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Cancer protection related to solar ultraviolet radiation, altitude and vitamin D

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SUMMARY

A whole host of epidemiological studies have reported lower cancer rates and mortality in high-altitude regions. These studies are reviewed and discussed in detail. Evidence for the salutary role of vitamin D in protecting against cancer and other maladies will also be reviewed and discussed. The dependence of vitamin D production on sunlight and its enhancement with altitude will be demonstrated. The hypothesis is advanced and developed that the lower cancer rates observed at high altitudes arise from enhanced sunlight-induced vitamin D production levels. Protective vitamin D mechanisms which support this hypothesis as well as other supportive medical evidence are also presented.

Introduction

Our understanding and appreciation of how vitamin D mediates biological responses have entered a new era. Historically, most interest in vitamin D had been relegated to its actions in calcium homeostasis and bone formation. However, over the past few decades new evidence has emerged from laboratory and human studies showing many additional physiological systems in which vitamin D generates positive and important biological responses. These include, amongst others, the immune, heart-cardiovascular, muscle, pancreas, and brain systems; as well as involvement in control of the cell cycle and thus of the disease process of cancer [1]. Reasons have also been advanced which strongly suggest that vitamin D provides protection against low-level radiation damage [2], influenza pandemics [3], as well as exerting salutary control/amelioration of various maladies contributing to human ageing [4].

There are several forms of vitamin D, two of which are of major importance: vitamin D_3 being of primary importance and vitamin D_2 less so. Vitamin D_3 (cholecalciferol) is found in a limited number of natural food sources, but more importantly is produced in the skin by solar ultraviolet (UV) radiation. (As a matter of fact, vitamin D production in nature always appears to require the presence of some ultraviolet light; even vitamin D in foodstuffs is ultimately derived from organisms which are not able to synthesize it except through the action of sunlight at some point in the synthesis chain.) In North America and Europe dietary vitamin D_3 intake is dwarfed by solar-induced D_3 synthesis [5]. The manufacture of vitamin D_3 by sunlight in the skin is extraordinarily rapid and remarkably robust; production after only a few minutes of sunlight easily exceeds dietary sources by an order of magnitude [6]. Vitamin D_2 (ergocalciferol) is found in some plant foods and is manufactured through ultraviolet irradiation of yeast and the plant sterol precursor, ergosterol [7]. Vitamin D_2 has markedly lower and shorter duration of action compared to that of vitamin D_3 [8]. Unless otherwise noted, henceforth vitamin D refers to vitamin D_3.

Increased solar ultraviolet irradiance is directly related to concomitant increased vitamin D production with more than 90% of vitamin D requirements for most individuals arising from casual exposure to sunlight [9]. Lack of sunlight exposure is accepted as an important risk factor for developing vitamin D deficiency and associated metabolic bone diseases such as rickets in children, painful osteomalacia in adults, and osteoporosis in the elderly [10]. Mechanisms by which vitamin D protects against cancer have been proposed. They will be reviewed and discussed. Various epidemiological studies have reported solar ultraviolet associated vitamin D decreases with increased risk for many different cancer types [11,12]. They too will be reviewed and discussed. Altitude, season, time of day, geographic latitude, as well as ozone and aerosol levels are important predictors of environmental ultraviolet radiation [13] and have been used as vitamin D surrogates in various epidemiological studies [14]. As will be developed, solar ultraviolet irradiance and concurrent vitamin D production is enhanced with altitude. Because of both the epidemiological evidence and mechanisms that have been proposed for vitamin D's protection against cancer, altitude-induced vitamin D enhancement would be expected to provide added protection against cancer. It is hypothesized that vitamin D enhancement with altitude produces reduced cancer risk. Reports of decreased cancer rates in high-altitude regions will be reviewed and discussed. These reports lend credence and support to the hypothesis being proposed here: cancer protection arising from altitude-enhanced vitamin D production.

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Mechanisms by which vitamin D protects against cancer

Vitamin D is recognized as being one of the most potent hormones/secosteroids for regulating cell growth [6]. The biologically active form of vitamin D inhibits proliferation and induces differentiation into normally functioning cells. Laboratory studies indicate that it helps to regulate cell growth and prevent cancer progression by reducing angiogenesis, increasing cell differentiation and programmed cell death (apoptosis and autophagy) of cancer cells, and reducing cell proliferation and metastases [15]. In addition to it role in gene regulation, laboratory studies have also shown that vitamin D stabilizes chromosomal structure and offers protection against endogenous- and exogenous-induced chromosomal aberrations, DNA strand breaks, and DNA-carcinogen adducts [16]. Because of the fact that the anticancer action mechanisms of vitamin D are basic to all cancers, it is reasonable to suppose that vitamin D plays an important role in protecting against cancer [2].

Vitamin D production from solar radiation

Ultraviolet radiation is divided into three broad spectral categories: UV-A (320–400 nm), UV-B (280–320 nm), and UV-C (100–280 nm). As already noted, the primary source of vitamin D in humans arises from solar ultraviolet radiation production in the skin. Production critically depends on the quantity (intensity) and quality (appropriate wavelength) of ultraviolet radiation penetrating into the skin. During sunlight exposure, UV-B photons produce robust photolysis of provitamin D_3 (the lanolin cholesterol derivative 7-dehydrocholesterol present in the plasma membranes of both epidermal keratonocytes and dermal fibroblasts) into previtamin D_3. Vitamin D synthesis is confined to the UV-B spectrum since previtamin D_3 production essentially ceases near the UV-A boundary [17], with extreme synthesis sensitivity to the shorter UV-B wavelengths [18]. Once formed previtamin D_3 undergoes rapid thermally-induced transformation to more thermodynamically stable vitamin D_3 (cholecalciferol). Vitamin D_3 exits the skin and is transported in the human circulation bound to plasma carrier proteins, the most prominent being the vitamin D binding protein, DBP [13].

Changes in UV-B radiation at or near the earth's surface do not primarily arise from direct solar irradiance changes. Planetary UV-B irradiance changes primarily arise from changes in solar UV-C photodissociation of atmospheric molecular oxygen. While solar UV-C radiation does not penetrate as far as the earth's surface, it controls high-altitude ozone which in turn controls the amount and changes of UV-B radiation reaching the earth's surface. During one recent 11-year Schwabe solar cycle, solar UV-B only changed by 0.4% whereas solar UV-C changed by 2% [19]. Changes in UV-B radiation at or near the earth's surface depend on many complicated atmospheric absorption and scattering processes. The most significant absorption at UV-B wavelengths is by ozone. Absorption by airborne aerosols such as smoke from forest fires or biomass burning generally has less wavelength-dependent structure and usually increases with decreasing wavelength. Scattering processes in the atmosphere include molecular Rayleigh scattering and scattering by larger particles that comprise clouds and nonabsorbing aerosols [20]. Rayleigh scattering evinces enhanced effects at UV because of its strong inverse wavelength dependence (λ^{-4}) [21].

The variation of planetary UV-B radiation depends on geometric factors (altitude, solar zenith angle, earth–sun distance) and atmospheric factors which in turn depend on altitude [ozone, clouds, small particles such as oxygen and nitrogen molecules, aerosols (locally pronounced in strongly polluted areas, regionally in areas affected by smoke plumes from biomass burning or desert dust, and globally after volcanic eruptions), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and anthropogenic trace gases], and surface albedo. At higher altitudes UV-B radiation travels through less atmosphere and therefore has less of an opportunity to interact with various atmospheric particles. Under cloud-free skies, the most important factors affecting planetary UV-B are stratospheric and tropospheric ozone, Rayleigh molecular scattering, aerosols and, to a lesser extent, NO_2 and SO_2 and other trace gases in the atmosphere of urban areas [22]. Changes in total atmospheric ozone are dominated by how much ozone is in the mid- to lower-stratosphere, with approximately 90% of the atmosphere's total ozone column being located in the stratosphere [23].

Observations of vitamin D production increases with altitude

The strong observational evidence for appreciable increases of solar-induced vitamin D with altitude will be reviewed. As being proposed, such increases are hypothesized to protect against cancer. The altitude effect depends on multiple factors: extinction by ozone, aerosols and clouds and variable atmospheric turbidity associated with air pollution, as well as on Rayleigh molecular scattering and surface and environmental albedos. The evidence will now be reviewed and discussed.

Erythemal-weighted UV irradiance (i.e., "skin-reddening" or "sunburning" irradiance) is often used to characterize the production of vitamin D in the human body. Measurements at 15 North American mid-latitude sites showed an erythemal increase with altitude of ~15% in the first kilometer, but with smaller rates above that level [24]. The rate of increase at lower altitudes was found to be about three times larger than expected for a Rayleigh scattering atmosphere which coupled with the lower increase at higher altitudes indicates the importance of boundary layer extinction by aerosols and tropospheric ozone. Additional wide-ranging erythemal UV altitude gradients have been reported, ranging from 10% to 40% km^{-1} in Germany, 18% km^{-1} between Austria and Switzerland, and 8–10% km^{-1} in South America [25]. These observations may also have been appreciably influenced by boundary layer effects [26]. Caution is warranted regarding the utility of using erythemal-weighted radiation to characterize vitamin D production. Erythemal radiation utilization is problematic since it includes a UV-A component which as already noted does not synthesize vitamin D. Quantitative differences between erythemal and UV-B estimates of vitamin D productions have been published [17,27–29].

More germane observations of explicit UV-B altitude dependence are available. Pronounced UV-B irradiance increases with altitude have been reported in and over the UV-B band: 24% km^{-1} at 300 nm and 11% km^{-1} at 320 nm inside the UV-B band vis-à-vis 9% km^{-1} at 370 nm outside UV-B [30,31]; and under low aerosol conditions 30% km^{-1} at 300 nm and 20% km^{-1} at 320 nm inside the UV-B band vis-à-vis 9% km^{-1} at 400 nm outside UV-B [32]. Additional pronounced UV-B band increases with altitude have also been reported [26]. Such irradiance increases in and over the UV-B band have been attributed to decreased concentrations of atmospheric ozone and gases with altitude. As already noted, Rayleigh gas scattering evinces enhanced effects with decreasing wavelength.

Epidemiological evidence explained by and supporting the hypothesis

Observational evidence will now be presented which strongly indicates that high-altitude regions are marked by decreased cancer rates and mortality. As hypothesized, these observations are explained by increased UV-B irradiance levels at high altitudes. The observational evidence arises from ecological epidemiological

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studies in which populations are treated as entities within geographic confines (whereas case-control and follow-up cohort epidemiological studies use data for individuals), measures of disease outcome and possible influencing factors are found for the populations in the various geographic units, and statistical correlations are determined.

Ecological studies including those being reported here are subject to problems arising from lack of information on exposure (in this case solar UV-B radiation) and disease onset at the individual level, as well as from confounding and other risk factors. Errors resulting when the seemingly natural assumption is made that inferences from an ecological analysis must pertain either to the individuals within the population or to individuals across populations is termed "the ecological fallacy" [33]. Confounding arises when a confounding factor is associated both with the disease under study and the exposure of interest, thus distorting the relationship. The confounding variable must be controlled for in order to obtain an undistorted estimate of the true relationship. The value of an ecological study is enhanced when potential confounding is examined using stratification or regression [34]. The general utility of ecological studies has been discussed [35]. Specific examples of its utility being identification of major dietary links to cancer [36] as well as the association of solar UV-B irradiance with reduced cancer risk [11,37]. Although subject to problems, ecological studies can play an important and productive role in epidemiology since they have the following positive attributes: maximum statistical power and precision since they usually include virtually all cases in a locality; lack of exclusion criteria, volunteer biases, and dropouts; and inclusion of exposures and outcomes at all ages which is of especial value for diseases that develop slowly, such as cancer [38]. It has been argued that in the testing of many hypothesizes that ecological studies perform better than studies of individuals, retrospective (case-control) studies perform better than prospective (cohort) studies, and even that randomized controlled trials (although theoretically supreme and usually regarded as the "gold standard") often do not offer a practical approach to answering many questions [39–41]. An important attribute of ecological studies is their value in identifying or formulating causal hypotheses (but not in hypothesis testing or determining causality) by serving as "beacons" signaling the presence or absence of effects warranting further investigation [42]. The ecological studies being reported here serve as quintessential beacons for formulating the causal hypothesis being presented here. Evidence from seven ecological studies for decreased cancer rates and mortality with altitude will now be presented.

Radon study of 1600 United States counties

A large scale ecological study has reported a clear inverse association between lung cancer rates and average radon levels in homes for 1600 United States counties [43]. A further analysis of that data set which compared lung cancer mortality rates with radon levels at different county elevations above sea level found that altitude stratification reduces by about 50% the overall negative slope of the best fit of lung cancer risk in relation to radon levels [44]. In a follow-up to the latter study it was explicitly stated that the analysis showed lung cancer decreases by 7.5% for every 1260 feet in altitude, a finding also stated to be completely independent of any radon concentration data and of importance to lung cancer epidemiology studies (ecological or otherwise) that derive cases from geographic locations with widely varying altitudes [45].

Cancer death in Rocky Mountain States

Data from the American Cancer Society ("Cancer mortality – 1998") show that age-adjusted overall cancer death rate in three low-altitude Gulf Coast American states are individually all higher than in three high-altitude Rocky Mountain American states, averaging 1.26 times higher [46]. Altitude and concurrent meteorology offers a ready explanation of these results. UV-B radiation west of and over the Rocky Mountains is higher than at the same latitude to the east for two reasons: surface elevations are generally higher in the west leading to reduced atmospheric attenuation via molecular scattering and the stratospheric ozone layer is thinner due to prevailing westerly winds pushing the tropopause up as air masses cross the Rocky Mountains [47,48]. Thus, UV-B has a skewed distribution in the United States, with pronounced east–west asymmetry due to geographic altitude. Various methodological critiques of this study have been responded to [49,50].

Argonne National Laboratory study

The Environmental Statement Project of the Argonne National Laboratory examined and compared various models and predictions of the carcinogenic and genetic hazards of low-level, low-rate ionizing radiation with various populations in the United States and elsewhere [51,52]. Simultaneous regressions of malignancy data with some 40 factors were carried out. These included geographic factors (altitude, temperature, rainfall, etc.), demographic factors (ethnic makeup, life expectancy, urbanization, migration, population growth, etc.), physical factors (medical radiographic exposures, atmospheric pollution, fallout levels, etc.), and socioeconomic factors (personal and family incomes, schooling, unemployment, crime rates, medical facilities, dietary levels, etc.). Analysis of the 50 states of the United States showed not only no increment in malignant mortality with increasing background ionizing radiation, but a consistent and continuous decrement. The high background/lower malignancy in states of the United States were linked to being higher and sunnier, with the declaration that "no observation, or even hypothesizes" were known which would causally link these two factors ("higher and sunnier") with the observed malignancy decreases. As being proposed here, in the interim a hypothesis has become available which provides the causal link between reduced malignancy and altitude: altitude-enhanced vitamin D.

University of Pennsylvania study

A study carried out by the University of Pennsylvania School of Medicine analyzed age-adjusted cancer mortality rates for United States counties averaged over the 20-year period, 1950–1969 [53]. It considered overall cancer mortality rates as well as 34 different site-specific categories. Comparing higher vis-à-vis lower altitude counties and using techniques to minimize confounding due to industrialization, urbanization, or selected cultural characteristics (ethnicity), it was found that for most comparison lower mortality rates were found in higher altitude counties. The largest differences between low- and high-altitude groups were found for cancers of the tongue and mouth, esophagus, larynx, lung, melanoma, and for all cancers combined. These finding were reported to be quite consistent for both males and females, and across virtually all levels of industrialization, urbanization, and ethnicity.

Analyses of UICC and WHO cancer data

Available data on cancer registrations from the International Union Against Cancer (UICC) and cancer deaths from the World Health Organization (WHO) were analyzed for possible correlation of age-specific cancer rates with population-weighted mean altitudes for each region surveyed [54]. Both age-specific cancer incidence and deaths of the six highest and six lowest altitude locations were found to be similar up to about age 60 or 65 years,

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but beyond those ages (where most overall cancer mortality is seen) there were statistically significant reductions in cancer at the higher altitudes.

Analysis of the United States Metropolitan Mortality Report

Mortality data from all cities listed in the United States Metropolitan Mortality Report for 1951–1961 were fitted with models that simultaneously incorporated altitude and background ionizing radiation as predictors of mortality [55]. It was found that uncovered negative correlations of background radiation and mortality from arteriosclerotic heart disease and cancer of the lung, intestine, and breast all disappeared or became positive once altitude was included in the models. In contrast, significant negative correlations with altitude held up even under simultaneous adjustment for background radiation. It was stated that these findings of high-altitude protection against cancer were consistent with findings of other ecological studies.

Leukemia and other cancer studies

Analysis of death certificates, 1950–1969, revealed statistically significant deficits in mortality from cancers other than leukemia in 53 United States counties with most of their land mass above 3000 feet elevation, as well as no increase in leukemia mortality in two high altitudes, highly urban areas [56]. In this study lower mortality rates at high altitudes were attributed to "rurality" rather than to altitude. Analysis of over 500 geographic locations segregated into altitude increments of 400 feet found leukemia mortality to increase slightly with altitude up to 2000 feet, then to decrease significantly with higher altitudes [57].

Summary and conclusions drawn from the epidemiological evidence

Seven ecological epidemiological studies have been presented and discussed. They demonstrate reduced cancer rates and mortality at high altitudes. These epidemiological studies lend credence and support to the hypothesis being proposed here: increased solar-induced UB-V irradiance at high altitudes induce lower cancer rates and mortality.

Discussion and conclusions

It is hypothesized that altitude-enhanced vitamin D explains the fact that high-altitude regions have lower cancer rates and mortality. The ecological epidemiological studies reviewed here serve as "beacons" in support of this hypothesis. The mechanisms whereby vitamin D protects against cancer lend additional credence to this hypothesis.

Alternative explanations have been forwarded to account for the observed reduction in cancer with altitude, including altitude acclimation induced acid–base changes in cancer cell division [54], and for inspired air greater oxidative DNA damage at lower elevations [44] and reduced oxygen pressure at higher altitudes [55]. Nevertheless, the hypothesis being advanced here is supported by other medical evidence. Ecological cardiology studies lend support/credence for the ameliorative/protective effect of altitude-induced vitamin D. These studies indicate that altitude as well as geographic latitude, season, and place of residence (urban or rural) are associated with cardiovascular disease (CVD) mortality, presumably as a result of sunlight exposure and concomitant vitamin D status and control. In most population studies the rate of CVD-related death is lower at high altitudes, elevated at higher latitudes, and increases during winter months; patterns consistent with an adverse effect of lack of essential vitamin D (hypovitaminosis D), which is more prevalent at lower altitude, higher latitudes, and during the winter. Ecological studies reporting an inverse relationship between altitude as a vitamin D surrogate and CVD have been explained as a manifestation of vitamin D control [14,58,59]. The ecological cardiology results and their interpretation are supported by clinical studies which report cross-sectional associations between lower vitamin D levels and prevalent CVD, higher plasma renin activity, and blood pressure [60].

Conflict of interest statement

The author has no financial and personal relationships with other people or organizations that could inappropriately influence (bias) his work.

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References

[1] Norman AW. From vitamin D to hormone D: fundamentals of the vitamin D endocrine system essential for good health. Am J Clin Nutr 2008:491S–9S.
[2] Hayes DP. The protection afforded by vitamin D against low radiation damage. Int J Low Radiat 2008;5:368–94.
[3] Hayes DP. Influenza pandemics, solar activity cycles, and vitamin D. Med Hypotheses 2010;74:828–31.
[4] Hayes DP. Vitamin D and ageing. Biogerontology 2010;11:1–16.
[5] DeLuca HF. Overview of general physiological features and functions of vitamin D. Am J Clin Nutr 2004;80(6 Suppl.):1689S–96S.
[6] Holick MF. High prevalence of vitamin D inadequacy and implications for health. Mayo Clin Proc 2006;81:353–73.
[7] Yetley EA. Assessing the vitamin D status of the US population. Am J Clin Nutr 2008;88:558S–64S.
[8] Houghton LA, Vieth R. The case against ergocalciferol (vitamin D_2) as a vitamin supplement. Am J Clin Nutr 2006;84:694–7.
[9] Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr 2004;80(6 Suppl.):1678S–88S.
[10] Fahrleitner A, Dobnig H, Obernosterer A, et al. Vitamin D deficiency and secondary hyperparathyroidism are common complications in patients with peripheral arterial disease. J Gen Intern Med 2002;7:663–9.
[11] Grant WB. Ecologic studies of solar UV-B radiation and cancer mortality rates. Recent Results Cancer Res 2003;164:371–7.
[12] Mohr SB. A brief history of vitamin D and cancer prevention. Ann Epidemiol 2009;19:79–83.
[13] Holick MF. Environmental factors that influence the cutaneous production of vitamin D. Am J Clin Nutr 1995;61(3 Suppl.):638S–45S.
[14] Zittermann A, Schleithoff SS, Korfer R. Putting cardiovascular disease and vitamin D insufficiency into perspective. Br J Nutr 2005;94:483–92.
[15] Van den Bemd G-JCM, Pols HAP, van Leeuwen JPTM. Anti-tumor effects of 1, 25-dihydroxyvitamin D_3 and vitamin D analogs. Curr Pharm Des 2000;6:717–32.
[16] Chatterjee M. Vitamin D and genomic stability. Mutat Res 2001;475:69–87.
[17] Pope SJ, Holick MF, Mackin S, Godar D. Action spectrum conversion factors that change erythemally weighted to provitamin D_3-weighted UV doses. Photochem Photobiol 2008;84:1277–83.
[18] Kimlin MG, Schallhorn KA. Estimation of the human 'vitamin D' UV exposure in the USA. Photochem Photobiol Sci 2004;3:1067–70.
[19] Rozema J, van Geel B, Bjorn LO, Lean J, Madronich S. Towards solving the UV puzzle. Science 2002;296:1621–2.
[20] Kerr JB. Understanding the factors that affect surface ultraviolet radiation. Opt Eng 2005;44:041002. 1–9.
[21] Loggie BW, Eddy JA. Solar considerations in the development of cutaneous melanoma. Semin Oncol 1988;15:494–9.
[22] Tourpali K, Bias AF, Kazantzakis A, et al. Clear sky UV simulations for the 21st century based on ozone and temperature projections from chemistry-climate models. Atmos Chem Phys 2009;9:1165–721.
[23] Follette-Cook MB, Hudson RD, Nedoluha GE. Classification of northern hemisphere stratospheric ozone and water vapor profiles by meteorological regime. Atmos Chem Phys 2009;9:5989–6003.
[24] McKenzie R, Bodeker G, Scott G, Slusser J, Lantz K. Geographical differences in erythemally-weighted UV measured at mid-latitude USDA sites. Photochem Photobiol Sci 2006;5:343–52.
[25] Herman JR, McKenzie RL, Diaz SB, Kerr JB, Madronich S, Seckmeyer G. Ultraviolet radiation at the earth's surface. In: UNEP/WMO scientific assessment of the ozone layer: 1998, Global ozone research and monitoring project, report no. 44. Geneva, Switzerland: World Meteorological Organization; 1999, p. 9.1–.46.

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[26] McKenzie R, Johnston PV, Smale D. Altitude effects on UV spectral irradiance deduced from measurements at Lauder, New Zealand, and at Mauna Loa Observatory, Hawaii. J Geophys Res 2001;106:22845–60.
[27] Kimlin MG, Olds WJ, Moore MR. Location and vitamin D synthesis: is the hypothesis validated by geophysical data? J Photochem Photobiol B 2007;86:234–9.
[28] Fioletov VE, McArthur LJB, Mathews TW, Marrett L. On the relationship between erythemal and vitamin D action spectrum weighted ultraviolet radiation. J Photochem Photobiol B 2009;95:9–16.
[29] Kazantzidis A, Bias AF, Zempila NM, et al. Calculations of the human vitamin D exposure from UV spectral measurements at three European stations. Photochem Photbiol Sci 2009;8:45–51.
[30] Blumthaler M, Webb AR, Seckmeyer G, Bais AF, Huber M, Mayer B. Simultaneous spectroradiometry: a study of solar UV irradiance at two altitudes. Geophys Res Lett 1994;21:2805–8.
[31] Blumthaler M, Ambach W, Ellinger R. Increase in solar UV radiation with altitude. J Photochem Photobiol B 1997;39:130–4.
[32] Grobner J, Albold A, Blumthaler M, et al. Variability of spectral ultraviolet irradiance in an Alpine environment. J Geophys Res 2000;105:26991–7003.
[33] Piantadosi S, Byar DP, Green S. The ecological fallacy. Am J Epidemiol 1988;127:893–904.
[34] Grant WB, Mohr SB. Ecological studies of ultraviolet B, vitamin D and cancer since 2000. Ann Epidemiol 2009;19:446–54.
[35] Ben-Shlomo Y. Real epidemiologists don't do ecological studies? Int J Epidemiol 2005;34:1181–2.
[36] Armstrong B, Doll R. Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. Int J Cancer 1975;15:617–31.
[37] Grant WB, 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;26:2687–99.
[38] Gorham ED. Personal communication, 2007.
[39] Byers T. The role of epidemiology in developing nutritional recommendations: past, present, and future. Am J Clin Nutr 1999;78(Suppl. 3):559S–69S.
[40] Byers T. What can randomized controlled trials tell us about nutrition and cancer prevention? CA Cancer J Clin 1999;49:353–61.
[41] Shapiro S. Looking at the 21st century: have we learned form our mistakes, or are we doomed to compound them? Pharmacoepidemiol Drug Saf 2004;13:257–65.
[42] Boice JD. Radiation epidemiology: past and present. In: Boice JD, editor. Implications of new data on radiation cancer risk, NCRP proceedings no. 18. Bethesda, MD: National Conference on Radiation Protection and Measurement; 1997, p. 7–28.
[43] Cohen BL. Test of the linear-no threshold theory of radiation carcinogenesis for inhaled radon decay products. Health Phys 1995;68:157–74.
[44] Van Pelt WR. Epidemiological associations among lung cancer, radon exposure and elevations above sea level-A reassessment of Cohen's county level radon study. Health Phys 2003;85:397–403.
[45] Van Pelt WR. Reply to B. Cohen's letter: "The Van Pelt reassessment of our lung cancer vs. radon study". Health Phys 2004;86:318.
[46] Jagger J. Natural background radiation and cancer death in Rocky Mountain States and Gulf Coast States. Health Phys 1998;75:428–30.
[47] Leffell DJ, Brash DE. Sunlight and skin cancer. Sci Am 1996;275(52–3):56–9.
[48] Lubin D, Jensen EH, Gies HP. Global surface ultraviolet radiation climatology from TOMS and ERBE data. J Geophys Res 1998;103:26061–91.
[49] Jagger J. Response to stebbings. Health Phys 1999;76:431–2.
[50] Jagger J. Response to archer. Health Phys 1999;76:694–5.
[51] Frigerio NA, Eckerman KF, Stowe RS. The argonne radiological impact program (ARIP). Carcinogenic hazard from low-level, low-rate radiation, report ANL/ES-26 part I. Argonne, IL: Argonne National Laboratory; 1973.
[52] Frigerio NA, Stowe RS. Carcinogenic and genetic hazard from background radiation. In: International symposium on the biological effects of low-level radiation with special regard to stochastic and non-stochastic effects, IAEA-SM-202/805. Vienna: International Atomic Energy Agency; 1983, p. 385–91.
[53] Amsel J, Waterbor JW, Oler J, Rosenwaike I, Marshall K. Relationship of site-specific cancer mortality rates to altitude. Carcinogenesis 1982;3:461–5.
[54] Burton AC. Cancer and altitude: does intracellular pH regulate cell division? Eur J Cancer 1975;11:365–71.
[55] Weinberg CR, Brown KG, Hoel DG. Altitude, radiation, and mortality from cancer and heart disease. Radiat Res 1987;112:381–90.
[56] Mason TJ, Miller RW. Cosmic radiation at high altitudes and US cancer mortality, 1950–1969. Radiat Res 1974;60:302–6.
[57] Eckhoff ND, Shultis JK, Clack RW, Ramer ER. Correlation of leukemia mortality rates with altitude in the United States. Health Phys 1974;27:377–80.
[58] Faeh D, Gutzwiller F, Bopp M. Swiss National Cohort Study Group. Lower mortality from coronary heart disease and stroke at higher altitudes in Switzerland. Circulation 2009;120:495–501.
[59] Zittermann A, Gummert JF. Sun, vitamin D, and cardiovascular disease. J Photochem Photobiol B 2010 Jan 22 [Epub ahead of print].
[60] Wang TJ, Pencina MJ, Booth SL, et al. Vitamin D deficiency and risk of cardiovascular disease. Circulation 2008;117:503–11.

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