ELSEVIER

Ecological Studies Of Ultraviolet B, Vitamin D And Cancer Since 2000

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PURPOSE: The purpose of this review is to summarize ecological studies of solar ultraviolet B (UVB), vitamin D and cancer since 2000.
METHODS: The journal literature is surveyed and summarized.
RESULTS: The ecological approach has been the primary tool used during the past two decades to extend the applicability of the UVB-vitamin D-cancer theory to include at least 18 types of cancer. Many of these studies were conducted in the United States, which has the advantages of availability of reliable age-standardized cancer incidence and mortality rate data for geographic areas at various spatial resolutions, and an asymmetric solar UVB dose pattern, with higher UVB irradiance in the west and lower in the east, at any particular latitude. In addition, indices for other cancer risk-modifying factors are readily available including those for smoking, alcohol consumption, ethnic background, urban/rural residence, socioeconomic status, air pollution, and in limited fashion, diet. The ecological approach has also been used to identify latitudinal variations in cancer mortality rates in Australia, China, Japan, and Spain, and in multicountry studies. It has been used to investigate the relative roles of solar UVB and dietary factors on a global scale. The ecological approach has also been applied to cancer survival. Studies in Norway and England found that individuals diagnosed with cancer in summer or fall, when serum 25-hydroxyvitamin D levels are highest, had a milder clinical course and longer survival than those diagnosed in winter or spring.
CONCLUSION: These findings provide strong evidence that vitamin D status plays an important role in controlling the outcome of cancer. Support for the UVB-vitamin D-cancer theory is now scientifically strong enough to warrant use of vitamin D in cancer prevention, and as a component of treatment. More research studies would help to explore whether there are benefits beyond the substantial effects that have been observed.
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KEY WORDS: Vitamin D, Calcidiol, Latitude, Ultraviolet Rays, Colonic Neoplasms, Breast Neoplasms, Incidence, Mortality, Neoplasms, Ecological Studies, Review.

INTRODUCTION

The ultraviolet B (UVB)–vitamin D–cancer theory was first proposed in 1980 on the basis of an ecological study of colon cancer mortality rates and annual sunlight levels in the United States (1). This study was reprinted with commentaries in a special issue of the *International Journal of Epidemiology* in 2006 (2–7). Much of the support for this theory also comes from subsequent ecological studies. The ecological approach is ideally suited for identifying and quantifying risk-modifying agents that are an integral part of the human environment, have sufficient spatial or temporal variation to have a measurable effect, and relate to effects that are well quantified. Examples of important ecological study findings include identification of major dietary links to cancer (8) and Alzheimer's disease (9). In conducting ecological studies, it is important to take measures to ensure the highest possible data quality, and to account for confounders, as in other observational studies. The value of the approach is enhanced when potential confounding is examined using stratification or regression. Further studies using other approaches are generally required to confirm findings of ecological studies. Nonetheless, much progress has been made in understanding the inverse association of UVB irradiance and positive association of vitamin D with lower risk of many cancer sites, mainly by informed use of the ecological approach. The article by Mohr (10) describes developments through 2000; this article reviews progress since then.

ECOLOGICAL STUDIES IN THE UNITED STATES, 2000 TO THE PRESENT

The Atlas of Cancer Mortality in the United States, 1950–1994 (11) had just been published when one of the authors (W.B.G.) joined the field in 2000 (12). At that time, there were five cancers that had been identified as UVB or vitamin D associated: breast, colon, ovarian, prostate, and rectal (10). However, an inspection of the maps in the Atlas

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Selected Abbreviations and Acronyms

UVB = ultraviolet B
TOMS = Total Ozone Mapping Spectrometer
NASA = National Aeronautics and Space Administration
NMSC = Non-Melanoma Skin Cancer
SCC = squamous cell carcinoma
NHL = non-Hodgkin's lymphoma
UVA = ultraviolet A
UCSD = University of California, San Diego

indicated that many cancers had geographic variations in mortality rates that were similar to those for breast, colon, rectal, and ovarian cancer. On the basis of these geographic differences, Grant investigated the number of different types of cancers that could be considered UVB or vitamin D associated, and the number of individuals in the United States (U.S.) who die prematurely each year from receiving too little UVB or vitamin D. He worked at the National Aeronautics and Space Administration (NASA) and was aware of a map of DNA-weighted UVB irradiance at ground level, derived from measurements taken by the Total Ozone Mapping Spectrometer (TOMS) in July 1992 (13). Greater exposure to solar UVB in areas with high solar irradiance results in greater cutaneous photosynthesis of vitamin D in populations in these areas, resulting in higher levels of vitamin D metabolites that reduce the risk of certain cancers (14). The latitudinal variation and East-West asymmetry of the geographic distribution of UVB irradiance matched the unusual distribution of many of the cancer mortality maps.

UVB irradiance levels east of the Rocky Mountains were lower than those at the same latitudes in the west. UVB irradiance at a particular latitude in the eastern U.S. was similar to irradiance in the West at a point approximately 700 km (6°) to the north. This east-west difference in UVB irradiance is due mainly to a thinner stratospheric ozone layer in the west, due to prevailing westerly winds pushing the tropopause up as air masses cross the Rocky Mountains. This difference is also due in many areas of the West to higher surface elevations.

To investigate this, Grant digitized the TOMS data to the state economic area resolution of the Atlas—temporarily omitting state economic areas adjacent to the Mexican border, where mortality rates were paradoxically high for some cancers, possibly due to non-etiological reasons, such as possible transborder migration of cancer cases from Mexico to the U.S. to obtain cancer treatment.

There were 18 anatomic sites of cancer that were inversely associated with UVB irradiance (Table 1) (15). The same study estimated that 17,000 to 23,000 individuals died prematurely from cancer annually in the U.S., due to insufficient UVB and vitamin D (15). This study did not attempt to account for confounders, and it excluded some areas. A further study included analysis of potential confounders on which data for states were available (16). The confounding factors were alcohol consumption, Hispanic heritage, urban/rural residence, poverty level, and, as a proxy for smoking the lung cancer mortality rate (16). All states were included in that study. Thirteen cancer sites were identified as having lower mortality rates in association with higher UVB (vitamin D) status (see Table 1).

A similar study was conducted examining the association of UVB irradiance with cancer mortality rates in black

TABLE 1. Cancer sites with incidence or mortality rates inversely associated with total solar or UVB irradiance, according to ecological studies, by region*

Cancer site or type	North America	Europe	Australia	Asia	Multi-continent
Bladder	(15, 20, 16)				
Breast	(15, 18–20, 16, 96)	(27, 35, 36, 44, 46)	(22)		(97)
Colon	(15, 20, 16)	(35, 36, 46)	(22)	(21, 98)†	
Esophagus	(15, 20, 16)	(27)		(21, 98)	
Gallbladder	(20, 16)	(27)		(21)	
Stomach	(15, 18, 20, 16)		(22)†	(21, 98)†	
Hodgkin's lymphoma	(16)	(45, 49)			
Lung	(15, 18, 99)	(27, 47)			(42)
Multiple myeloma	(20)	(27, 36)			
Non-Hodgkin's lymphoma	(15, 20, 57, 16)	(100)	(58)		
Ovary	(15, 20, 16)		(22)†		(39)
Pancreas	(15, 20, 16)	(27, 36)		(101)	
Prostate	(15, 20, 16, 102)	(36, 44)	(22)		
Rectum	(15, 18, 20, 16)	(27, 36)	(22)†	(21)	
Kidney	(15, 20, 16)			(98)†	(38)
Thyroid	(20)	(27)			
Uterine corpus	(15, 20, 16)	(27			(40)
Vulva	(20)				

*Numbers in parentheses on each line provide the citation number in the reference list.
†Favorable trend, $0.05 < p < 0.10$.

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Americans (17). Solar UVB irradiance was inversely correlated with breast, colon, esophageal, gastric, and rectal cancer, albeit with lower associations than those for white Americans. This finding is consistent with black Americans obtaining less vitamin D from solar UVB irradiance due to darker skin. A characteristically low serum 25-hydroxyvitamin D (calcidiol) level may be one reason that black Americans have generally poorer survival from many types of cancer than white Americans (18).

There have been several other recent ecological studies regarding solar UVB and cancer in the U.S. In one, a death certificate–based case-control study was conducted for female breast, colon, ovarian, prostate, and nonmelanoma skin cancer (NMSC) in association with residential and occupational exposure to sunlight (19). Residential exposure to sunlight was inversely associated with mortality rates from female breast, ovarian, prostate, and colon cancer, but was positively associated with the mortality rate from NMSC. Occupational sunlight exposure was inversely associated with mortality from colon cancer and female breast cancer.

In another study, more than 3 million incident cancer cases during the period 1998–2002 and 3 million cancer deaths between 1993 and 2002 in the continental U.S. were regressed against satellite-derived annual erythemally weighted solar UVB levels (20). Counties were excluded from the analysis if more than one-fifth of the population moved between 1995 and 2000 from an area with an average annual exposure that was different by more than 100 kJ/m^2 per year. Nineteen cancers were found to have inverse correlations with solar UVB (see Table 1) (20). The inverse correlation of solar UVB was about twice as strong for mortality as for incidence rates of breast, colon, other biliary, rectal, and vulvar cancer. This suggests that vitamin D has a greater impact in the latter stages of cancer, which would imply mechanisms such as reduction of angiogenesis and metastasis.

OTHER COUNTRIES

Evidence that solar UVB explains geographic variations in cancer mortality rates in other countries as well continues to mount. In general, latitude is used as the estimate of UVB irradiance in such studies. There were six cancer sites that had higher age-standardized mortality rates at higher solar UVB irradiance levels in Japan (see Table 1) (21). Several cancer sites have higher age-standardized mortality rates at higher latitudes in Australia (Table 1) (22). A possible contribution of greater cosmic ray intensity in circumpolar regions has been mentioned, but this is unlikely to account for the observed latitudinal variation. Although cosmic ray intensity decreases with distance from the poles, it increases with elevation, and lower overall cancer rates have been observed at higher elevations in some studies (23).

We sought an index than might be related to exposure to solar UVB irradiance at the population level: incidence or mortality rates from NMSC. The primary risk factor for squamous cell carcinoma (SCC) is integrated lifetime UVB irradiance (24), whereas that for basal cell carcinoma includes both ultraviolet A (UVA) (320–400 nm) and UVB irradiance resulting in sunburns (24). Approximately 80% of NMSC deaths for fair-skinned people are due to SCC.

Cigarette smoking is also a substantial risk factor for NMSC (25). An adjustment was made for a proxy measure of smoking in a meta-analysis of incidence of second cancers after diagnosis of NMSC. Relative risks for subsequent cancers of cancers of the colon, rectum, and stomach following SCC were less than 1.0 after adjusting for the proxy measure for smoking, with the odds ratio for renal cancer being less than 1.0, but of only borderline statistical significance. After a diagnosis of NMSC, relative risks for cervical, esophageal, gastric, and rectal cancer were significantly less than 1.0; those for colon and gallbladder cancer were less than 1.0 but of only borderline significance (26).

On the basis of these findings, Grant conducted an ecological study of age-standardized cancer mortality rates in Spain, using the regional NMSC mortality rate as a proxy for population-averaged solar UVB during the period 1978–1993, for the 48 continental provinces. Seventeen types of cancer were found to be inversely correlated with this proxy measure of UVB irradiance, including lung cancer and melanoma (27).

To address the possibility that NMSC deaths are so uncommon in Spain that mortality rates of the disease might not be a suitable index of UVB irradiance, additional multiple linear regression analyses were performed that included latitude (and lung cancer, as a proxy for cigarette smoking). NMSC mortality rates remained inversely correlated in both sexes with pleural cancer, and in one sex each for cancers of the brain, breast, colon, esophagus, gallbladder, ovary; Hodgkin's lymphoma, melanoma, and non-Hodgkin's lymphoma (NHL). The finding for melanoma was consistent with a protective effect of solar UVB in populations whose skin pigmentation is well adapted to long-term regional solar UV irradiance (28–31).

MULTICOUNTRY STUDIES

Given the findings for individual countries, lower cancer rates would be expected in all countries with higher UVB irradiance. However, dietary factors also play an important role in variation in cancer risk among countries (8). Therefore, such studies should try, when possible, to account for effects of dietary factors.

In addition, different criteria may also be used for recording cancer incidence (32), and there are different practices regarding cancer screening, and levels of health care provided. These and other effects may complicate any multicountry ecological study of cancer risk–modifying factors. Also, three different indices are used for solar UVB doses in different studies, ranging from latitude to measured annual solar UVB irradiance or dosage.

Skin pigmentation varies with latitude among members of populations living in their ancestral homelands (33); to produce the same level of vitamin D, individuals with very dark skin require about five times the total UVB irradiance as those with fair skin (34).

Several multicountry ecological studies have been performed of the UVB–vitamin D–cancer association. Early studies using latitude as the index of solar UVB doses were reported for breast (35) and multiple cancers (36). Dietary factors were also included in the analyses. In these studies, the countries included in the analysis were restricted geographically to minimize the effect of some potential confounders.

More recently, the University of California, San Diego (UCSD) group has been applying the ecological approach to investigate the global effect of solar UVB doses on cancer incidence rates. In their study of renal cancer, incidence rates for 2002 were obtained from the International Agency for Research in Cancer GLOBOCAN 2002 database (37). 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 analysis in 139 countries that provided dietary data (38). According to multivariate analysis, UVB irradiance was inversely associated with renal cancer incidence rates, whereas percentage of cloud cover and intake of calories from animal sources were independently positively associated.

By using multiple linear regression, one 2006 study on ovarian cancer from the UCSD group examined the association of solar UVB irradiance, stratospheric column ozone, and fertility rates at ages 15–19 years with incidence rates of ovarian cancer in 175 countries in 2002 (39). Age-adjusted ovarian cancer incidence rates generally were highest in countries located at higher latitudes. According to multivariate analysis, UVB irradiance and fertility rates at ages 15–19 years were inversely associated with incidence rates, whereas thickness of the stratospheric ozone layer, which reduces transmission of UVB, was positively associated with incidence (39).

For endometrial cancer, UVB was inversely correlated with incidence, whereas the proportion of overweight women, calories from animal sources, and per capita health expenses were directly correlated (40). This finding underscores the importance of including several risk-modifying factors in the analysis when trying to describe the contribution of solar UVB irradiance.

Multicountry studies allow plotting of estimated age-standardized incidence rates of cancer according to the latitude of the population centroid of each country. The age-standardized estimates provided by GLOBOCAN (37) were based on reports from population-based cancer registries where available and other sources, including hospital-based registries and vital statistics data in areas lacking population-based cancer registries. For most cancer sites studied to date, the plot has the shape of a parabola, with the highest incidence rates in countries located at latitudes most distant from the equator in both hemispheres. There are published examples for cancers of the lung (41), kidney (38), and ovary (39). The curve of age-standardized annual incidence rates of renal cancer by latitude is parabolic in males (Fig. 1) and females (Fig. 2).

SURVIVAL WITH RESPECT TO SEASON OF CANCER DIAGNOSIS

The studies of UVB dose with respect to cancer incidence and mortality rates generally cannot distinguish between effects on cancer prior to the stage where it can be easily detected and the subsequent stage. However, some identified mechanisms whereby vitamin D reduces the risk of cancer include reduction of angiogenesis around tumors and inhibition of metastasis (42, 43).

Studies of cancer survival rates with respect to season of discovery have also disclosed an effect of season on survival. A study of survival rates for breast, colon, and prostate cancer in Norway (44) reported the pioneering work on this topic. Patients diagnosed in the fall had an approximately 30% higher 18-month survival rate than those diagnosed in winter or spring. The Norwegian group has extended this work (45, 46) and has added lung cancer (47) and Hodgkin's lymphoma (48) to cancers showing this effect. Their work is reviewed in Porojnicu et al. (49).

A similar study in England found evidence of substantial seasonality in cancer survival, with diagnosis in summer and fall associated with improved survival compared with that in winter, especially in female breast cancer patients and both male and female lung cancer patients (hazard ratios 0.86 [95% confidence interval {CI} 0.83–0.89], 0.95 [95% CI 0.92–0.97] and 0.95 [95% CI 0.93–0.98], respectively) (50).

EVALUATION OF ECOLOGICAL STUDIES

Five independent reviews of single-country ecological studies of solar UVB irradiance and cancer risk have been conducted recently, two by those actively developing and extending the theory (51–55). All five reviews reported that there is reasonably strong evidence for a beneficial effect of solar radiation, particularly for the more common cancer sites.

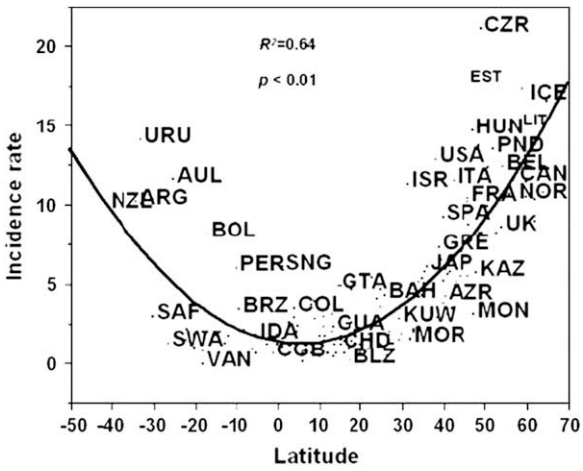

FIGURE 1. Annual standardized incidence rates of renal cancer, by country, males, 2002. *Source*: Mohr et al .(38) based on GLOBOCAN data from the International Agency for Research on Cancer (41). Alphabetical abbreviations are shown where space allows. *Country abbreviations*: AFG Afghanistan, ALB Albania, 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 Côte 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 Serbia 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. (Used with permission from International Journal of Cancer.)

NON-HODGKIN'S LYMPHOMA

There are uncertainties regarding the role of solar UVB and vitamin D in reducing the risk of certain types of cancer. One of these is NHL. Studies at high latitudes generally have found a direct correlation between regional solar UV irradiance and mortality rates (56), whereas studies at lower latitudes generally have reported inverse correlations of regional solar UV irradiance with mortality rates (57, 58). Mortality rates of NHL also are correlated in some regions with mortality rates of melanoma and non-melanoma skin cancer (59). However, it is becoming increasingly apparent that in cases where solar UV irradiance is a factor, UVA is the important part of the spectrum associated with melanoma (60–63), whereas UVB is associated with reduced risk of melanoma in populations whose melanin pigmentation is consistent with the usual UV irradiance of the region (28, 29, 31).

It has been asserted that UVA may contribute to risk of NHL, with immunosuppression as a suspected mechanism (64). Ecological study results, especially in the United States (15, 17, 57, 65) suggest that there may be crossover point near 35°N latitude in the eastern United States where the possible adverse effects of UVA, and the possible beneficial effects of UVB, on risk of NHL are approximately equal. More studies are needed to more fully explore this association.

ASSESSING CAUSALITY

The approach used to establish causality in biological systems involves evaluating the preponderance of the evidence, and applying the criteria for causality in a biological systempostulated by Hill (67). The most relevant of the Hill criteria are strength of association, doseresponse relationship, having accounted for confounding factors, confirmation in different populations and studies, understanding of possible mechanisms, and experimental confirmation, when possible. These criteria are generally satisfied for the favorable association of UVB and vitamin D with invasive cancers (Table 2). The primary element lacking was experimental confirmation (See recent review [68]). The recent Women's Health Initiative study did not find a beneficial effect of 400 IU per day of vitamin D3 supplementation on risk of colon cancer (69).

The recent Women's Health Initiative study did not find a beneficial effect of 400 IU per day of vitamin D_3 supplementation on risk of colon cancer (69). However, this dosage was too low to produce a meaningful increase in

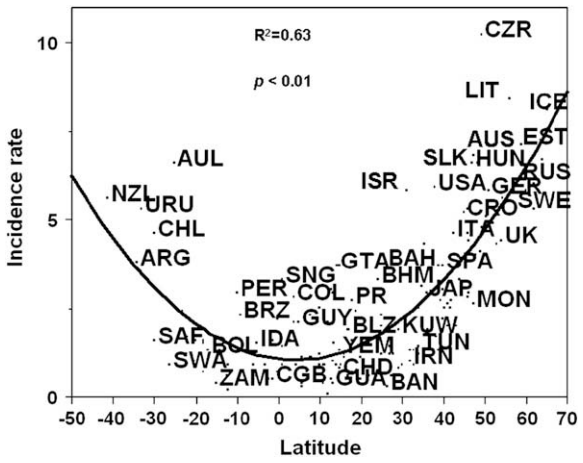

FIGURE 2. Annual standardized incidence rates of renal cancer, by country, females, 2002. *Source*: Mohr et al. (38), based on GLOBOCAN data from the International Agency for Research on Cancer (41). For country abbreviations, see Fig. 1. (Used with permission of the journal.)

serum calcidiol or reduced incidence of colon cancer (70, 71). However, individuals who had high serum calcidiol levels at the outset of the study had 40% lower incidence of colon cancer than those with low levels (72).

A more recent randomized controlled clinical trial by Lappe and her colleagues (73) in Omaha, Nebraska found that intake of 1,100 IU/day of vitamin D3 and 1,450 mg/day of calcium was associated with a 50%–77% reduction in incidence of all cancers combined. About half of the benefit could be attributed directly to vitamin D, and an approximately equal proportion to calcium (73). Dosage is a critical factor in prediction of vitamin D benefits. These findings suggest that any future clinical trials should include at least 2000–4000 IU per day of vitamin D_3 and should ideally include an invention arm that includes both vitamin D_3 and calcium supplementation. This finding supports an earlier prediction that the effect of vitamin D and calcium on cancer is parallel to that of both on incidence and cure of rickets (74).

Ecological studies are the most important foundation of the UVB–vitamin D–cancer theory; they were the basis of all subsequent discoveries. They now encompass data for millions of people in 175 countries that have been studied in a variety of ways. The results of ecological studies have been supported by nested case-control studies of prediagnostic calcidiol levels in major cohorts (70,75), case-control studies (76,77), a limited number of observational studies of oral intake and cancer risk in which oral intake was sufficient (78–81), and laboratory studies of the mechanisms (42,43,82).

RECOMMENDATIONS FOR FURTHER OBSERVATIONAL STUDIES

More observational studies with individuals would be worthwhile. One set of studies would involve measuring serum calcidiol levels at a time preceding cancer diagnosis as well as measures of long-term UV irradiance, such as history of actinic keratosis, skin cancer, skin elasticity, and vacations to sunny areas (26,36,83–86). Another worthwhile study would involve studying cancer survival with respect to serum calcidiol levels at the time of diagnosis; although separating the effects of calcidiol levels from other effects may be difficult.

TABLE 2. Key predictions of the UVB–vitamin D–cancer theory and evidence that they have been satisfied

Factor	Satisfied?	References
Incidence and mortality rates of cancer of many sites are lower in regions where there is higher UVB irradiance on risk.	Yes	(15, 19, 20, 66)
Dark skin pigmentation reduces the beneficial effect of UVB irradiance on risk.	Yes	(15, 18, 66)
Similar associations are found in distinctly different populations.	Yes	Australia (22, 58), China (98), Japan (21, 101), Spain (27)
Survival rates are highest in summer and fall.	Yes	(42, 44–48, 63)
There is an inverse association with biomarkers of exposure to solar UVB irradiance.	Yes	(103)
Dietary intake of vitamin D is associated with reduced risk.	Yes, if sufficient intake	Colon (71, 78), breast (104), ovary (105), melanoma (106), pancreas (107), NHL (108)
Serum calcidiol is associated with reduced risk.	Yes	Colon (75, 109), breast (70, 110), ovary (111)
Long-term population exposure to solar UVB irradiance is associated with lower risk, using NMSC mortality rate as a proxy.	Yes	(26, 27, 83, 84, 86)
Higher incidence and mortality rates in the southern tier of the U.S. cannot be readily accounted for by known potential confounders.	Yes	(17, 18)

NHL = non-Hodgkin's lymphoma.

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SUMMARY

The ecological approach has played an indispensable role in identifying solar UVB as an important risk reduction factor for many types of cancer and providing some indicators of its effect. Although more observational studies should be performed to extend these findings, as well as intervention studies, the findings to date are consistent with having great confidence in the roles of adequate intake of vitamin D_3 and moderate exposure to solar UVB for a few minutes per day in reducing the risk of cancer of many sites, and improving survival rates once cancer is diagnosed.

There are other health benefits of both UVB and vitamin D (87–92), including reduced risk for infectious viral diseases (93, 94). These may substantially outweigh reasonably anticipated adverse effects of a few minutes per day of exposure to sunlight (95). Vitamin D is available from solar UVB, dietary sources, or supplements. The vitamin D status of the population should be increased substantially in order to reduce the incidence rates of cancers of many sites and to improve survival rates at these and other sites.

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REFERENCES

1. Garland C, Garland F. Do sunlight and vitamin D reduce the likelihood of colon cancer? Int J Epidemiol. 1980;9:227–231.
2. Armstrong BK. Commentary: seeing the light. Int J Epidemiol. 2006;35:231–232.
3. Cross HS. Commentary: from epidemiology to molecular biology—vitamin D and colorectal cancer prevention. Int J Epidemiol. 2006;35:225–227.
4. Egan KM. Commentary: sunlight, vitamin D, and the cancer connection revisited. Int J Epidemiol. 2006;35:227–230.
5. Garland CF, Garland FC. Commentary: progress of a paradigm. Int J Epidemiol. 2006;35:220–222.
6. Giovannucci E. Commentary: vitamin D and colorectal cancer—twenty-five years later. Int J Epidemiol. 2006;35:222–224.
7. Grant WB. Dietary links to Alzheimer's disease. Alz Dis Rev 1997;2:42–55 http://www.sunarc.org/JAD97.pdf (accessed January 26, 2009)
8. Armstrong B, Doll R. Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. Int J Cancer. 1975;15:617–631.
9. Grant WB. Dietary links to Alzheimer's disease. Alz Dis Rev. 1997;2:42–55. http://www.sunarc.org/JAD97.pdf (accessed January 26, 2009).
10. Mohr SB. A brief history of vitamin D in cancer prevention. Ann Epidemiol. 2008.
11. Devesa S, Grauman D, Blot W, Pennello G, Hoover R, Fraumeni J Jr. Atlas of cancer mortality in the United States, 1950-94 (NIH Publication No. 99-4564). Bethesda: National Cancer Institute; 1999.
12. Grant WB. Solar ultraviolet radiation and vitamin D as overlooked risk reduction factors for breast cancer. BMJ. 2000 Electronic Letters:321.
13. Leffell DJ, Brash DE. Sunlight and skin cancer. Sci Am. 1996;275:52–53 56–9.
14. Holick M. Photosynthesis of previtamin D3 in human skin and the physiological consequences. Science. 1980;210:203–205.
15. Grant WB. An estimate of premature cancer mortality in the U.S. due to inadequate doses of solar ultraviolet-B radiation. Cancer. 2002;94:1867–1875.
16. Grant WB, Garland CF. 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. 2006;26:2687–2899.
17. 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;19:614–622.
18. Grant WB. Lower vitamin-D production from solar ultraviolet-B irradiance may explain some differences in cancer survival rates. J Natl Med Assoc. 2006;98:357–364.
19. Freedman DM, 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;59:257–262.
20. Boscoe FP, Schymura MJ. Solar ultraviolet-B exposure and cancer incidence and mortality in the United States, 1993–2002. BMC Cancer. 2006;6:264.
21. Mizoue T. Ecological studies of solar radiation and cancer mortality in Japan. Health Phys. 2004;87:532–538.
22. Astbury A. Non uniformity in cancer mortality in the USA and Australia appears to share a common pathway. Triumf report, TRI-PP-05–01. Available at: www.triumf.ca/publications/pub/arch05/pp-05-01.pdf. Accessed July 2, 2008.
23. Weinberg CR, Brown KG, Hoel DG. Altitude, radiation, and mortality from cancer and heart disease. Radiat Res.. 1987;112:381–390.
24. Vitasa BC, Taylor HR, Strickland PT, Rosenthal FS, West S, Abbey H, et al. Association of nonmelanoma skin cancer and actinic keratosis with cumulative solar ultraviolet exposure in Maryland watermen. Cancer. 1990;65:2811–2817.
25. Grant WB. Smoking overlooked as an important risk factor for squamous cell carcinoma. Arch Dermatol. 2004;140:362–363 author reply 363.
26. Grant WB. A meta-analysis of second cancers after a diagnosis of nonmelanoma skin cancer: additional evidence that solar ultraviolet-B irradiance reduces the risk of internal cancers. J Steroid Biochem Mol Biol. 2007;103:668–674.
27. Grant WB. An ecologic study of cancer mortality rates in Spain with respect to indices of solar UVB irradiance and smoking. Int J Cancer. 2007;120:1123–1128.
28. Garland FC, White MR, Garland CF, Shaw E, Gorham ED. Occupational sunlight exposure and melanoma in the U.S. Navy. Arch Environ Health. 1990;45:261–267.
29. Gandini S, Sera F, Cattaruzza MS, Pasquini P, Picconi O, Boyle P, et al. Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. Eur J Cancer. 2005;41:45–60.
30. Boniol M, Doré JF, Autier P, Smans M, Boyle P. Ch. 10 in Ringborg U, Brandberg Y, Breitbart EW, Greinert R. Skin Cancer Prevention. Informa Healthcare. New York. 2007:203–223.
31. Rass K, Reichrath J. UV damage and DNA repair in malignant melanoma and nonmelanoma skin cancer. Adv Exp Med Biol. 2008;624:162–178.
32. Colonna M, Grosclaude P, Faivre J, Revzani A, Arveux P, Chaplain G, et al. Cancer registry data based estimation of regional cancer incidence: application to breast and colorectal cancer in French administrative regions. J Epidemiol Community Health. 1999;53:558–564.

33. Jablonski NG, Chaplin G. The evolution of human skin coloration. J Hum Evol. 2000;39:57–106.
34. Webb AR. Who, what, where and when–influences on cutaneous vitamin D synthesis. Prog Biophys Mol Biol. 2006;92:17–25.
35. Grant WB. An ecologic study of dietary and solar ultraviolet-B links to breast carcinoma mortality rates. Cancer. 2002;94:272–281.
36. Grant WB. Ecologic studies of solar UV-B radiation and cancer mortality rates. Recent Results Cancer Res. 2003;164:371–377.
37. Ferlay J, Bray F, Pisani P, Parkin D. GLOBOCAN 2002: Cancer Incidence, Mortality and Prevalence Worldwide: IARC CancerBase No. 5. version 2.0. Available from: http://www-dep.iarc.fr/. Accessed July 10, 2008.
38. Mohr SB, Gorham ED, Garland CF, Grant WB, Garland FC. Are low ultraviolet B and high animal protein intake associated with risk of renal cancer? Int J Cancer. 2006;119:2705–2709.
39. Garland CF, Mohr SB, Gorham ED, Grant WB, Garland FC. Role of ultraviolet B irradiance and vitamin D in prevention of ovarian cancer. Am J Prev Med. 2006;31:512–514.
40. Mohr SB, Garland CF, Gorham ED, Grant WB, Garland FC. Is ultravioletB irradiance inversely associated with incidence rates of endometrial cancer: an ecological study of 107 countries. Prev Med. 2007;45:327–331. Epub 2007 Feb 4. Also available at: http://www.elsevier.com/wps/find/journaldescription.cws_home/622934/description#description.
41. Mohr SB, Garland CF, Gorham ED, Grant WB, Garland FC. Could ultraviolet B irradiance and vitamin D be associated with lower incidence rates of lung cancer? J Epidemiol Community Health. 2008;62:69–74.
42. van den Bemd GJ, Chang GT. Vitamin D and vitamin D analogs in cancer treatment. Curr Drug Targets. 2002;3:85–94.
43. Krishnan AV, Peehl DM, Feldman D. The role of vitamin D in prostate cancer. Recent Results Cancer Res. 2003;164:205–221.
44. Robsahm TE, Tretli S, Dahlback A, Moan J. Vitamin D3 from sunlight may improve the prognosis of breast-, colon- and prostate cancer (Norway). Cancer Causes Control. 2004;15:149–158.
45. Moan J, Porojnicu AC, Robsahm TE, Dahlback A, Juzeniene A, Tretli S, et al. Solar radiation, vitamin D and survival rate of colon cancer in Norway. J Photochem Photobiol B. 2005;78:189–193.
46. Porojnicu AC, Lagunova Z, Robsahm TE, Berg JP, Dahlback A, Moan J. Changes in risk of death from breast cancer with season and latitude: sun exposure and breast cancer survival in Norway. Breast Cancer Res Treat. 2007;102:323–328.
47. Porojnicu AC, Robsahm TE, Dahlback A, Berg JP, Christiani D, Bruland OS, et al. Seasonal and geographical variations in lung cancer prognosis in Norway. Does Vitamin D from the sun play a role? Lung Cancer. 2007;55:263–270.
48. Porojnicu AC, Robsahm TE, Ree AH, Moan J. Season of diagnosis is a prognostic factor in Hodgkin's lymphoma: a possible role of sun-induced vitamin D. Br J Cancer. 2005;93:571–574.
49. Porojnicu A, Robsahm TE, Berg JP, Moan J. Season of diagnosis is a predictor of cancer survival. Sun-induced vitamin D may be involved: a possible role of sun-induced Vitamin D. J Steroid Biochem Mol Biol. 2007;103:675–678.
50. Lim HS, Roychoudhuri R, Peto J, Schwartz G, Baade P, Moller H. Cancer survival is dependent on season of diagnosis and sunlight exposure. Int J Cancer. 2006;119(7):1530–1536.
51. Garland CF, Garland FC, Gorham ED, Lipkin M, Newmark H, Mohr SB, et al. The role of vitamin D in cancer prevention. Am J Public Health. 2006;96:252–261.
52. Grant WB. Epidemiology of disease risks in relation to vitamin D insufficiency. Prog Biophys Mol Biol. 2006;92:65–79.
53. Krause R, Matulla-Nolte B, Essers M, Brown A, Hopfenmuller W. UV radiation and cancer prevention: what is the evidence? Anticancer Res. 2006;26:2723–2737.
54. Kricker A, Armstrong B. Does sunlight have a beneficial influence on certain cancers? Prog Biophys Mol Biol. 2006;92:132–139.
55. van der Rhee HJ, de Vries E, Coebergh JW. Does sunlight prevent cancer? A systematic review. Eur J Cancer. 2006;42:2222–2232.
56. McKenna DB, Stockton D, Brewster DH, Doherty VR. Evidence for an association between cutaneous malignant melanoma and lymphoid malignancy: a population-based retrospective cohort study in Scotland. Br J Cancer. 2003;88:74–78.
57. Hu S, Ma F, Collado-Mesa F, Kirsner RS. Ultraviolet radiation and incidence of non-Hodgkin's lymphoma among Hispanics in the United States. Cancer Epidemiol Biomarkers Prev. 2004;13:59–64.
58. Hughes A, Armstrong B, Vajdic C, Turner J, Grulich A, Fritschi L, et al. Sun exposure may protect against non-Hodgkin lymphoma: a case-control study. Int J Cancer. 2004;112:865–871.
59. Zhang Y, Holford TR, Leaderer B, Boyle P, Zhu Y, Wang R, et al. Ultraviolet radiation exposure and risk of non-Hodgkin's lymphoma. Am J Epidemiol. 2007;165:1255–1264.
60. Garland C, Garland F, Gorham E. Could sunscreens increase melanoma risk? Am J Public Health. 1992;82:614–615.
61. Garland C, Garland F, Gorham E. Rising trends in melanoma: an hypothesis concerning sunscreen effectiveness. Ann Epidemiol. 1993;3:103–110.
62. Hu S, Federman DG, Ma F, Kirsner RS. Skin cancer and non-Hodgkin's lymphoma: examining the link. Dermatol Surg. 2005;31:76–82.
63. Moan J, Porojnicu AC, Dahlback A, Setlow RB. Addressing the health benefits and risks, involving vitamin D or skin cancer, of increased sun exposure. Proc Natl Acad Sci U S A. 2008;105:668-673.
64. Norval M. The mechanisms and consequences of ultraviolet-induced immunosuppression. Prog Biophys Mol Biol. 2006;92:108–118.
65. Freedman DM, Zahm SH, Dosemeci M. Residential and occupational exposure to sunlight and mortality from non-Hodgkin's lymphoma: composite (threefold) case-control study. BMJ. 1997;314:1451–1455.
66. Grant W, Garland C. 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. 2006;26:2687–2699.
67. Hill AB. The environment and disease: association or causation? Proc R Soc Med. 1965;58:295–300.
68. Grant WB. How strong is the evidence that solar ultraviolet B and vitamin D reduce the risk of cancer? An examination using Hill's criteria for causality. Dermato-Endocrinology. 2009;1:17-24.
69. Wactawski-Wende J, Kotchen JM, Anderson GL, Assaf AR, Brunner RL, O'Sullivan MJ, et al. Calcium plus vitamin D supplementation and the risk of colorectal cancer. N Engl J Med. 2006;354:684–696.
70. Gorham ED, Garland CF, Garland FC, Grant WB, Mohr SB, Lipkin M, et al. Optimal vitamin D status for colorectal cancer prevention: a quantitative meta analysis. Am J Prev Med. 2007;32:210–216.
71. Grant WB, Garland CF. A critical review of studies on vitamin D in relation to colorectal cancer. Nutr Cancer. 2004;48:115–123.
72. Holick MF. Calcium plus vitamin D and the risk of colorectal cancer. N Engl J Med. 2006;354:2287–2288 author reply 2288.
73. Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. Am J Clin Nutr. 2007;85:1586–1591.
74. Garland C, Garland F, Gorham E. Colon cancer parallels rickets. In: Lipkin M, Newmark H, Kelloff G, eds. Calcium, vitamin D, and prevention of colon cancer. Boca Raton: CRC Press; 1991:81–111.
75. Garland CF, Gorham ED, Mohr SB, Grant WB, Giovannucci EL, Lipkin M, et al. Vitamin D and prevention of breast cancer: pooled analysis. J Steroid Biochem Mol Biol. 2007;103:708–711.
76. Lowe LC, Guy M, Mansi JL, Peckitt C, Bliss J, Wilson RG, et al. Plasma 25-hydroxy vitamin D concentrations, vitamin D receptor genotype and breast cancer risk in a UK Caucasian population. Eur J Cancer. 2005;41:1164–1169.

77. Abbas S, Linseisen J, Slanger T, Kropp S, Mutschelknauss EJ, Flesch-Janys D, et al. Serum 25-hydroxyvitamin D and risk of post-menopausal breast cancer—results of a large case-control study. Carcinogenesis. 2008;29:93–99.
78. Garland C, Shekelle RB, Barrett-Connor E, Criqui MH, Rossof AH, Paul O. Dietary vitamin D and calcium and risk of colorectal cancer: a 19-year prospective study in men. Lancet. 1985;1(8424):307–309.
79. Giovannucci E. Vitamin D and cancer incidence in the Harvard cohorts. Ann Epidemiol. 2008 Feb 19. Epub ahead of print.
80. Giovannucci E, Liu Y, Rimm EB, Hollis BW, Fuchs CS, Stampfer MJ, et al. Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. J Natl Cancer Inst. 2006;98:451–459.
81. Gorham ED, Garland CF, Garland FC, Grant WB, Mohr SB, Lipkin M, et al. Vitamin D and prevention of colorectal cancer. J Steroid Biochem Mol Biol. 2005;97:179–194.
82. Lamprecht SA, Lipkin M. Chemoprevention of colon cancer by calcium, vitamin D and folate: molecular mechanisms. Nat Rev Cancer. 2003;3:601–614.
83. de Vries E, Soerjomataram I, Houterman S, Louwman MW, Coebergh JW. Decreased risk of prostate cancer after skin cancer diagnosis: a protective role of ultraviolet radiation? Am J Epidemiol. 2007;165:966–972.
84. Grant WB. The effect of solar UVB doses and vitamin D production, skin cancer action spectra, and smoking in explaining links between skin cancers and solid tumours. Eur J Cancer. 2008;44:12–15.
85. Rukin NJ, Zeegers MP, Ramachandran S, Luscombe CJ, Liu S, Saxby M, et al. A comparison of sunlight exposure in men with prostate cancer and basal cell carcinoma. Br J Cancer. 2007;96:523–528.
86. Tuohimaa P, Pukkala E, Scelo G, Olsen JH, Brewster DH, Hemminki K, et al. Does solar exposure, as indicated by the non-melanoma skin cancers, protect from solid cancers: vitamin D as a possible explanation. Eur J Cancer. 2007;43:1701–1712.
87. Grant WB, Holick MF. Benefits and requirements of vitamin D for optimal health: a review. Altern Med Rev. 2005;10:94–111.
88. Holick MF. High prevalence of vitamin D inadequacy and implications for health. Mayo Clin Proc. 2006;81:353–373.
89. Holick MF. Vitamin D deficiency. N Engl J Med. 2007;357:266–281.
90. Peterlik M, Cross HS. Dysfunction of the vitamin D endocrine system as common cause for multiple malignant and other chronic diseases. Anticancer Res. 2006;26:2581–2588.
91. Zittermann A. Vitamin D and disease prevention with special reference to cardiovascular disease. Prog Biophys Mol Biol. 2006;92:39–48.
92. Zittermann A, Schleithoff SS, Koerfer R. Vitamin D insufficiency in congestive heart failure: why and what to do about it? Heart Fail Rev. 2006;11:25–33.
93. Aloia JF, Li-Ng M. Re: epidemic influenza and vitamin D. Epidemiol Infect. 2007;135:1095–1096 author reply 1097–1098.
94. Cannell JJ, Vieth R, Umhau JC, Holick MF, Grant WB, Madronich S, et al. Epidemic influenza and vitamin D. Epidemiol Infect. 2006;134:1129–1140.
95. Grant W, Garland C, Holick M. Comparisons of estimated economic burdens due to insufficient solar ultraviolet (UV) irradiation/vitamin D and excess solar UV irradiation. Photochem Photobiol. 2005;81:1276–1286.
96. Gorham ED, Garland FC, Garland CF. Sunlight and breast cancer incidence in the USSR. Int J Epidemiol. 1990;19:820–824.
97. Mohr SB, Garland CF, Gorham ED, Grant WB, Garland FC. Relationship between low ultraviolet B irradiance and higher breast cancer risk in 107 countries. Breast J. 2008;14:255–260.
98. Grant WB. Does solar ultraviolet irradiation affect cancer mortality rates in China? Asian Pac J Cancer Prev. 2007;8:236–242.
99. Zhou W, Heist RS, Liu G, Asomaning K, Neuberg DS, Hollis BW, et al. Circulating 25-hydroxyvitamin D levels predict survival in early-stage non-small-cell lung cancer patients. J Clin Oncol. 2007;25:479–485.
100. Smedby KE, Hjalgrim H, Melbye M, Torrang A, Rostgaard K, Munksgaard L, et al. Ultraviolet radiation exposure and risk of malignant lymphomas. J Natl Cancer Inst. 2005;97:199–209.
101. Kinoshita S, Wagatsuma Y, Okada M. Geographical distribution for malignant neoplasm of the pancreas in relation to selected climatic factors in Japan. Int J Health Geogr. 2007;6:34.
102. Hanchette CL, Schwartz GG. Geographic patterns of prostate cancer mortality. Evidence for a protective effect of ultraviolet radiation. Cancer. 1992;70:2861–2869.
103. John EM, Schwartz GG, Koo J, Van Den Berg D, Ingles SA. Sun exposure, vitamin D receptor gene polymorphisms, and risk of advanced prostate cancer. Cancer Res. 2005;65:5470–5479.
104. Nunez C, Carbajal A, Belmonte S, Moreiras O, Varela G. [A case control study of the relationship between diet and breast cancer in a sample from 3 Spanish hospital populations. Effects of food, energy and nutrient intake]. Rev Clin Esp. 1996;196:75–81 Spanish.
105. Salazar-Martinez E, Lazcano-Ponce EC, Gonzalez Lira-Lira G, Escudero-De los Rios P, Hernandez-Avila M. Nutritional determinants of epithelial ovarian cancer risk: a case-control study in Mexico. Oncology. 2002;63:151–157.
106. Millen AE, Tucker MA, Hartge P, Halpern A, Elder DE, Guerry D 4th, et al. Diet and melanoma in a case-control study. Cancer Epidemiol Biomarkers Prev. 2004;13:1042–1051.
107. Skinner HG, Michaud DS, Giovannucci E, Willett WC, Colditz GA, Fuchs CS. Vitamin D intake and the risk for pancreatic cancer in two cohort studies. Cancer Epidemiol Biomarkers Prev. 2006;15:1688–1695.
108. Polesel J, Talamini R, Montella M, Parpinel M, Dal Maso L, Crispo A, et al. Linoleic acid, vitamin D and other nutrient intakes in the risk of non-Hodgkin lymphoma: an Italian case-control study. Ann Oncol. 2006;17:713–718.
109. Garland CF, Comstock GW, Garland FC, Helsing KJ, Shaw EK, Gorham ED. Serum 25-hydroxyvitamin D and colon cancer: eight-year prospective study. Lancet. 1989;2:1176–1178.
110. Bertone-Johnson ER, Chen WY, Holick MF, Hollis BW, Colditz GA, Willett WC, et al. Plasma 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D and risk of breast cancer. Cancer Epidemiol Biomarkers Prev. 2005;14:1991–1997.
111. Tworoger SS, Lee IM, Buring JE, Rosner B, Hollis BW, Hankinson SE. Plasma 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D and risk of incident ovarian cancer. Cancer Epidemiol Biomarkers Prev. 2007;16:783–788.