwartz, 2005, Norval, 2006). Many deaths in China are attributed to both cervical cancer and nasopharyngeal carcinoma (NPC), both of which have risk linked to viral infections (Cheng et al., 2002; Chang et al., 2006; Wu et al., 2006; Zhao et al., 2006;), so increasing the understanding of their risk factors is important.

Most of the ecologic studies of solar UVB and cancer risk reduction have been for white people (Grant, 2002b; Freedman et al., 2002; Grant, 2003; Boscoe and Schymura, 2006; Grant 2006a,b; Grant and Garland, 2006) or African Americans (Grant, 2006), with only two specifically targeting Southeast Asians (Kato et al., 1985; Mizoue et al., 2004). One study of cancer rates for females

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in China did report a correlation with latitude, finding that cancer of the stomach, liver, and rectum increased with latitude for females in China and the United States, but attributed this finding to dietary variations with latitude (Archer, 1989). Thus, extending the analysis to China is useful.

The cancer mortality rate datasets in Diet, Life-style and Mortality in China (Chen et al., 1990a) from a nationwide survey in 1973-5 (Li et al., 1981) are quite useful, especially because they are coupled to more than 300 datasets on factors related to disease outcome including dietary factors, serum components and urinary by-products, physical and lifestyle parameters, and geographical data (Chen et al., 1981; Li, 1989). Thus, the analyses can include many other risk-modifying factors and examine possible confounding factors. However, to my knowledge, no one has yet used these datasets to examine the role of solar ultraviolet radiation (UVR) on risk of cancer and other diseases. The data in Chen et al., 1990a are used in a multifactorial ecologic study of cancer mortality rates in China.

Materials and Methods

The data were obtained from (Chen et al., 1990a). The annual cancer mortality rate data were for 65 rural counties included in the nationwide survey of all deaths in the 3-year period, 1973–5, and were age adjusted to the population of China. Data for some cancers, such as breast and esophageal, were considered highly reliable since the diagnosis was relatively straightforward, whereas for others, such as lung cancer or leukemia, there may be systematic differences in how the cancers were recorded in different regions of China. To limit the uncertainties of the data, the authors limited the data to those who died before the age of 65 years. The cancer data were reported for two age ranges: 0–64 years and 35–64 years. The truncated age range values were generally about three times those of the full age range data. This study used the truncated data.

The ancillary data were collected in the autumn of 1983 at the end of the harvest season from about 50 people aged 35–64 years, with approximately equal numbers of people in each 10-year age group, in each of two cities for each of the 65 counties. Five types of data were collected: intakes of foods and nutrients, levels of various blood constituents, excretion levels of a few urinary by-products, questionnaire-based information on lifestyle, and various constituent levels of virtually all plant foods identified and measured in the survey. Data on geographic and population factors were added later. Cross correlations between the data for the 65 counties were presented in that study.

Readily apparent from the maps in Chen et al., 1990a is that cancer rates on the southeast coast of China are generally much higher than for interior sites at the same latitudes. This effect is attributed to a more affluent lifestyle near the coast because of more interaction with foreign countries. For example, plasma albumin levels, alcohol consumption rates, and height were similar for all east coast counties but had latitudinal gradients in the interior counties. Since including such counties would probably mask any effect of solar UVB irradiance on cancer risk, the analysis presented here was based counties limited to the region between 102.9° and 114° E, which includes 40 counties. Two counties to the west, Dunhuang and Tuoli, were omitted from the reduced set since they were far from the other counties (40.1° N, 94.8° E and 46.0° N, 83.7° E, respectively) and were thought to have several differences from the other counties. Also, noncancer data for one county, Xuanwei, were often missing, so it, too, was omitted. Thus, the results presented here are based on 39 counties. A description of the cancer data used is presented in Table 1.

The data examined here include the data for cancers with geographic variations for people aged 35–64 years and most of the factors that were significantly linked to these cancers in the cross correlation analyses for all 65 counties, those reported correlated with cancer by other researchers (Lam, 1986; Campbell et al., 1990; Chen, 1991; Chen et al., 1990b; Forman et al., 1990; Guo et al., 1990; Hsing et al., 1991; Chen et al., 1992; Marshall et al., 1992; Guo et al., 1993, 1994; Chen et al., 2003), or those that exhibited a generally monotonic variation with latitude. The factors included in the model were varied until only those that were statistically significant or nearly so were identified. Stepwise regression analyses were conducted to guard against spurious results due to cross correlations of the data. The number of factors was generally limited to three since there were 39 counties. The Bonferroni criterion for significance at the 95% confidence level, $p<0.05/n$, where n is the number of factors in the model, was used, and factors not satisfying this criterion were generally omitted. Square roots of the values were used for most data to reduce the effect of extreme values. The data were used in multiple linear regression analyses using the SPSS 13.0 analysis program (SPSS, Chicago, IL). The term β is the normalized regression coefficient, r; in linear regression analysis, the two are identical.

Table 1. Description of the Cancer Data for the 39-County Datasets for those Aged 35-64 Years.

Cancer	Sex	Minimum*	Mean*	Maximum*
All	M	34.7	262.0	625.3
	F	35.2	168.1	430.2
All-lung	M	32.1	246.9	613.2
	F	34.3	161.5	419.6
Breast	F	1.5	8.5	20.0
Cervical	F	4.4	34.4	97.0
Colorectal	M	1.3	10.2	38.6
	F	2.1	7.1	19.6
Esophageal	M	1.4	75.9	435.5
	F	0.0	38.2	285.8
Gastric	M	5.9	70.2	266.6
	F	1.7	33.2	129.2
Liver	M	6.9	53.7	248.3
	F	2.7	18.7	62.6
Lung	M	2.6	15.1	40.4
	F	0.0	6.5	26.1
Nasopharyngeal	M	0.0	15.5	75.0
	F	0.0	6.9	26.0

* deaths/100,000/year

Table 2. Regression Results for those Aged 35-64 Years for the 39-County Data Set

Cancer	Sex, N[a]	First term (β, *p*)	Second Term (β, *p*)	Third Term (β, *p*)	Adjusted R^2, F, *p*
All	M	-0.50, * Lipids	0.45, * Lung M	0.32, 0.01 Eggs	0.52, 15, *
All	F	-0.78, * Heat zone	0.29, 0.005 Eggs		0.65, 36, *
All	F	0.75, * Latitude	0.24, 0.03 Eggs		0.60, 29, *
All-lung	M	-0.53, * Lipids	0.40, 0.002 Lung M	0.32, 0.01 Eggs	0.49, 13, *
All-lung	F	-0.62, * Heat zone	0.38, * Eggs	-0.31, 0.006 Lipids	0.68, 28, *
All-lung	F	0.58, * Latitude	0.32, 0.003 Eggs	-0.30, 0.01 Lipids	0.63, 23, *
Breast	F	0.42, 0.02 Eggs	-0.35, 0.04 Iodine		0.24, 5.5, 0.01
Cervical	F	-0.61, * Heat zone	0.29, 0.02 Lung M		0.54, 23, *
Cervical	F	0.69, * Latitude			0.46, 33, *
Colorectal	M	0.52, 0.001 Lung M			0.25, 14, 0.001
Colorectal	F	-0.54, * Heat zone	0.43, 0.001 Refined carb		0.45, 16, *
Colorectal	F	0.41, 0.005 Latitude	0.36, 0.01 Refined carb		0.28, 8.4,0.001
Esophageal	M	0.67, * Latitude			0.44, 31, *
Esophageal	F	0.64, * Latitude			0.40, 26, *
Gastric	M, 25	0.54, 0.002 Latitude	0.39, 0.02 C. pylori	0.28, 0.09 Lung M	0.56, 11, *
Gastric	F, 25	0.73, * Latitude	0.26, 0.05 C. pylori		0.63, 21, *
Liver	M	-0.54, 0.001 Latitude	0.43, 0.005 Lung M		0.28, 8.6, 0.001
Liver	M	-0.60, * Latitude	0.34, 0.04 Lung M	0.23, 0.17 Hepatitis antibodies	0.30, 6.5,0.001
Lung	M	-0.53, * Agriculture	0.43, 0.002 Latitude		0.37, 12, *
Lung	F	0.52, 0.001 Plasma copper			0.25, 14, *
Nasopharyngeal	M	-0.92, * Latitude	0.47, * Lung M		0.76, 61, *
Nasopharyngeal	F	-0.82, * Latitude	0.54, * Lung, M		0.64, 35, *
Nasopharyngeal	F	-0.80, * Latitude	0.49, * Lung, F		0.59, 28, *

[a]N, number of counties, = 39 unless otherwise stated; * p<0.001; _, normalized regression coefficient; agriculture, agricultural employment; carb, carbohydrates; F, females; lung, lung cancer; M, males

Three indices can be used for solar UVB and UVR in China: latitude, heat zone, and elevation. Annual average UVB and UVR decrease with increasing latitude. The temperature of the heat zones decreases with latitude, and the cross correlation between heat zones and latitude is very high. There were only six heat zones tabulated in China, so it is a much coarser index than latitude. The atmosphere blocks less solar UVB at higher altitudes, leading to more UVR irradiance (Deng et al., 2006); however, elevation may not be an independent indicator of solar UVB since elevation is highly correlated with several factors including fiber, weight, and wheat. Since food was not fortified with vitamin D in China in the 1970s and 1980s, and since animal sources of vitamin D such as oily cold-water ocean fish are not an important source of vitamin D in rural China, solar UVB was the primary source of vitamin D in China.

Lung cancer was used as the index of adverse health outcome due to inhaled smoke (Leistikow, 2004; Grant and Garland, 2006). Although cigarette smoking is the primary risk factor for lung cancer in Western developed countries, home cooking fires were a major source of inhaled smoke in continental China in the 1970s and early 1980s. However, the ratio of female to male lung cancer mortality rates had a mean value of 0.44 with a range from 0.0 to 1.11. This finding indicates that smoking probably played an important role in the etiology of lung cancer of both men and women because (i) women would be indoors more than men and (ii) men were 10–100 times more likely to smoke than women in the past six months (Table 6006 in Chen et al., 1990a). Thus, there were probably effects of secondhand smoke.

Factors used in the analysis but for which no significant results were found in multiple linear regressions include the following: albumin, animal protein, arsenic, green vegetables, height, industrial employment, lipid peroxide, longitude, moldy peanuts, rice, salt, selenium, urea, vegetable protein, and wheat flour. Alcohol consumption by females was low, so this index was not used for females.

Results

The results of the multiple linear regression analyses are presented in Table 2. In the analyses, five cancers plus all and all less lung cancer (females) were found to have mortality rates increasing with increasing latitude or varying inversely with heat zone: cervical, colorectal (females), esophageal, gastric, and lung (males) cancer. Lung cancer mortality rates for males were correlated with all less lung (males), cervical, colorectal (males), lung cancer (males), and NPC. Presence of Campylobacter pylori antibodies was correlated with gastric cancer risk. Latitude was inversely correlated with liver cancer (males) and NPC.

Several dietary factors were also correlated with cancer rates. Egg consumption was correlated with all, all less lung, and breast cancer. Agricultural employment was inversely correlated with lung cancer (males), while plasma copper was directly correlated with lung cancer (females). Refined carbohydrates and sugar was correlated with colorectal cancer (females). Iodine was weakly inversely correlated with breast cancer.

Discussion

All the cancers for which at least one of the stronger

UVB-linked indices was correlated—colorectal, esophageal, gastric, and lung cancer—have been identified as vitamin D sensitive in one or more studies (Grant, 2002b; Freedman et al., 2002; Grant, 2003; Boscoe and Schymura, 2006; Grant 2006a,b; Grant and Garland, 2006;). Three of these, colorectal, esophageal, and gastric cancer, were among the five identified in an ecologic study in Japan (Mizoue, 2004). Pancreatic cancer rates were also found to increase in Japan (Kato et al., 1985; Mizoue, 2004), but there were no data available for China. Thus, these results both add to previous findings that solar UVB reduces the risk of many types of cancer and suggest that cancer rates in China could be reduced if vitamin D production or oral intake were higher.

That male lung cancer mortality rates were more highly correlated with all, all less lung, cervical, colorectal, and NPC indicates that smoking tobacco products had a more significant impact on cancer rates than did indoor cooking fires. Smoking is a well-known risk factor for many types of cancer (Sasco et al., 2004). In addition, the results might indicate the effects of secondhand smoke (Sasco et al., 2004).

The results for cervical cancer are consistent with those from a recent study in the U.S. (Grant and Garland, 2006). However, no other study has found that UVB or vitamin D reduces the risk of cervical cancer, so this finding should be treated cautiously.

Agricultural employment often correlates with lower mortality rates for lung and other cancers in other studies (Keller and Howe, 1993). Perhaps agricultural workers spend more time outdoors and thus are exposed to less indoor pollution and more solar UVB irradiance (Xu et al,. 1989).

Although breast cancer is generally found to be UVB- and vitamin D sensitive, it was not in this study: breast cancer rates were low in China because of low-risk factors such as a diet high in animal products (Grant, 2002a), which increases levels of both estrogen and insulin-like growth factor-I (IGF-I). One of the effects of vitamin D is to attenuate growth-inducing signals such as from estrogen and IGF-I (van den Bemd and Chang, 2002; Lamprecht and Lipkin, 2003). However, the correlation with eggs is consistent with animal products' being an important risk factor (Grant, 2002a), and the literature supports the inverse correlation with iodine (Smyth, 2003).

Total energy consumption (higher weight) and refined carbohydrates are thought to be associated with increased risk of colorectal cancer (Giovannucci, 2001; Gunter and Leitzmann, 2006), in agreement with the results of this study, although more likely through weight gain than insulin (Larsson et al., 2007) since sugar consumption is correlated with increased weight (Grant, 2004).

The etiology of NPC has been puzzling (Chang and Adami, 2006). Intake of preserved foods at an early age, smoking, and occupational exposure to formaldehyde and wood are significant risk factors (Yu and Yuan, 2002). However, NPC rates are high in Guangdong Province, but the reasons for these high rates have not been determined (Jia et al., 2004). In the United States, NMSC correlates strongly with NPC, as does lung cancer and urban residence, whereas UVB is inversely correlated. UVB irradiance can impair the immune system response to viral infections (Cheng et al., 2002; Schwartz, 2005; Norval, 2006). Epstein-Barr virus (EBV) is a high-risk factor for NPC. Immunodeficiency permits EBV to induce sustained target-cell proliferation (Purtilo et al., 1984). Thus, solar UVB irradiance may be an important risk factor for NPC through immunosuppression, leading to EBV's increased virulence. Further study is required to confirm this hypothesis.

The inverse correlation of latitude with liver cancer for males does not appear to be due to aflatoxin, which is more prevalent in hot, humid environments (Campbell et al., 1990), but rather hepatitis infection (Hsing et al., 1991). Smoking is also a risk factor for liver cancer. A weak association with hepatitis antibodies was found in this study.

Vitamin D in China

Serum calcidiol levels tend to be low in China (Fraser, 2004). Undergraduates in Shenyang (41° N) were found to experience less than 1% of the daily solar UVR (Liu et al., 2006). A study in Shenyang Province (41°–42° N, 48-m elevation) of 194 healthy volunteers found that calcidiol levels were 28 ± 13 nmol/L for old men and 41 ± 14 nmol/L for old women (Yan et al., 2000). Values for young men and women were similar to those for older men and women. These values are much lower than the values of greater than 55–60 nmol/L for females in Boston (41° N) in winter (Harris and Dawson-Hughes, 1998; Harris et al., 2000) and 85 ± 33 nmol/L for females in summer in Boston (Harris and Dawson-Hughes, 1998). Serum calcidiol levels in elderly Chinese living in Taiwan (25° N) were much higher (90 ± 16 nmol/L) (Lee et al., 2002). Thus, these results both confirm the assumption that calcidiol levels among the Chinese are directly related to solar UVB irradiance and underscore that serum calcidiol levels are not adequate for optimal health. The sufficiency range is considered to be 33-80 ng/mL (83-200 nmol/L) (Grant and Holick, 2005).

Limitations and strengths

Since this was an ecologic study, it is subject to the limitations of such studies. One omission from the data set was the effect of aerosols on solar UVB reaching the surface. A study in 1999 estimated that atmospheric haze aerosols reduced the amount of solar UVB reaching the surface in the agricultural regions (Chameides et al., 1999). That study was updated recently for surface temperature (Huang et al., 2006). Also, both sulfur dioxide emissions and tropospheric ozone absorb in the UVB region, further decreasing UVB at the surface.

However, in general, carefully done ecologic studies have made many important contributions to understanding the role of various disease risk–modifying factors, often identifying important risk factors years-to-decades before they are confirmed using other approaches (Armstrong and Doll, 1975; Garland and Garland, 1980; Grant, 1997). Although the factors used in the analyses of the various cancers were carefully chosen, some important factors may not have been used with specific cancers, and some of the factors that correlated with some of the cancers may not have been risk-modifying factors. A potential problem with the datasets is that the non-cancer data were obtained five years after the cancer data. This problem is thought to be minor since at that time, the rural Chinese were not very mobile, and changes in diet and lifestyle were slow (Food and Agriculture Organization, 1996). Another problem is that aerosols from fossil fuel combustion and sandstorms as well as clouds also reduce the amount of solar UVR reaching the surface in an irregular variation with latitude, but these factors were not included in the analysis.

The primary advantage of this study is that data for a great many factors are available, which helps to either include or rule out confounding factors. An important advancement for studying cancer risks in China was the use of a 39-county subset of the data less affected by increased affluence and contact with the West. There may be other subsets that could also be used to shed more light on cancer risks in China. As with any observational study, these results should be investigated using other approaches.

Summary and conclusion

This ecologic study found significant inverse correlations with indices of solar UVB irradiance for cervical, colorectal (females), esophageal, gastric, lung (males) and all and all cancers other than lung cancer (females). These results are generally consistent with ecologic studies in other countries. Most of the other correlations found here are in general agreement with the literature, such as risk associated with smoking, diet, and microorganisms. Thus, this work indicates that cancer incidence and mortality rates could be reduced if population-level serum calcidiol levels were higher, especially at the higher latitudes and for those who do not spend enough time in the sun, as well as during the winter when producing vitamin D from solar UVB irradiance is difficult or impossible (Webb and Engelsen, 2006).

The incidence and mortality rates for cancers previously common in China such as cervical, esophageal, and gastric cancer are trending down, whereas those more common in Western developed countries such as female breast, colorectal, lung, prostate, and renal cancer are increasing (Gu, 2003; Yang et al., 2003, 2005; Chen et al., 2006; Tian and Chen, 2006). Dietary changes may explain some of these trends. Since the cancers with increasing incidence rates are vitamin D sensitive, investigating the role of vitamin D in health and making appropriate policy recommendations would be worthwhile for China.

References

Archer VE (1989). Latitudinal variation of digestive tract cancers in the US and China. *Nutr Cancer*, **12**, 213-23.

Armstrong B, Doll R (1975). Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. *Int J Cancer*, **15**, 617-31.

Boscoe FP, Schymura MJ (2006). Solar ultraviolet-B exposure and cancer incidence and mortality in the United States, 1993-2000. *BMC Cancer*, **6**, 264.

Campbell TC, Chen JS, Liu CB, et al (1990). Nonassociation of aflatoxin with primary liver cancer in a cross-sectional ecological survey in the People's Republic of China. *Cancer Res*, **50**, 6882-93.

Chameides WL, Yu H, Liu SC, et al (1999). 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*, **96**,13626-33.

Chang ET, Adami HO (2006). The enigmatic epidemiology of nasopharyngeal carcinoma. *Cancer Epidemiol Biomarkers Prev*, **15**, 1765-77.

Chen J (1991) Dietary practices and cancer mortality in China. *IARC Sci Publ*, **105**, 18-21.

Chen J, Campbell TC, Li J, et al (1990a). Diet, Life-style and Mortality in China. Oxford University Press.

Chen J, Geissler C, Parpia B, et al (1992). Antioxidant status and cancer mortality in China. *Int J Epidemiol*, **21**, 625-35.

Chen JG, Zhu J, Parkin DM, et al (2006). Trends in the incidence of cancer in Qidong, China, 1978-2002. *Int J Cancer*, **119**, 1447-54.

Chen JS, Brun TA, Campbell TC, et al (1990b). Plasma cotinine, smoking, and lung cancer in China. *Lancet*, **335**, 1225-6.

Chen ZM, Liu BQ, Boreham J, et al (2003). Smoking and liver cancer in China: case-control comparison of 36,000 liver cancer deaths vs. 17,000 cirrhosis deaths. *Int J Cancer*, **107**, 106-12.

Cheng WM, Chan KH, Chen HL, et al (2002). Assessing the risk of nasopharyngeal carcinoma on the basis of EBV antibody spectrum. *Int J Cancer*, **97**, 489-92.

Deng D, Hang Y, Chen H, et al (2006). Prevalence of photodermatosis in four regions at different altitudes in Yunnan province, *China. J Dermatol*, **33**, 537-40.

Food and Agriculture Organization (1996). Food Balance Sheets. Rome.

Forman D, Sitas F, Newell DG, et al (1990). Geographic association of *Helicobacter pylori* antibody prevalence and gastric cancer mortality in rural China. *Int J Cancer*, **46**, 608-11.

Fraser DR (2004). Vitamin D-deficiency in Asia. *J Steroid Biochem Mol Biol*, **89-90**, 491-5.

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

Garland CF, Garland FC (1980). Do sunlight and vitamin D reduce the likelihood of colon cancer? *Int J Epidemiol*, **9**, 227-31.

Garland CF, Garland FC, Gorham ED, et al (2006). The role of vitamin D in cancer prevention. *Am J Public Health*, **96**, 252-61.

Garland CF, Mohr SB, Gorham ED, et al (2006). Role of ultraviolet-B irradiance and vitamin D in the prevention of ovarian cancer. *Am J Prev Med*, **31**, 512-4.

Garland CF, Gorham ED, Mohr SB, et al (2007). Vitamin D and prevention of breast cancer: Pooled analysis. *J Steroid Biochem Molec Biol*, **103**, 708-11.

Giovannucci E (2001). Insulin, insulin-like growth factors and colon cancer: a review of the evidence. *J Nutr*, **131**, 3109-20.

Giovannucci E, Liu Y, Rimm EB, et al (2006). Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. *J Natl Cancer Inst*, **98**, 451-9.

Gorham ED, Garland CF, Garland FC, et al (2005). Vitamin D and prevention of colorectal cancer. *J Steroid Biochem Mol Biol*, **97**, 179-94.

Gorham ED, Garland CF, Garland FC, et al (2007). Optimal vitamin D status for colorectal cancer prevention a quantitative meta analysis. *Am J Prev Med*, **32**, 210-6.

Grant WB (1997). Dietary links to Alzheimer's disease. Alz Dis Rev, 2:42-55. http://www.sunarc.org/JAD97.pdf, (accessed March 11, 2007)

Grant WB (2002a). An ecologic study of dietary and solar ultraviolet-B links to breast carcinoma mortality rates. *Cancer*, **94**, 272-81.

Grant WB (2002b). An estimate of premature cancer mortality in the U.S. due to inadequate doses of solar ultraviolet-B radiation. *Cancer*, **94**, 1867-75.

Grant WB (2003). Ecologic studies of solar UV-B radiation and cancer mortality rates. *Recent Results Cancer Res*, **164**, 371-7.

Grant WB (2004). The primary role of sweeteners in the body mass indexes of women from developing countries: implications for risk of chronic disease. *Am J Clin Nutr*, **80**, 527-8.

Grant WB (2006a). Lower vitamin-D production from solar ultraviolet-B irradiance may explain some differences in cancer survival rates. *J Natl Med Assoc*, **98**, 357-64.

Grant WB (2006b). The likely role of vitamin D from solar ultraviolet-B irradiance in increasing cancer survival. *Anticancer Res*, **26**, 2605-14.

Grant WB (2006c). Epidemiology of disease risks in relation to vitamin D insufficiency. *Progress Biophys Molec Biol*, **92**, 65-79.

Grant WB (2007). An ecologic study of cancer mortality rates in Spain with respect to indices of solar UV irradiance and smoking. *Int J Cancer*, **120**, 1123-7.

Grant WB, Garland CF (2006). The association of solar ultraviolet B (UVB) with reducing risk of cancer: multifactorial ecologic analysis of geographic variation in age-adjusted cancer mortality rates. *Anticancer Res*, **26**, 2687-99.

Grant WB, Holick MF (2005). Benefits and requirements of vitamin D for optimal health: a review. *Altern Med Rev*, **10**, 94-111.

Gu F (2003). Changing constituents of genitourinary cancer in recent 50 years in Beijing. *Chin Med J (Engl)*, **116**, 1391-3.

Gunter MJ, Leitzmann MF (2006). Obesity and colorectal cancer: epidemiology, mechanisms and candidate genes. *J Nutr Biochem*, **17**, 145-56.

Guo W, Zheng W, Li JY, et al (1993). Correlations of colon cancer mortality with dietary factors, serum markers, and schistosomiasis in China. *Nutr Cancer*, **20**, 13-20.

Guo WD, Li JY, Blot WJ, et al (1990). Correlations of dietary intake and blood nutrient levels with esophageal cancer mortality in China. *Nutr Cancer*, **13**, 121-7.

Guo WD, Chow WH, Zheng W, et al (1994). Diet, serum markers and breast cancer mortality in China. *Jpn J Cancer Res*, **85**, 572-7.

Harris SS, Dawson-Hughes B (1998). Seasonal changes in plasma 25-hydroxyvitamin D concentrations of young American black and white women. *Am J Clin Nutr*, **67**, 1232-6.

Harris SS, Soteriades E, Coolidge JA, et al (2000). Vitamin D insufficiency and hyperparathyroidism in a low income, multiracial, elderly population. *J Clin Endocrinol Metab*, **85**, 4125-30.

Hsing AW, Guo W, Chen J, et al (1991). Correlates of liver cancer mortality in China. *Int J Epidemiol*, **20**, 54-9.

Huang Y, Dickinson RE, Chameides WL (2006) Impact of aerosol indirect effect on surface temperature over East Asia. *Proc Natl Acad Sci U S A*, 103, 4371-6.

Hughes AM, Armstrong BK, Vajdic CM, et al (2004) Sun exposure may protect against non-Hodgkin lymphoma: a case-control study. *Int J Cancer*, **112**, 865-71.

Jia WH, Feng BJ, Xu ZL, et al (2004) Familial risk and clustering of nasopharyngeal carcinoma in Guangdong, China. *Cancer*, **101**, 363-9.

Kato I, Tajima K, Kuroishi T, et al (1985). Latitude and pancreatic cancer. *Jpn J Clin Oncol*, **15**, 403-13.

Keller JE, Howe HL (1993). Risk factors for lung cancer among nonsmoking Illinois residents. *Environ Res*, **60**, 1-11.

Kricker A, Armstrong B (2006). Does sunlight have a beneficial influence on certain cancers? *Prog Biophys Mol Biol*, **92**, 132-9.

Lam NS (1986). Geographical patterns of cancer mortality in China. *Soc Sci Med*, **23**, 241-7.

Lamprecht SA, Lipkin M (2003). Chemoprevention of colon cancer by calcium, vitamin D and folate: molecular mechanisms. *Nat Rev Cancer*, **3**, 601-14.

Larsson SC, Giovannucci E, Wolk A (2007). Dietary carbohydrate, glycemic index, and glycemic load in relation to risk of colorectal cancer in women. *Am J Epidemiol*, **165**, 256-61.

Lee WP, Lin LW, Yeh SH, et al (2002). Correlations among serum calcium, vitamin D and parathyroid hormone levels in the elderly in southern Taiwan. *J Nurs Res*, **10**, 65-72.

Leffell DJ, Brash DE (1996). Sunlight and skin cancer. *Sci Am*, **275**, 52-3, 56-9. http://toms.gsfc.nasa.gov/ery_uv/dna_exp.gif (accessed Jun 12, 2007)

Leistikow B (2004). Lung cancer rates as an index of tobacco smoke exposures: validation against black male approximate non-lung cancer death rates, 1969-2000. *Prev Med*, **38**, 511-5.

Li JY (1989). Cancer mapping as an epidemiologic research resource in China. *Recent Results Cancer Res*, **114**, 115-36.

Li JY, Liu BQ, Li GY, et al (1981). Atlas of cancer mortality in the People's Republic of China. An aid for cancer control and research. *Int J Epidemiol*, **10**, 127-33.

Liu Y, Ono M, Yu D, Wang Y, et al (2006). Individual solar-UV doses of pupils and undergraduates in China. *J Expo Sci Environ Epidemiol*, **16**, 531-7.

Marshall JR, Qu Y, Chen J, et al (1992). Additional ecological evidence: lipids and breast cancer mortality among women aged 55 and over in China. *Eur J Cancer*, **28**, 1720-7.

Mizoue T (2004). Ecological study of solar radiation and cancer mortality in Japan. *Health Phys*, **87**, 532-8.

Mohr SB, Gorham ED, Garland CF, et al (2006). Are low ultraviolet B and high animal protein intake associated with risk of renal cancer? *Int J Cancer*, **119**, 2705-9.

Norval M (2006). The Effect of Ultraviolet Radiation on Human Viral Infections. Photochem Photobiol [Epub ahead of print]

Purtilo DT, Manolov G, Manolova Y, et al (1984). Squamous-cell carcinoma, Kaposi's sarcoma and Burkitt's lymphoma are consequences of impaired immune surveillance of ubiquitous viruses in acquired immune deficiency syndrome, allograft recipients and tropical African patients. *IARC Sci Publ*, **63**, 749-70.

Sasco AJ, Secretan MB, Straif K (2004). Tobacco smoking and cancer: a brief review of recent epidemiological evidence. *Lung Cancer*, **45 Suppl 2**, S3-9.

Schwarz T (2005). Mechanisms of UV-induced immuno sup pression. *Keio J Med*, **54**, 165-71.

Skinner HG, Michaud DS, Giovannucci E, et al (2006) Vitamin D intake and the risk of pancreatic cancer in two cohort studies. *Cancer Epidemiol Biomarkers Prev*, **15**, 1688-1695.

Smedby KE, Hjalgrim H, Melbye M, et al (2005). Ultraviolet radiation exposure and risk of malignant lymphomas. *J Natl Cancer Inst*, **97**, 199-209.

Smyth PP (2003). The thyroid, iodine and breast cancer. *Breast Cancer Res*, **5**, 235-8.

Tian J, Chen JS (2006). Time trends of incidence of digestive system cancers in Changle of China during 1988-2002. *World J Gastroenterol*, **12**, 4569-71.

van den Bemd GJ, Chang GT (2002). Vitamin D and vitamin D analogs in cancer treatment. *Curr Drug Targets*, **3**, 85-94.

van der Rhee HJ, de Vries E, Coebergh JW (2006). Does sunlight prevent cancer? A systematic review. *Eur J Cancer*, **42**, 2222-32.

Webb AR, Engelsen O (2006). Calculated ultraviolet exposure levels for a healthy vitamin D status. *Photochem Photobiol*, **82**, 1697-703.

Wu Y, Chen Y, Li L, et al (2006) Associations of high-risk HPV types and viral load with cervical cancer in China. J Clin Virol, 35:264-9.

Xu ZY, Blot WJ, Xiao HP, et al (1989). Smoking, air pollution, and the high rates of lung cancer in Shenyang, China. *J Natl Cancer Inst*, **81**, 1800-6.

Yan L, Prentice A, Zhang H, et al (2000). Vitamin D status and parathyroid hormone concentrations in Chinese women and men from north-east of the People's Republic of China. Eur *J Clin Nutr*, **54**, 68-72.

Yang L, Parkin DM, Li L, et al (2003). Time trends in cancer mortality in China: 1987-1999. *Int J Cancer*, **106**, 771-83.

Yang L, Parkin DM, Ferlay J, et al (2005). Estimates of cancer incidence in China for 2000 and projections for 2005. *Cancer Epidemiol Biomarkers Prev*, **14**, 243-50.

Yu MC, Yuan JM (2002). Epidemiology of nasopharyngeal carcinoma. *Semin Cancer Biol*, **12**, 421-9.

Zhao FH, Forman MR, Belinson J, et al (2006). Risk factors for HPV infection and cervical cancer among unscreened women in a high-risk rural area of China. *Int J Cancer*, **118**, 442-8.