DERMATO-ENDOCRINOLOGY
2016, VOL. 8, NO. 1, e1137400 (24 pages)
http://dx.doi.org/10.1080/19381980.2015.1137400

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REVIEW

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The role of geographical ecological studies in identifying diseases linked to UVB exposure and/or vitamin D

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ABSTRACT

Using a variety of approaches, researchers have studied the health effects of solar ultraviolet (UV) radiation exposure and vitamin D. This review compares the contributions from geographical ecological studies with those of observational studies and clinical trials. Health outcomes discussed were based on the author's knowledge and include anaphylaxis/food allergy, atopic dermatitis and eczema, attention deficit hyperactivity disorder, autism, back pain, cancer, dental caries, diabetes mellitus type 1, hypertension, inflammatory bowel disease, lupus, mononucleosis, multiple sclerosis, Parkinson disease, pneumonia, rheumatoid arthritis, and sepsis. Important interactions have taken place between study types; sometimes ecological studies were the first to report an inverse correlation between solar UVB doses and health outcomes such as for cancer, leading to both observational studies and clinical trials. In other cases, ecological studies added to the knowledge base. Many ecological studies include other important risk-modifying factors, thereby minimizing the chance of reporting the wrong link. Laboratory studies of mechanisms generally support the role of vitamin D in the outcomes discussed. Indications exist that for some outcomes, UVB effects may be independent of vitamin D. This paper discusses the concept of the ecological fallacy, noting that it applies to all epidemiological studies.

ARTICLE HISTORY
Received 22 December 2015
Accepted 28 December 2015

KEYWORDS
autism; cancer; dental caries; diabetes mellitus type 1; ecological fallacy; ecological study; inflammatory bowel disease; multiple sclerosis; Parkinson disease; sepsis; UV; vitamin D

Introduction

By now a large body of journal literature describes the health benefits of ultraviolet-B (UVB) exposure and vitamin D. The classical role of vitamin D is to help regulate calcium absorption and metabolism. Rickets was the first disease linked to inadequate sun exposure and vitamin D, with highest rates in the early 20th century among those living in crowded and polluted cities where people had little sun exposure.[1] This paper reviews the history of discovery of the role of UVB exposure and/or vitamin D in health outcomes for which geographical ecological studies have been reported, especially those in which such studies played an important role in understanding the role of vitamin D. The goal is to examine the relative contributions of all types of studies in establishing the links as well as to assess the current understanding of the robustness of the links. The motivation is to see whether geographical ecological studies should be given more credit than is generally the case.

Four methods exist to determine whether UVB exposure and vitamin D affect disease outcomes: ecological studies, observational studies, laboratory studies, and clinical trials.

Ecological studies can be of 2 types:

- *Geographical*. Health outcomes and risk-modifying factors are averaged for populations divided along geographical lines.
- *Temporal*. Health outcomes are examined for seasonal variations or trends.

Observational studies come in several forms:

- *Case–control*. Risk-modifying factors measured at the time of disease diagnosis.
- *Cohort and nested case–control*. Subjects are enrolled in a study, risk-modifying factors are assessed, and then the cohort is monitored (for up to many years). Those who develop diseases are compared with like individuals who did not.
- *Cross-sectional*. An entire population is sampled, with health status and health parameters and risk-modifying factors measured.

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Laboratory studies are generally of 3 types:

- *Animal studies*. Animal models of various diseases are challenged with various agents.
- *Detailed cell and tissue analysis*. Cells and tissues from patients can be examined for genetic variations, etc.

In clinical trials, people are enrolled and randomly assigned to take a substance or a placebo for a specified time. The object is to see whether taking the agent yields a better result for the outcome of interest.

Health policy is generally based on clinical trials; however, observational study results are used if, for example, clinical trial results are not available—perhaps due to ethical concerns, such as was the case for linking smoking to lung cancer and other diseases.[2]

Ecological studies have played important roles in understanding how diet affects risk of disease. A 1975 multicountry ecological study linked dietary factors to cancer incidence rates in 23 countries and mortality rates in 32 countries.[3] Meat and animal protein generally had the highest correlation with many cancers common in Western developed countries. This finding was preceded by similar findings such as a study of cancer rates in ethnic groups living in or near Chicago in the early 1900s. People from countries that ate large amounts of meat had high cancer rates, whereas people from countries such as Italy, where people favored pasta, or China, where people ate rice, had low rates of cancer.[4] However, it took many years before the findings of the 1975 study were generally accepted since observational studies involving older people did not confirm the findings. However, researchers eventually realized that diet's effect might be more strongly linked to diet in early life. Therefore, when younger women were used in a study of diet and breast cancer, meat was considered an important risk factor.[5] Observational studies in Uruguay offers strong support for meat as an important risk factor for many cancers.[6] A recent multi-country study involving 157 countries generally confirmed the findings of the 1975 study and added some other factors such as smoking and per capita gross domestic product.[7]

Another example of the value of ecological studies is for Alzheimer disease (AD). The first study linking diet to risk of AD was an ecological one. That study strongly correlated total fat and total energy supply with risk, with fish and cereals/grains inversely correlated.[8] Those results led to observational studies that confirmed the basic findings.[9,10] More recently, I used the ecologic study approach to link the dramatic rise in AD rates in Japan to the nutrition transition from the traditional Japanese diet to the Western diet with a lag of about 25 y[11] Also, national diets with a greater proportion of foods cooked at high temperature such that they have high levels of advanced glycation end products [12] also correlate with AD rates.[13] Two recent reviews underscored the importance of diet in affecting risk of AD.[14,15]

Methods and Data

This is a narrative review, with papers chosen to show how different study types ascertain the role of UVB exposure and vitamin D in reducing risk of adverse health outcomes. The papers cited here were generally found by searching the National Library of Medicine's PubMed database (pubmed.gov) with terms including the name of the condition or disease along with *geographical, latitude, vitamin D, 25-hydroxyvitamin D, ecologic, ecological*, and *mechanisms*.

Results

Infectious diseases

Dental Caries

An account of a latitudinal gradient in missing teeth was reported for those exempted from service in the Union Army during the Civil War, with much higher rates in northern states.[16] It was first demonstrated that vitamin D could reduce the risk of dental caries in the 1920. Mellanby and Pattison reviewed their work on dietary vitamin D and vitamin D_2 supplementation on reducing development and spread of dental caries.[17] They attributed the beneficial effects of vitamin D to higher calcium content of the teeth, but they noted that in the arrested dental caries, the microorganisms appeared "inactive." Vitamin D's role in killing bacteria had, of course, not been identified then, but as good scientists they reported what they saw. Only recently was it realized that vitamin D induced production of cathelicidin, which has antibiotic properties and plays an important role in killing bacteria that cause dental caries.[18] Several ecological studies reported on the relation between dental caries and solar UVB doses in the 1930s (e.g., [19]) and in Oregon in the 1950s (e.g.,, [20]), reviewed in.[18] One paper reported dental rank by state for dental disease (higher rank for greater incidence of dental disease) for 3

groups of US servicemen from 1918 to 1943.[21] A scatter plot of average rank *versus* solar UVB doses for July 1992 showed a rapid decrease in rank from solar UVB doses of 3.5 to 7.0 kJ/m^2 followed by little change thereafter.[18] In the 1920s–1940s, controlled clinical trials of vitamin D to reduce dental caries took place; those studies showed significant beneficial results.[22] Unfortunately, modern dentistry has forgotten these studies.

Mononucleosis

Risk of infectious mononucleosis (IM) has long been known to be linked to that of multiple sclerosis (MS).[23,24] A study in England found that the geographical variation of hospital admissions for IM was similar to that for MS.[25] In addition, incidence of IM was highest in spring in Italy and Norway.[26] Epstein–Barr virus is a risk factor for IM.[27] Vitamin D is very likely to reduce risk of Epstein–Barr virus diseases.[28]

Pneumonia

A 1997 paper proposed that pneumonia incidence among children with rickets in Ethiopia was due to low 25(OH)D concentrations.[29] An ecological study found that solar UVB doses from either summertime or wintertime reduced the fatality rate of influenza during the 1918–1919 pandemic influenza in the US.[30] The mechanisms proposed were that vitamin D induced production of cathelicidin, which has antibiotic properties, and that vitamin D reduced the cytokine storm associated with influenza, thereby reducing damage to the epithelial layer of the lung and reducing risk of bacterial infection. Vitamin D reduces risk of community-acquired pneumonia.[31] However, 1,25-dihydroxyvitamin D [1,25(OH)$_2$D] is the important metabolite of vitamin D in combating community-acquired pneumonia, and some people cannot convert 25(OH)D to 1,25(OH)$_2$D efficiently.[32]

Respiratory Syncytial Virus

A study of weekly incidence of respiratory syncytial virus (RSV) with respect to meteorological conditions found that a 13% reduction in incidence rates could be attributed to UVB doses in Miami, 5% in Buffalo, and 0.5% in Winnipeg, Manitoba.[33] A laboratory study using RSV-infected epithelial cells found that vitamin D decreases the inflammatory response to viral infections in airway epithelium by reducing production of proinflammatory cytokines and chemokines.[34] Cord blood 25(OH)D deficiency was associated with RSV bronchiolitis.[35]

Sepsis

Cathelicidin, which has antibiotic and antiendotoxin effects and is induced by 1,25(OH)$_2$D,[36] has been called an antisepsis molecule.[37] A paper reporting that the seasonal chance of sepsis was highest in the northeastern US [38] was the inspiration for the UVB–vitamin D–sepsis hypothesis.[39] Additional evidence cited included higher rates for black Americans than white Americans, comorbid diseases linked to low 25(OH)D concentrations, and higher rates in urban than in rural regions. A study in Georgia found directly correlated concentrations of cathelicidin with 25(OH)D concentrations for people with sepsis.[40] Low 25(OH)D concentration is now considered causally linked to risk of sepsis.[41] A study in Boston associated 25(OH)D concentrations <25 nmol/L with a multifactor adjusted odds ratio of 1.95 (95% CI =1.22–3.12) for hospital-acquired bloodstream infection.[42] A study in Utah found that having 25(OH)D concentration <37 nmol/L was associated with an odds ratio of 1.89 (95% CI = 1.09–3.31) of developing sepsis.[43] Similar results were found in Graz, Austria.[44]

Cancer

Cancers with Increased Risk from UV Exposure

Researchers generally consider UV exposure to be the primary risk factor for melanoma and nonmelanoma skin cancer (basal cell carcinoma and squamous cell carcinoma). Because conducting trials on humans with UV radiation to see whether they develop skin cancer would be unethical, researchers must use other types of studies—in general, observational studies and ecological studies. Ecological studies have several advantages over observational studies. Those advantages include involving more cases and the use of UV exposure indices that are generally more reliable than those of personal recall. However, occupational exposure to UV is also a good measure.

The first ecological study linking skin cancer to latitude in the US was based on data collected from 10 large metropolitan areas in 1937–1938.[45] The study was repeated, using data from 1947–1948.[46] In that study, age-adjusted skin cancer incidence rates varied from 130 cases/100,000people/yr for females and 190/100,000/yr for males in Birmingham (33.3° N) to

22/100,000/yr for females and 30/100,000/yr for males in Chicago (41.9° N). Skin cancer rates have been inversely correlated with latitude in Chile.[47] Nonmelanoma skin cancer incidence rates were directly correlated with long-term mean daily sunshine hours but not with environmental arsenic or mean household radon levels.[48]

One interesting use of the ecological approach regarding skin cancer was to investigate in various countries how latitude varied among light-skinned people. From the slope of incidence and mortality rates, that study deduced that UVA radiation is more important for melanoma, whereas UVB is clinically more important for basal cell carcinoma and squamous cell carcinoma.[49]

A 1988 ecological study linked salivary gland cancer to UV exposure.[50] Those same authors extended the link to lip cancer by comparing incidence of lip cancer and melanoma for people diagnosed with salivary gland cancer.[51]

An occupational study in Sweden found increased risk of myeloid leukemia (relative risk [RR] = 2.0, 95% confidence interval [95% CI] = 1.1–3.6) and lymphocytic leukemia (RR = 1.7, 95% CI = 0.9–3.2) in the high–UV exposure group; the risk of non-Hodgkin's lymphoma increased nonsignificantly (RR = 1.3, 95% CI = 0.9–1.9).[52] Recently I proposed that UVA may increase the risk of lymphoma by impairing the immune system response, whereas UVB reduces risk; in high-latitude countries the UVA to UVB ratio is higher than that in low-latitude countries.[53]

Both cervical and pharyngeal cancer rates were directly correlated with UV doses for white people in the United States.[54] Both cancers are linked to human papillomavirus. An observational study involved >900,000 consecutive, serially independent, interpretable screening Pap smears obtained by a single cervical cancer screening laboratory in Leiden, Holland, over 16 y from 1983 through 1998. Human papillomavirus activity peaked in August.[55] Those authors later attributed the finding to reduced immune function due to UV exposure.[56]

Cancer with UVB as a Risk-Reduction Factor

Several ecological studies have assessed cancer incidence and/or mortality rates with respect to indices of solar UVB doses. Studies in single midlatitude countries have yielded the best results, in part since the populations are relatively homogeneous or, if not, the variations in ethnic background can be modeled as in the US.[57] Ecological studies reporting inverse correlations between incidence and/or mortality rates for several types of cancer with respect to indices of solar UVB doses, generally with other risk-modifying factors included in the analysis, have been reported for Australia,[58,59] China,[60] France,[61] Spain,[62] and the US.[57,63,64] In addition, a study based on UV exposure by occupation found inverse correlations with the UVB index (lip cancer less lung cancer) for 14 cancers for males and 4 for females.[65]

Ecological studies of cancer incidence and/or mortality rates with respect to geographical variations in solar UVB doses have been crucial to understanding how UVB exposure and vitamin D affect risk for and survival of many cancers. For example, Garland and Garland's 1980 ecological study of colon cancer and annual sunlight[66] led to their dietary vitamin D study in 1985 [67] and their serum 25(OH)D concentration study in 1989.[68] One test of a good scientific hypothesis is whether predictions based on it prove correct, and the 3 papers by the Garland brothers and colleagues serve as an example of prediction and confirmation. In addition, the ecological study extending the UVB–vitamin D–cancer hypothesis to 15 cancers[63] led to an observational study that used "predicted vitamin D" in the Health Professionals Follow-Up Study[69] and analysis of a clinical trial originally designed to study the effect of vitamin D and calcium on risk of osteoporosis.[70] A meta-analysis shows that breast cancer incidence rates are reduced for higher 25(OH)D concentrations as long as follow-up time is considered.[71] For colorectal cancer, a gradual reduction in the effect occurs with increasing follow-up time, whereas for breast cancer, most studies with follow-up times longer than 3 y do not find significant inverse correlations with respect to 25(OH)D concentration. The dichotomy is explained in terms of the much more rapid progression of breast cancer to the point of being detectable. Few other cancers exist for which observational studies based on 25(OH)D concentrations found significant inverse correlations; bladder cancer is one such example.[72] Cancer survival rates are higher for higher 25(OH)D concentrations at time of diagnosis for breast cancer, colorectal cancer, lung cancer, and lymphoma.[73,74]

The mechanisms whereby vitamin D reduces risk of cancer and increases survival are largely known and include effects on cellular differentiation, proliferation

and apoptosis, angiogenesis, metastasis, and inflammation.[75,76]

Some reports find higher risk of cancer at higher 25(OH)D concentrations. The most notable example is prostate cancer, for which a U-shaped relation with 25(OH)D concentration was first reported in 2004.[77] Pancreatic cancer, with direct correlations at high latitudes,[78,79] is another example. The U-shaped 25(OH)D concentration–prostate cancer incidence relation has been confirmed in many studies since 2004 [80] as well as a direct correlation with UVB dose in a study in a high–UVB dose region of Australia.[81] Although the first suggestion that UVB reduced the risk of prostate cancer mortality came from an ecological study,[82] a more recent investigation found that the geographical variation of prostate cancer mortality rate in the US [83] is linked primarily to life expectancy, with rates directly correlated with life expectancy.[84] As for pancreatic cancer, analysis of results from 2 US cohort studies shows that pancreatic cancer incidence rate is inversely correlated with 25(OH)D concentration.[85] Also, ecological studies show inverse correlations between solar UVB doses and pancreatic cancer rates.[76] The likely explanation for the finding of a direct correlation between 25(OH)D concentration and incidence of pancreatic cancer at higher latitudes is that since UVB doses are low, some people started taking vitamin D supplements shortly before enrolling in the study. Support for this hypothesis comes from 2 studies of frailty with respect to 25(OH)D concentration in the US: for women, the relation is U-shaped,[86] whereas for men an inverse relation occurs.[87] Elderly women in the US are much more likely to be advised to take vitamin D supplements than are elderly men. In addition, an analysis of 3.8 million laboratory analyses of 25(OH)D concentration in the US found that for those with $25(OH)D_{total}$ >125 nmol/L, the percentages with $25(OH)D_2$ >10 nmol/L were 76% in the north, 15% in the center, and 9% in the south.[88]

Some disagreement persists over whether vitamin D reduces risk of diseases in general and cancer in particular. The primary reason stated is that clinical trials offer little support for observational studies.[89-93] Such findings led some to suggest that low 25(OH)D concentration is a result of poor health, rather than a cause of it.[89] The primary reason that clinical trials do not provide much support seems to be that they have not been properly designed. Heaney recently outlined guidelines for nutritional trials that apply to vitamin D trials.[94] The key points are as follows:

1. Start with an understanding of the 25(OH)D concentration–health outcome relation.
2. Measure 25(OH)D concentration for prospective participants.
3. Enroll only those with concentrations near the low end of the relation.
4. Supplement with enough vitamin D_3 to raise concentrations to the upper region.
5. Remeasure 25(OH)D concentrations.
6. Make sure that conutrient status is optimized.

A recent review concluded that clinical trials with baseline 25(OH)D concentration <48 nmol/L had a 50% chance of finding a significant reduction in biomarkers of inflammation but that trials with baseline 25(OH)D concentration >50 nmol/L had only a 26% chance.[95] In fact, one vitamin D-plus-calcium clinical trial did show significant reductions in breast and all-cancer incidence rates and nonsignificant reductions in colorectal cancer incidence for people who had not taken vitamin D or calcium supplements before entering the study.[96]

Another way to assess the strength of the UVB–vitamin D–cancer hypothesis is to use results of geographical ecological studies. Ecological studies in mid-latitude countries and an occupational study in Nordic countries find significant inverse correlations between indices of solar UVB doses or exposure and cancer incidence and/or mortality rates for 15–20 types of cancer, often after considering other cancer risk–modifying factors. Therefore, it has to be concluded that UVB exposure reduces the risk of many cancers. UVB exposure is the most important source of vitamin D, which has many cancer-reducing mechanisms.[76] An alternative hypothesis would be that UVB reduces cancer risk through non–vitamin D mechanisms. One animal study found that such mechanisms related to cancer progression might exist, but not those related to cancer incidence.[97] Thus, the UVB–cancer hypothesis does not work without vitamin D.

Table 1 lists key papers supporting beneficial roles of UVB and/or vitamin D, and risk of cancer in historical order. Ecological studies have played key roles since 1941.

There are, of course, a number of studies that reported null or adverse effects of UVB exposure,

Table 1. Key papers supporting beneficial roles of UVB and/or vitamin D in reducing risk of cancer.

Year	Type of study	Finding	Reference
1937	Observational	"Skin irritation" associated with reduced risk of internal cancers	98
1941	Ecological	Inverse correlation of cancer with respect to solar radiation	99
1980	Ecological	Colon cancer morality rate inversely correlated with annual solar radiation; vitamin D suggested as mechanism	66
1981	Laboratory	Differentiation of mouse leukemia cells induced by 1,25-dihydroxyvitamin D	100
1981	Laboratory	1,25-dihydroxivitamin D interacted with vitamin D receptors to reduce melanoma cell growth	101
1985	Observational	Dietary vitamin D and calcium associated with reduced risk of colon cancer	67
1985	Ecological	Direct correlation of latitude with pancreatic cancer mortality rates in Japan	102
1989	Observational	Colon cancer incidence inversely correlated with 25(OH)D concentration in the US	68
1990	Ecological	Breast cancer mortality rate inversely correlated with solar radiation in the US	103
1992	Ecological	Prostate cancer mortality rate found inversely correlated with prostate cancer mortality rate in the US	104
2002	Ecological	15 cancers in the US inversely correlated with July UVB doses	63
2004	Observational	U-shaped 25(OH)D-prostate cancer incidence relation found	77
2006	Ecological	15 cancers in the US inversely correlated with July UVB doses; other risk-modifying factors included	57
2006	Observational	Many cancers inversely correlated with "predicted 25(OH)D concentration"	69
2007	Clinical trial	All-cancer incidence rates significantly reduced with 1100 IU/d of vitamin D_3 and 1500 mg/d of calcium	70
2011	Clinical trial	In women who were not taking personal calcium or vitamin D supplements at randomization, taking calcium plus vitamin D significantly decreased the risk of total, breast, and invasive breast cancers by 14%–20% and nonsignificantly reduced the risk of colorectal cancer by 17%	96
2012	Observational	Better survival rates for cancers of the breast, colon, lung, and lymphoma for higher 25(OH)D concentration at time of diagnosis	73
2012	Ecological?	Outdoor occupation inversely correlated with 15 cancers in Nordic countries	65
2013	Ecological	Review of single-country ecological mechanisms	76
2015	Observational	Meta-analyses of breast and colorectal cancer with respect to 25(OH)D concentration and follow-up time	105

vitamin D intake, or 25(OH)D concentrations on cancer incidence. A few such key papers are listed in Table 2 along with suggested reasons why they failed to find a beneficial effect.

Autoimmune and/or inflammatory diseases

Diabetes Mellitus Type 1

In the 1980s and 1990s it was realized that prevalence of type 1 diabetes mellitus (T1DM) had a latitudinal gradient, with highest rates in Europe in the Nordic countries,[111] lower rates in Italy,[112] and a significant increase with latitude in Sweden.[113] A 7-country study in Europe found that "Vitamin D supplementation was associated with a decreased risk of Type I diabetes without indication of heterogeneity. The Mantel–Haenszel combined odds ratio was 0.67 (95% confidence limits: 0.53, 0.86)."[114] The case was made that vitamin D deficiency was a risk factor for autoimmune diseases, including T1DM, partly on the basis of the geographical variation in prevalence.[115] Shortly thereafter, a study reported that infants at age 1 y in Finland who received 2000 IU/d of vitamin D had a very low risk of developing T1DM compared with the risk of those who did not take vitamin D supplements, whereas those with rickets had a risk of T1DM by age 31 y increased by a factor of 3.[116] Another ecological study in Australia also found a direct correlation between latitude and prevalence of T1DM.[117] A later study in Western Australia found that "There was a strong latitudinal gradient of 3.5% (95% CI, 0.2–7.2) increased risk of T1DM per degree south of the Equator, as averaged across the range 15–35° south. This pattern is consistent with the hypothesis of vitamin D deficiency at higher latitudes. In addition there was a 2.4% (95% CI, 1.3–3.6) average increase in T1DM incidence per year."[118] The observed increase is probably due to the success of the campaign to reduce UV exposure in Australia to try to reduce the incidence of skin cancer and melanoma.[119] A prospective 5.4-year study of US military personnel associated serum 25 (OH)D concentrations >100 nmol/L with a 44% reduced incidence rate of T1DM, compared with concentrations <75 nmol/L.[120] A meta-analysis associated vitamin D supplementation in infancy with reduced risk of T1DM, but no such association existed for maternal vitamin D supplementation during pregnancy.[121]

Inflammatory Bowel Disease: Crohn's Disease and Ulcerative Colitis

An animal model study showed that $1,25(OH)_2D$ prevents and ameliorates symptoms of experimental murine inflammatory bowel disease (IBD).[115] Vitamin

Table 2. Key papers reporting null or adverse effects of UVB and/or vitamin D on cancer incidence.

Year	Type of Study	Finding	Reference	Reason	Reference
2006	Observational	Direct correlation between 25(OH)D concentration and incidence of pancreatic cancer	78	Likely that those with the highest 25 (OH)D concentrations had only recently begun supplementing with vitamin D	
2006	Randomized controlled trial	No effect of 400 IU/d vitamin D_3 plus 1500 mg/d calcium on risk of colorectal cancer	106	Too little vitamin D_3 for those already taking vitamin D or calcium prior to enrolling in study	96
2009	Observational	Direct correlation between 25(OH)D concentration and incidence of pancreatic cancer at higher US latitudes	79	Those with high 25OHD concentrations had only begun supplementation with vitamin D shortly before entering the study	88
2010	Observational	No inverse correlation between 25(OH) D concentration and incidence of rarer types of cancer	107	Long (9 y follow up); too few cases at higher 25(OH)D concentrations	108
2011	Observational	Direct correlation of 25(OH)D concentration with incidence of colon cancer	109	At odds with nearly all other studies on colon cancer; possibly due to long follow-up time	108
2014	Meta-analysis of observational studies	Non-significant effect of 25(OH)D concentrations on incidence of breast cancer	110	Breast cancer develops so rapidly that for follow-up times >3 years, no significant inverse correlation is found	108

D's role in reducing risk of autoimmune disorders, including IBD, was outlined in 2001.[122] Its role in reducing risk of IBD was outlined in 2005.[123] In the United States, rates for Crohn's disease (CD) and ulcerative colitis are highest in the northeast and lowest in the south for children and lowest in the south for adults.[124-126] Colitis caused by the bacterium *Clostridium difficile* is highly correlated with both prevalence and mortality rates by state for CD and ulcerative colitis in the United States, suggesting a pathological link.[126,127] A clinical study found a reduced relapse rate with vitamin D supplementation for those with CD.[128] Predicted 25(OH)D concentration was inversely correlated with incidence of CD.[127] A study in France inversely correlated residential sun exposure with incidence of CD.[129] A meta-analysis found that IBD patients generally have low 25(OH)D concentrations.[130]

Lupus Erythematosus, Cutaneous and Systemic

Systemic lupus erythematosus (SLE) is an autoimmune disease in which the body's immune system mistakenly attacks healthy tissue. SLE can affect the skin, joints, kidneys, brain, and other organs.[131] Cutaneous lupus erythematosus (CLE) manifests as reddening of the skin but may also involve organs and may be associated with SLE.[132] It was known before 1965 that peoplewith lupus had adverse reactions to UV radiation.[133] A US ecological study reported that in 10 selected clusters, lupus mortality rates were higher in northern states than southern states and that Hispanic heritage and poverty explained much of the additional variance.[134] A letter to the editor pointed out that the north–south difference was related to solar UVB doses.[135] The ecological study was later extended with the finding that UVB radiation doses, Hispanic population, and poverty explained more than half of the geographical variation of lupus mortality rates in the 10 clusters.[136] Incidence of lupus nephritis decreases with latitude in China by approximately a factor of 3 from 20° N to 45° N.[137] A study in Hefei, China (32° N) found that SLE activity was lowest in autumn and correlated most strongly with sunshine duration.[138] A recent paper reported that people with SLE have increased risk for many types of cancer.[139] The likely explanation was that people with SLE tend to avoid sun exposure and, as a result, have lower 25(OH)D concentrations.

In addition, 25(OH)D concentration has been inversely correlated with disease activity of CLE[140] and SLE.[141] Thus, supplementing people with lupus with vitamin D would seem sensible.[142] In fact, vitamin D was used to treat lupus as early as 1950.[143] Recent clinical trials have found beneficial effects on disease activity of vitamin D supplementation in CLE patients,[144] in SLE patients in restoring regulatory and effector T-cell balance and B-cell homeostasis,[145] and on inflammatory and hemostatic markers and disease activity.[146]

Multiple Sclerosis

The increase in MS prevalence with latitude has been known for many years.[147,148] The first suggestion that vitamin D deficiency was a possible cause of MS appears to have been made in 1960 by Acheson.[147] Wintertime UVB exposure was more important than summertime UVB exposure in reducing risk of MS in Australia.[149] Vitamin D supplementation reduced MS relapse rates.[150] Munger and colleagues linked low 25 (OH)D concentrations to risk of MS.[151] More recently, a Mendelian randomization study involving a Canadian and an international cohort, only single nucleotide polymorphisms (SNPs) involved in 25(OH)D synthesis or metabolism were strongly inversely correlated with MS susceptibility.[152] Animal studies have found that UV exposure reduces risk of MS in an animal model independently of vitamin D production.[153] Some support exists for an independent role of UVB in human studies in Australia, although it cannot be ruled out that the effects attributed to UVB were not, in fact, due to vitamin D production.[154] A more recent paper from Australia associated reported sun exposure, not 25(OH)D concentration, with reduced depressive symptoms and fatigue for people with MS.[155]

Rheumatoid Arthritis

High-dose vitamin D was used to treat rheumatoid arthritis (RA) in the 1940s.[156] Unfortunately, the dose was often too high, up to 200,000 IU/d for a year, such that hypercalcemia developed.[157] A later study found that oral high-dose $1,25(OH)_2D_3$ had a positive effect on disease activity for 89% of patients.[158] The Iowa Women's Health Study associated higher oral intake of vitamin D with incidence of RA.[159] Several studies have found an inverse correlation between 25(OH)D concentrations and RA activity levels.[160-162] A study in Rome found that people with hypovitaminosis D responded less well to treatment than others, suggesting that vitamin D supplementation would help.[163]

No latitudinal gradient was found for RA prevalence in Australia in 1995.[117] In France, "The highest regional rates of RA were observed in the south (range 0.59–0.66%), and the lowest in the north (range 0.14–0.24%), with a national rate of 0.31% (95% CI 0.18–0.48%).."[164] However, the Nurses' Health Study found a significantly increased risk of incident RA for women living in the northeast US for women aged 30–55 y in 1976 [165] and again based on location in 1988 at an older age.[166] The Nurses' Health Study also associated higher ambient UVB doses with a 21% lower risk of incident RA for women aged 30–55 y in 1976, but not in women aged 25–42 y in 1989.[167] The lack of association for the later study was attributed to increased sun-protective behaviors. Thus, evidence appears to exist for an inverse correlation between incidence or prevalence of RA and solar UVB doses only in the US. Evidently, factors other than UVB exposure and vitamin D play important roles in the etiology of RA and, since the risk factors for RA are not well known, may not have been included in the studies.

Other diseases

Anaphylaxis/Food Allergy

The epidemiological evidence for a role of vitamin D comes largely from studies of the geographical variations in anaphylactic symptoms and seasonality of births among children with food allergies. The first epidemiological study was ecology-based on regional differences in US. EpiPen prescriptions in 2004.[168] The highest rates were in the northeast (8–12 prescriptions/1000 people), whereas the lowest rates were in the southwest (2–3 prescriptions/1000 people). Anaphylaxis rates are inversely correlated with solar UVB doses in the US, which is highest in the southwest and lowest in the northeast.[169,170] The distribution is highly asymmetric for 3 reasons: higher surface elevations and thinner stratospheric ozone layer in the west and higher aerosol and cloud loading in the northeast. The thin ozone layer is due to the prevailing westerly winds crossing the Rocky Mountains and pushing the tropopause higher.

A similar study in Australia found a significant increase in EpiPen prescription rates going from 20° S to 45° S[171]. Because Australia has no mountain ranges, solar UVB doses decrease with increasing latitude. Other factors did not significantly affect the finding. A related study in Australia also found higher use rates of hypoallergenic formula for infants in the southern and eastern regions.[171] A study of visits to US emergency departmentsfor acute allergic reactions found the highest rates in the northeast, with a stronger association seen when the reactions were limited to those caused by food allergy.[172] More recently, a study in Chile also associated increasing latitude and decreasing solar UVB doses with increased risk of anaphylaxis in children.[173] A recent paper reviewed how vitamin

D's immune-modulatory actions on food allergy are related to "the vitamin D receptor and enzymes in monocytes, dendritic cells, epithelial cells, T lymphocytes and B lymphocytes."[174]

Atopic Dermatitis and Eczema

Eczema is an inflammatory condition of the skin characterized by redness, itching, and oozing vesicular lesions which become scaly, crusted, or hardened (www.merriam-webster.com/dictionary/eczema). Atopic dermatitis is the most common of the many types of eczema.

Phototherapy using UVA radiation treated atopic dermatitis in the 1970s,[175] and combination UVA–UVB phototherapy was used in the 1980s.[176] Evidently the search for the risk factors related to UV exposure did not begin until much later. A study in 12 European countries found that the prevalence of eczema symptoms increased with latitude and decreased with mean annual temperature.[177] A study in Italy found that seaside holidays led to complete resolution of atopic dermatitis in 91% of patients, supporting the hypothesis that UV exposure benefited those with the disease.[178] A study of children living on Australia's eastern seaboard found significant higher incidence of eczema in the central and southern regions than in the northern region.[179] A US study involving 91,642 children found significantly increased prevalence of eczema associated with several measures of lower solar UVB dose.[180]

At least 3 clinical trials have examined vitamin D supplementation and atopic dermatitis in adults. Although the 2 conducted in Iran found beneficial effects,[181,182] the one conducted in the US did not.[183] A clinical trial in children in Mongolia found that taking 1000 IU/d of vitamin D_3 for a month in winter reduced the eczema score by about 50%.[44] The successful trials were conducted on populations with low 25-hydroxyvitamin D [25(OH)D] concentration, whereas the unsuccessful trial was conducted on a population with a baseline 25(OH)D concentration of 71 nmol/L. As a study of vitamin D trials on biomarkers of inflammation showed, baseline 25(OH)D concentrations should be below 50 nmol/L to yield a 50% chance of significant effects.[184]

A recent review found that the evidence was inconclusive whether vitamin D status affects the development of atopic eczema.[185] The evidence regarding maternal 25(OH)D concentration and development of infant eczema were considered inconsistent. However, 2 studies did find inverse correlations between cord blood 25(OH)D concentration and infant eczema—one with a mean 25(OH)D concentration of 58.4 nmol/L [186] and the other with 44.5 nmol/L.[187] However, cord blood 25(OH)D concentrations were similar in the studies that did not find an inverse correlation (Table 1 in Ref. [185]).

In summary, UV exposure is inversely correlated with risk of atopic dermatitis and eczema and is used to treat these diseases. Vitamin D trials involving people with low baseline 25(OH)D concentrations reduce the symptoms. Incidence of atopic eczema with respect to cord blood 25(OH)D concentration is mixed, but 25(OH)D concentration after birth might have a greater influence on risk. It cannot be ruled out that non–vitamin D effects of UV exposure can reduce risk and symptoms. However, a search of pubmed.gov found no mechanisms other than vitamin D production that might explain UV phototherapy's mechanism of action.

Attention Deficit Hyperactivity Disorder

The first study reporting a possible relation between attention hyperactivity disorder (ADHD) and vitamin D was a 2013 ecological study.[188] Figure 1 in that paper showed lowest rates of ADHD in the southwest and highest rates in the southeast. It also showed solar radiation for the US with highest intensity in the southwest and lowest in the northeast. The authors considered vitamin D an explanation, but they could not find supporting evidence in the journal literature for either ADHD or autism. Instead, they suggested that bright sunlight disturbed sleep. I pointed out my paper showing that autism prevalence was inversely correlated with solar UVB.[189] The evidence regarding vitamin D was published after that study. A case–control study in Qatar found that children with ADHD had a mean 25(OH)D concentration of 41.5 nmol/L, compared with 58.8 nmol/L for controls.[190] A similar study in Turkey found that children with ADHD had a mean 25(OH)D concentration of 52.3 nmol/L, compared with 87.3 nmol/L for controls.[191] A study in Spain of mother–child pairs found significant inverse correlations between maternal 25(OH)D concentration at 13 weeks' gestation and ADHD symptoms at age 4–5 y[192] Another birth-related study found a greatly increased risk of ADHD for extremely preterm birth in Australia.[193] Maternal vitamin D deficiency is a risk factor for preterm birth.[194] A study in China

found that children with ADHD had a mean 25(OH)D concentration of 42.5 nmol/L, compared with 57.5 nmol/L for controls.[195] Finally, a recent paper proposed a model "whereby insufficient levels of vitamin D, EPA, or DHA, in combination with genetic factors and at key periods during development, would lead to dysfunctional serotonin activation and function and may be one underlying mechanism that contributes to neuropsychiatric disorders and depression."[196] Thus, strong observational evidence indicates that low 25(OH)D concentration is a risk factor for ADHD, along with a model to explain why. However, since most of the studies were cross-sectional, having ADHD may have led to actions that resulted in lower 25(OH)D concentrations. Thus, having clinical trials to show that vitamin D reduces risk of ADHD would be helpful.

Autism

John Cannell proposed that vitamin D reduced risk of autism. He based that assertion in part on higher prevalence of autism in regions with lower sunlight, whether due to latitude or clouds.[197] A later paper reported higher autism rates in regions of the US. West Coast with higher precipitation rates.[198] Children with autism generally have lower 25(OH)D concentrations.[199] Reviews of vitamin D and autism have been published.[200,201] A recent ecological study of autism prevalence among those aged 6–17 y found significant inverse correlations with respect to solar UVB doses.[189] A study in Australia found that maternal 25(OH)D concentration <49 nmol/L at 18 weeks of pregnancy was associated with a significantly increased risk of the offspring being diagnosed with autism.[202] In 2013, Cannell raised the question, Will vitamin D treat the core symptoms of autism?.[203] Several papers have reported that the answer is yes.[80,204] A recent paper reported that parental and child alleles of the vitamin D receptor were significantly correlated with risk of autism, as was, in children, an allele of *CYP2R1*. That gene encodes production of 25-hydroxylase, the enzyme that converts vitamin D to 25(OH)D.[205] A recent paper analyzed how vitamin D could affect risk of autism through its effects on tryptophan and serotonin production.[206]

Lower Back Pain

A study in Great Britain first reported an increase in lower back pain with increasing latitude.[207] Vitamin D deficiency was reported as a risk factor for nonspecific lower back pain in 2003.[208,209] In a study in Saudi Arabia, those with lower back pain treated with vitamin D reported significant reductions in back pain.[208] Data on lumbar pain in Southeast Asian countries indicates an increasing rate from Malaysia (5° N) (8.8%) through 23° N (13%), 32° N (15.8%) to Beijing (40° N) (35%).[210] A letter to the editor linked the findings of the recent global survey of lower back pain [211] to overweight/obesity and vitamin D deficiency.[212] A clinical trial conducted in Israel found that taking 4000 IU/d of vitamin D_3 significantly reduced inflammatory and pain-related cytokines for patients with musculoskeletal pain.[213]

Hypertension

An ecological study found a significant inverse correlation between latitude and hypertension, suggesting that UV radiation reduced blood pressure.[214] Risk of developing hypertension has been found inversely correlated with 25(OH)D concentration.[215,216] Many prospective and cross-sectional studies found that 25(OH)D concentrations were inversely correlated with incidence and prevalence of hypertension for younger, but not elderly, participants.[217] A Mendelian randomization study found a minor effect of vitamin D genes on blood pressure and a 10% reduced risk of hypertension.[218] However, clinical trials offer little support for vitamin D in reducing blood pressure.[219]

An alternative hypothesis is that long-wave UV (UVA) reduces blood pressure, evidently through release of nitric oxide from endothelial nitric oxide synthase [6,220] as well as through other mechanisms.[221] If one combines the findings from the 2 approaches, low 25(OH)D concentrations may be due to UVB exposure, with nitric oxide actually reducing blood pressure.

Parkinson Disease

Using age-adjusted death rate data from1959–1961, Kurtzke and Goldberg found that both white and black Americans had higher Parkinson disease (PD) death rates in northern US states than in southern states.[222] Using mortality rate data for 1988, that study found that the north–south pattern for whites persisted, but not for blacks.[223] What had happened is that black Americans worked less on farms in the south in the latter generation, with many moving north to work in automobile and other factories. The

UVB–vitamin D–PD hypothesis was apparently proposed in part on the basis of the higher rate of PD in the northern states.[224] Outdoor work has also been associated with reduced risk of PD.[225] A 29-year follow-up study in Finland involving 3173 men and women, among whom 50 developed PD, found a relative risk between highest and lowest 25(OH)D quartiles of 0.33 (95% CI = 0.14–0.80).[226] A US study found that people with early-stage PD have lower 25(OH)D concentrations.[227] A study in China found a significant inverse correlation between 25(OH)D concentration and severity of PD.[221]

Rickets

The history of the understanding of rickets was reviewed in.[228] In the 17th century, rickets was due to lack of sunshine caused by living in cities with heavy smog.[229] However, whether this fact was understood then is unclear. The first study of the geographical variation of rickets rates was published in 1890.[230] By 1921, research showed that sunlight and artificial UV could cure rickets[231]—and in 1922, vitamin D was identified as the active agent in preventing rickets.[232]

Table 3 summarizes the major findings regarding geographical variations in disease rates, correlations with 25(OH)D concentrations, clinical trials, and hypotheses regarding UV exposure and vitamin D in keeping with the discussion to this point. In some cases, ecological studies preceded observational studies, such as for autism, several cancers, MS, and RSV, whereas in other cases observational studies came first but ecological studies offered more support for the role of solar UVB and vitamin D in reducing risk of disease. The studies identified are thought to be correct, but there may be some inadvertent omissions.

Ecological Fallacy

Critics often use the term *ecological fallacy* to disparage ecological studies. However, linking that term solely to ecological studies is incorrect. According to the Web Center for Social Research Methods, "The ecological fallacy occurs when you make conclusions about individuals based only on analyses of group data. For instance, assume that you measured the math scores of a particular classroom and found that they had the highest average score in the district."

Table 3. Pioneering studies regarding ecological and observational studies and clinical trials for diseases reviewed in this paper.

Disease	Latitude but vitamin D not identified	Geographical,due to UVB and vitamin D	Hypothesis	25(OH)D	Clinical trial
Infectious					
Dental caries	1965 [233]	1939 [19]	1928 [17]		1928 [17]
Mononucleosis		2011 [25]			
Pneumonia		2009 [30]	1997 [29]		
Respiratory syncytial virus		2007 [33]		2011 [35]	
Sepsis		2009 [39]		1987 [234]	
Cancer, UV as risk factor; skin	1944 [45]				
Lip and salivary gland	1988 [50]				
Cervical and pharyngeal cancer	2104 [54]				
Cancer	1941 [99]		1980 [66]		2007 [70]
Breast		1990 [103]	1989 [235]	2005 [236]	2011 [96]
Colon		1980 [66]	1980 [66]	1989 [68]	2011 [96]
Ovarian		1994 [237]	1994 [237]	2010 [238]	
Pancreatic	1985 [102]	2002 [63]		2006 [69]	
Prostate		1990 [82]	1990 [82]	1993 [239]	
Non-Hodgkin's lymphoma	1996 [240,241]	2002 [63]			
Autoimmune					
Crohn's disease		2007 [124]	2005 [123]		
Diabetes mellitus type 1	1985 [111]	2000 [115]	1997 [242]		
Lupus	2001 [134]	2003 [135]		1995 [243]	2014 [144]
Multiple sclerosis		1960 [147]	1978 [244]	2006 [151]	
Rheumatoid arthritis		2008 [165]		2004 [159].	
Other					
Anaphylaxis		2007 [168]	2007 [168]		
Attention deficit hyperactivity disorder	2013 [188]		2013 [245]	2014 [190]	
Atopic dermatitis		2004 [177]			2011 [181]
Autism		2008 [197]	2008 [197]	2012 [199]	2015 [80 204]
Hypertension		1997 [214]			
Lower back pain	1992 [207]		2003 [208,209]	2003 [208,209]	2015 [213]
Parkinson disease	1988 [222]		2007 [224]	2010 [226]	
Rickets	1890 [230]			1922 [232]	

[http://www.socialresearchmethods.net/kb/fallacy.php]. Other examples exist, such as assuming that various pharmaceutical drugs, which were found to have a significant beneficial effect for the group tested may, in fact, have detrimental effects for some individuals. For example, taking aspirin can reduce the risk of cancer and cardiovascular disease, but doing so entails the risk of internal bleeding.[246] Also, there are about 20 genes that affect about 80 medications or about 7% of FDA-approved medications.[247] The choice of population for any type of epidemiological study may substantially affect the outcome, which could be due to differences in religious practices, diet, lifestyle, and/or genetics. For example, a study recently linked the fact that the Inuit thrive on a high-fat diet to the genetic adaptation of living in a cold environment.[248] Several papers have discussed multilevel analyses, that is, results based on studies of groups and individuals, and how to assess the findings as the basis for public health policies.[249-251]

Discussion

UVB Exposure Benefits Independent of Vitamin D Production

A few recent papers suggest that health benefits of UVB exposure may be independent of or in addition to those from vitamin D production. Some such studies were discussed with respect to outcomes such as MS. While reviewing that body of literature is not the intention, a few of these reviews appear in the following papers.[252-256]

Vitamin D–Sensitive Diseases with Temporal but not Geographical Variations

Some vitamin D–sensitive diseases such as influenza [257] and cardiovascular disease (CVD)[258] have pronounced seasonal variations, generally higher in winter,[257,130] but do not exhibit geographical variations related to solar UVB doses. For influenza, the seasonal variation is due to seasonal variations not only in solar UVB doses [257] but also in temperature and relative humidity.[259] For CVD, significant associations are present with $PM_{2.5}$ particular matter concentrations in the US.[260,261] Although 25(OH)D concentration is inversely correlated with incidence of CVD,[262] the geographical variation of many other CVD-modifying risk factors (such as smoking, diet, physical activity, body mass index, blood pressure, total cholesterol, and fasting glucose) evidently plays a more important role in determining the geographical variation.[263]

Future Applications of the Ecological Approach

Given the advantages of the ecological approach, such as large number of cases and ready availability of public-access data sets for both health outcomes and risk-modifying factors, it should be used more widely. One application might be to identify additional health outcomes related to geographic variations in solar UVB doses. However, a more important application might be to monitor trends in health conditions linked to UV exposure and vitamin D. For example, breast cancer incidence and/or mortality rate patterns in the US have changed dramatically since the 1950s,[83] (http://ratecalc.cancer.gov/), with the characteristic inverse relation to solar UVB dose in July being less pronounced in recent years (http://ratecalc.cancer.gov/). Although some of the factors responsible for changes include mammographic screening and changes in hormone replacement therapy,[264] 25(OH)D concentrations may also have decreased owing to spending more time indoors and using sunscreen when outdoors.[265]

Ecological studies have been used in cancer prevention research for many years, identifying both dietary factors[3,7] and solar UVB/vitamin D [66,76] as important risk-modifying factors and providing estimates of the effects. Although clinical trials are the most appropriate approach for assessing the benefits—if not the risks—of pharmaceutical drugs, they may not be for both diet and UVB/vitamin D. Alan Kristal outlined the problems with clinical trials for cancer prevention. Those problems include appropriate doses, compliance, the long durations required, and personal choice changes due to widely publicized health findings.[266] To his list should also be added the small number of cases due to the costs of large trials, as well as the fact that the population chosen may not be appropriate for assessing the effects on other populations.

Conclusion

Geographical ecological studies of health outcomes with respect to solar UVB doses have made important contributions to the understanding of the roles of UVB exposure and vitamin D in reducing risk of many types of disease. In many cases, ecological

studies were the first to make such connections and leading to other types of studies that confirmed and extended the findings. Such ecological studies will continue to provide useful information such as regarding trends in diseases with respect to changes in UVB exposures and the relative contributions of UVB exposure and other risk-modifying factors in health outcomes.

Disclosure of potential conflicts of interest

I receive funding from Bio-Tech Pharmacal, Inc. (Fayetteville, AR) and the Vitamin D Society (Woodstock, ON, Canada) and have received funding recently from the Vitamin D Council (San Luis Obispo, CA). In the past, I received funding from the UV Foundation (McLean, VA), and the Sunlight Research Forum (Veldhoven).

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