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Progress in Biophysics and Molecular Biology 92 (2006) 140–149
Progress in Biophysics & Molecular Biology
www.elsevier.com/locate/pbiomolbio

Review

Considering the potential benefits as well as adverse effects of sun exposure: Can all the potential benefits be provided by oral vitamin D supplementation?

Robyn M. Lucas[a,*], Anne-Louise Ponsonby[b]

[a]*National Centre for Epidemiology and Population Health (NCEPH), The Australian National University (ANU), Canberra 0200, Australia*
[b]*Murdoch Children's Research Institute, Melbourne, Australia*

Available online 28 February 2006

Abstract

Exposure to ultraviolet radiation (UVR) is associated with both adverse and beneficial health effects. While many of the adverse effects of excessive exposure are well known, the adverse effects of insufficient UVR exposure are less clear-cut, but may include a heightened risk of several cancers and autoimmune disorders as well as of bone diseases such as rickets, osteomalacia and osteoporosis.

Although some of the postulated beneficial effects of UVR exposure may occur through the maintenance of adequate levels of vitamin D, it is not clear that this can account for all of these effects. We briefly review the epidemiological literature with respect to vitamin D, UVR exposure and autoimmune diseases. We further outline alternative pathways, whereby UVR could alter the risk of development of some cancers and autoimmune disorders, independent of effects on vitamin D synthesis.

Recognition of the beneficial effects of UVR exposure has led to a reconsideration of sun avoidance policies. It is important to recognize that all of the beneficial effects of UVR exposure may not occur only through UVR-induced vitamin D synthesis. Thus maintaining current sun avoidance policies while supplementing food with vitamin D may not be sufficient to avoid the risks of insufficient exposure to UVR.

Keywords: Ultraviolet radiation; Vitamin D; Policy; Immunosuppression

Contents

*Corresponding author. Tel.: +61 02 6125 3448; fax: +61 02 6125 5614.
E-mail address: Robyn.lucas@anu.edu.au (R.M. Lucas).

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doi:10.1016/j.pbiomolbio.2006.02.019

1. Introduction

Sun exposure has both beneficial and deleterious effects on human health depending on dose, dietary vitamin D and host responses (Lucas and Ponsonby, 2002). For many years the health focus has been on the hazards of excessive exposure to ultraviolet radiation (UVR)—skin cancers, cataracts of the lens, tumours of the eye and diseases aggravated by UVR-induced immunosuppression, including the reactivation of some latent viruses. Vigorous sun protection programs have been developed and concerns over the adverse effects of excessive sun exposure have prompted global collaboration and stimulated research and research funding.

Skin cancers, particularly cutaneous malignant melanoma (CMM) and basal cell carcinoma, appear to have a long latent period between excessive UVR exposure and clinically evident skin cancer (Gallagher et al., 1995; Kennedy et al., 2003). Thus there will be a long lag before successful sun-safe programs affect skin cancer incidence. There is, however, early evidence from some countries that sun-safe messages are beginning to show an effect on the burgeoning skin cancer rates that prompted their development. In most developed countries, incidence rates for the three UVR-induced skin cancers continue to increase (Stern, 1999). However, recent studies from Australia and Switzerland indicate a decrease in the incidence of non-melanoma skin cancers specifically in those less than 50, despite increases in the overall age-standardized incidence (Staples et al., 1998; Levi et al., 2001). In Canada, Northern Europe, Australia and New Zealand the incidence rates of CMM are plateauing (Bulliard et al., 1999; Marrett et al., 2001; de Vries et al., 2003; Martin and Robinson, 2004). These changes are thought to reflect the effectiveness of sun avoidance programs over the past 50 years (Staples et al., 1998; Bulliard et al., 1999; Marrett et al., 2001). However, the age-standardized incidence rates of CMM in Southern and Eastern Europe are now increasing steeply in all ages (de Vries et al., 2003).

That there should also be adverse health effects due to insufficient UVR exposure seems logical. If variations in skin pigmentation evolved partly under the evolutionary pressure of joint influences to avoid destruction of folate but promote UVR-induced vitamin D synthesis (Jablonski and Chaplin, 2000), then pale skin was an evolutionary adaptation that allowed for optimal survival in low UVR climes, assuming a traditional outdoor lifestyle and diet.

Recently there has been renewed interest in the importance of UVR exposure to human health, but research into beneficial effects is in its infancy. And we should proceed carefully, with due consideration of the need for evidence on all possible pathways, before assuming only particular pathways are important. For example, much of the protective effect of UVR exposure on various diseases is considered to occur via enhanced vitamin D synthesis, with biologically plausible mechanisms of effect. However, we need to carefully consider whether all of the beneficial effects of UVR exposure occur only through vitamin D production. Continuing to advocate current sun avoidance strategies, while adding advice on dietary vitamin D supplementation, should not be assumed to be the optimal course to relieve the hazards associated with insufficient UVR exposure.

Here we briefly review some current evidence for possible beneficial effects of UVR exposure, but omit those related to cancers as they are dealt with elsewhere in this review and to bone health, as these are well-established (Zittermann, 2003). We finish with a brief consideration of some of the arguments for and against dietary vitamin D supplementation in combination with current sun avoidance messages, versus guidance towards appropriate, safe, sun exposure.

2. UVR exposure and autoimmune disorders

The evidence of a beneficial effect of UVR exposure is perhaps stronger for autoimmune disorders than for cancers (as reviewed elsewhere in this volume), but still requires cautious interpretation.

2.1. Multiple sclerosis

Ecological studies show, in general, higher incidence and prevalence of multiple sclerosis (MS) at higher latitudes (McMichael and Hall, 2001; van der Mei et al., 2001). Individual-level studies of sun exposure indicate that higher overall UVR exposure, as evidenced by skin damage (van der Mei et al., 2003) or a history of skin cancer (Goldacre et al., 2004), is inversely associated with the development of MS. In a case control study examining the age span of exposure, the highest magnitude for an inverse association between UVR exposure and MS onset was for winter sun exposure at ages 6–15 years (van der Mei et al., 2003). We might question why this period of 6–15 years is important—is there perhaps an interaction with delayed infection with common infectious diseases (the hygiene hypothesis) (Bach, 2002)? Further, why was wintertime sun exposure important? At the high latitude location of this study (Tasmania, major city is 42°S) wintertime sun exposure might be expected to be insufficient to stimulate marked vitamin D synthesis. However, wintertime sun exposure in childhood does appear to be associated with higher subsequent vitamin D levels in Tasmania (Jones et al., 1999) and possibly serum 25OHD below a threshold is important to consider.

A prospective study has shown supplemental vitamin D, at doses >400 mg/day, to be associated with a reduced risk of MS onset (Munger et al., 2004). Here, the pertinent age of exposure was older—late adolescence and young adulthood. These findings are important to the questions under consideration in this review—is the entire protective effect of UVR exposure working via enhanced vitamin D synthesis, and is dietary vitamin D able to reliably boost serum vitamin D to adequate levels?

2.2. Type 1 diabetes

Ecological studies show a latitudinal gradient with higher incidence at higher latitude (Staples et al., 2003). One cohort and two case control studies have shown that vitamin D given antenatally or during infancy is protective for the development of type 1 diabetes in childhood (Eurodiab, 1999; Stene et al., 2000; Hypponen et al., 2001). To our knowledge no studies have specifically examined the association of UVR exposure history to the risk of type 1 diabetes.

2.3. Rheumatoid arthritis

Latitudinal gradients in the incidence of rheumatoid arthritis are less clear-cut than those for other autoimmune diseases (Staples et al., 2003). However, the Iowa cohort study reported that dietary and supplemental vitamin D intake among older women was associated with a reduced risk of subsequent rheumatoid arthritis (Merlino et al., 2004). Further, intervention trials of vitamin D or vitamin D analogues, such as 1α-vitamin D, on disease activity in patients with rheumatoid arthritis have been reviewed by Zitterman (Zittermann, 2003). Intervention trials with a dosage of 1 μg 1α-vitamin D were not associated with an improved outcome. However, administration of higher amounts of 1α-D or other vitamin D forms was associated with improved pain symptomatology and a significant reduction in C reactive protein, a marker of inflammatory disease activity (Andjelkovic et al., 1999; Zittermann, 2003).

3. UVR exposure modulates the immune system

The immunomodulatory role of sun exposure is also important to consider in other immune disorders. For example, UVB and UVA exposure was associated with improved atopic eczema in a randomized controlled trial (Reynolds et al., 2001). Vitamin D insufficiency has been associated with increased susceptibility to active tuberculosis (Chan, 2000) with greatest risk in those with very low serum 25(OH)D and the *ff* VDR genotype (OR = 5.1, 95%CI 1.4–18.4) (Wilkinson et al., 2000). This finding is consistent with experimental evidence which indicates that 1,25 dihydroxyvitamin D is important to the suppression of intracellular growth of Mycobacterium tuberculosis by mononuclear phagocytes (Rockett et al., 1998).

At present the evidence for a beneficial role of sun exposure in the prevention of cancers and autoimmune diseases is not conclusive. However, population attributable risk estimates (Table 1) indicate that if these

Table 1
Selected examples of attributable risk among those exposed to low UVR or vitamin D for various associated diseases

Health outcome	Exposure categories	Reference category	Attributable risk in the exposed[a]	Population attributable risk (95% CI)[a]	Multivariate adjusted population attributable risk[b]
Breast cancer incidence (Shin et al., 2002)	Total vitamin D intake $\leqslant$500 IU/day	Vitamin D >500 IU/day	0.23	0.20 (0.07–0.33)	0.16
NHL incidence (Smedby et al., 2005)	Never sunbathing at 20 years	Ever sunbathing at 20 years	0.26	0.06 (0.04–0.08)	0.10
Prostate cancer incidence vs BPH (Bodiwala et al., 2003)	Lower 3 quartiles of adult sunbathing score	Highest adult sunbathing score	0.73	0.70 (0.53–0.86)	NA
Colorectal cancer incidence (Tangrea et al., 1997)	Lowest 2 quintiles of vitamin D	Highest 3 quintiles of vitamin D	0.45	0.30 (0.11–0.50)	0.30
CMM mortality (Berwick et al., 2005)	Solar elastosis absent	Solar elastosis present	0.49	0.31 (0.07–0.56)	0.31
Multiple sclerosis incidence (van der Mei et al., 2003)	1–2 h or less sun exposure in summer on leisure days, aged 6–15 years	2–3 h or more in sun per day (summer leisure days) aged 6–15 years	0.59	0.12 (0.05–0.19)	0.12
Type 1 diabetes incidence (Hypponen et al., 2001)	No or irregular vitamin D supplementation in infancy	Regular vitamin D supplements in infancy	0.36	0.06 (−0.03–0.16)	0.06
Rheumatoid arthritis incidence (Merlino et al., 2004)	Lowest tertile of total vitamin D intake	Highest 2 tertiles of total vitamin D intake	0.32	0.14 (0.02–0.25)	0.13

Note: These attributable risks pertain to the statistical association between low UVR or vitamin D and these outcomes; causality has not been established at present. Studies were selected based on the level of information provided to calculate attributable risk.
BPH—benign prostatic hypertrophy.
NHL—Non Hodgkin lymphoma.
[a]Kahn and Sempos (1989).
[b]Bruzzi et al. (1985); Rockhill et al. (1998).

associations were causal in nature, inadequate sun exposure or inadequate vitamin D intake could be important problems at the population level.

4. Beneficial effects of UVR exposure—enhanced vitamin D synthesis may not be the only pathway

It is important to note that vitamin D is not the only pathway whereby UVR exposure might have beneficial effects on human health. Indeed, both MS and type 1 diabetes are more common in those with fair skin (Ziegler et al., 1990; Harrison's Online, 2004)—a phenotype associated with rapid vitamin D synthesis under UVB irradiation (compared to darker skin) (Clemens et al., 1982). Similarly, MS and type 1 diabetes are uncommon in those with deeply pigmented skin (Harrison's Online, 2004)—although people with darker skin residing in higher latitude regions are more likely to have vitamin D deficiency than people with lighter skin (Ponsonby et al., 2002). And there may be critical periods in life where adequate UVR exposure is important, e.g. to risk of MS.

Some possible pathways for beneficial effects of UVR exposure that are likely to be independent of vitamin D synthesis are described below:

1. *Direct immunosuppression by UVR*: Both UVA and UVB have direct immunosuppressive effects in humans (Halliday et al., 2004). UVB appears to upregulate secretion of TNF-α, IL-10 and T regulatory cells,

providing both local and systemic immunosuppression (Ponsonby et al., 2005). T regulatory cells may be particularly important in removing self-reactive T cells that have escaped clonal deletion in the thymus (Sakaguchi et al., 2001), and thus in protecting against the development of autoimmune diseases (Sakaguchi et al., 2001; Rutella and Lemoli, 2004; Ponsonby et al., 2005).

2. *Immunosuppression due to inhibition of melatonin production*: Melatonin is synthesized from tryptophan via serotonin by the pineal gland under the influence of the dark/light cycle, with increased melatonin output over night (approximately 10 fold increase) (Liebmann et al., 1997). Suppression of melatonin secretion is particularly responsive to shorter wavelength blue light (460 nm) (Lockley et al., 2003) and brighter light intensity (Reiter, 1992). Melatonin secretion is associated with increased serum levels of Th-1 cytokines (Maestroni, 2001), and may play an adverse role in autoimmune diseases (due to Th-1 upregulation) (Maestroni, 2001). However, animal evidence suggests that melatonin may slow the progression of some cancers (Liebmann et al., 1997). Serotonin (an intermediate in melatonin synthesis) turnover is also positively associated with the duration and intensity of bright sunlight, and seasonal affective disorder may be related to a lowered turnover of brain serotonin during winter (Lambert et al., 2002). Suppression of melatonin secretion occurs predominantly in response to photoreception in the eye. A recent study has however suggested that the skin may contain UVR-sensitive extraretinal photoreceptors that can upregulate circadian clock genes and thus contribute to circadian rhythm modulation (Kawara et al., 2002) and suppression of melatonin (Brainard et al., 1994). In this way, skin exposure to UVR may modulate melatonin secretion and related cellular immune function.
3. *Calcitonin gene related peptide* (*CGRP*): CGRP is a potent vasodilator and immunomodulator found in cutaneous nerve fibres, in close association with Langerhans cells (LCs) (Seiffert and Granstein, 2002). CGRP release following UVR irradiation inhibits production of IL-2, TNF-α and IFN-γ, stimulates production of IL-10 in macrophages and may inhibit antigen presentation by LCs. Even at non-erythemal doses, CGRP release is associated with impairment of induction of immunity and the development of specific immunological tolerance (Seiffert and Granstein, 2002).
4. *Alpha melanocyte stimulating hormone* (α-*MSH*): UVB irradiation stimulates the production of α-MSH from keratinocytes and melanocytes and upregulation of MC1R mRNA expression and MSH binding activity. α-MSH stimulates melanocytes via activation of the MC1R receptor to proliferate and to produce melanin (Scott et al., 2002; Pichler et al., 2004). MC1R is thus a primary regulator of melanin synthesis; allelic variants of MC1R are over-expressed in individuals with red hair and poor tanning ability and result in loss of function of the receptor (Scott et al., 2002). α-MSH modulates the function of MC1R-expressing antigen presenting cells and monocytes, inhibits T cell production of proinflammatory cytokines such as IFN-γ and antagonizes the effects of IL-6 and IL-1 (Seiffert and Granstein, 2002). IL-10 production by monocytes and keratinocytes is upregulated and this may account for induction of hapten-specific tolerance and systemic immunosuppression (Luger et al., 2003).
5. *Other mechanisms*: the neuropeptide Substance P, released from cutaneous sensory nerve fibres following UV irradiation, induces lymphocyte proliferation and chemotaxis; nitric oxide, co-located with substance P and CGRP in cutaneous sensory nerves may contribute to local immunosuppression. UVR-induced DNA damage and other UVR-related changes can deplete Langerhan's cells (Halliday et al., 1998; Aubin, 2003) and also impair their antigen-presenting function (Aubin, 2003).

Thus, apart from enhanced vitamin D synthesis, there are a number of pathways whereby UV irradiation may affect immune function, with possible subsequent effects on autoimmune disorders and cancers. The clinical outcome of the combined effects of UVA and UVB, taking account of the ratios in which they occur naturally, their relative skin penetrance and the production of vitamin D, remains unclear.

5. Both over- and under-exposure to UVR contribute to disease burden

In a recent assessment of the global burden of disease due to UVR exposure, excessive UVR exposure accounted for 0.1% of the total global burden of disease in DALYs (Lucas et al., 2006). Melanoma and the non-melanoma skin cancers (SCC and BCC) are largely attributable to excessive UVR exposure (PAR = 0.6–0.9, (Armstrong and Kricker, 1993)), although the lack of precision in exposure measurement

in most individual-level studies means that this strong effect may not be evident in these studies (Armstrong and Kricker, 2001). The attributable risk for cataracts and disorders associated with immunosuppression, e.g. reactivation of latent viruses, is difficult to calculate with confidence from the epidemiological literature. But around 20–30% of the burden of disease caused by these diseases may be attributable to excessive UVR exposure (Lucas et al., 2006). Although diseases caused by excessive UVR exposure are extremely common, they tend to occur in older age groups (due both to the long lag between exposure and tumour development or a requirement of cumulative exposure) and be relatively benign, thus incurring a relatively low burden of disease despite their high prevalence.

In contrast, disorders of UVR insufficiency and deficiency affect the young as well as older persons. Vitamin D deficiency causes infantile rickets and both rickets (Lulseged, 1990; Muhe et al., 1997)and subclinical vitamin D deficiency (Wayse et al., 2004) are associated with increased risk of pneumonia and death. Deformities following infantile rickets cause a lasting burden of disease, while osteoporosis and muscle weakness in the elderly contribute to falls and their sequelae, skeletal fractures (Lips, 2001). The burden of disease avoided by maintaining adequate vitamin D levels or adequate levels of sun exposure, even considering only diseases of the musculoskeletal system, is enormous (Lucas et al., 2006). However, Table 1 indicates that if the associations between low vitamin D or low UVR and various additional non-bone outcomes are, in fact, proven to be causal, the proportion of diseased who may have disease due to inadequate levels of these exposures could be high. This makes the issue of the beneficial health effects of UVR exposure an extremely important one to assess further in terms of public health significance.

6. Conclusion

To achieve adequate vitamin D levels, there are arguments for and against policies advocating vitamin D supplementation versus messages encouraging moderate sun exposure. A full discussion of these policy issues is beyond the scope of this paper. However, some of the pertinent issues to be considered are outlined in Box 1.

Box 1
Arguments for and against vitamin D supplementation of food versus liberalizing current sun-safe messages, to avoid health effects of UVR insufficiency.

Arguments for vitamin D supplementation of food:

- Widespread reach to people in the community without them having to take any action, e.g. additional supplements;
- Easy, with the cooperation of industry;
- Should ameliorate those disorders associated with vitamin D insufficiency and deficiency;
- May be particularly important to high risk groups, e.g. the elderly, deeply pigmented persons with limited UVR exposure, indoor-dwellers; or those with a proven susceptibility to the adverse effects of UVR exposure, including persons with a prior history of skin cancer and transplant recipients.

Arguments against vitamin D supplementation of food:

- Cannot be sure what dose is being delivered and who is getting it:
  - If the dose received is insufficient then the problems of vitamin D insufficiency and limited UVR exposure remain, i.e. may not get the benefit of the direct immunosuppressive effects of UVR exposure, which may be important. Although there is supplementation of milk and breakfast cereals (optional) in the US, vitamin D insufficiency is not uncommon (Looker et al., 2002). There are now calls to increase vitamin D fortification of foods (Calvo et al., 2005), including mandatory supplementation of cereal-grain products with vitamin D (Newmark et al., 2004).

- Excessive doses may cause toxicity. But even modest levels within the normal range may be associated with an increased risk of prostate cancer (Tuohimaa et al., 2004). Risk of excessive doses may be increased in individuals who are also taking supplements or vitamin D as medication (in addition to routine dietary supplementation). Long term supplementation may be associated with an adverse blood lipid profile (Heikkinen et al., 1997).

- Is vitamin D the whole story—there may be specific UVR effects that are not mediated via vitamin D adequacy (as outlined in the text).

Arguments for limited (safe) UVR exposure:

- Toxic levels of vitamin D do not occur through UVR exposure (Zittermann, 2003);
- There may be beneficial effects of UVR exposure that are not mediated thru vitamin D;
- Cheap, easy;
- Current sun avoidance messages are probably not appropriate, especially for particular populations, e.g. deeply pigmented persons living at high latitude, but also persons with a largely indoor lifestyle.

Arguments against limited (safe) UVR exposure:

- Difficult to provide advice for optimal individual UVR exposure:
  - Due to skin pigmentation, dietary habits, clothing habits and regional and seasonal variation in ambient UVR;
  - Difficult to establish the (individual) balance between excessive and insufficient exposure;
  - Liberalizing the sun safe message may offer people an excuse to over-expose;
  - Sun exposure/vitamin D levels may be important at particular stages of development (critical periods). This means there needs to be particular care with revised sun exposure messages.

It now seems clear that balanced sun exposure is optimal to human health and also that the point of optimal exposure varies by skin type. For some diseases, an adequate dietary intake of vitamin D may negate the effect of inadequate UVR exposure, but this cannot be assumed to be so for all disorders. This is particularly so for immune disorders because UVR can have important immunomodulatory effects that do not involve vitamin D. Further work on the possible beneficial health effects of UVR and the related pathways is now required.

Acknowledgments

Dr Lucas is supported by a NHMRC Capacity building grant, ''Environment and Population Health: Research Development from Local To Global, 2003-2007'' (No. 224215).

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