Skin Cancer and Vitamin D

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In a striking symmetry, the association of skin cancer and sunlight in sun-soaked sailors, and that of rickets with sun deprivation were both made towards the end of the 19th century [1] [2]. In the 21st century, vitamin D deficiency (the cause of rickets) and skin cancer are again intertwined, linked by sunshine. The World Health Organisation records 2 to 3 million non-melanoma skin cancers and 132,000 melanoma cancers each year [3], although true numbers may be even higher. Incidences are growing, affected by environmental and behavioural changes, and by increasing life expectancies. In 2010, the UK saw 2,203 deaths from malignant melanoma, and 546 from non-melanomas [4]. Simultaneously, rickets rates are rising in Britain [5], and the WHO admits concern over worldwide vitamin D deficiency. The challenge is to reduce deficiency without risking sun overexposure.

Vitamin D synthesis, roles and deficiency

For humans, the most important types of vitamin D are D_2 (received in the diet) and D_3, although there are also types D_1, D_4 and D_5. For this essay's purposes 'vitamin D' means D_3, a steroid-like molecule. Of this, 90% is synthesised in the skin from UVB wavelengths, optimally at 297nm, with diet supplying a small proportion [1]. 7-dehydrocholesterol is converted to pre-vitamin D3, and then hydroxylated twice, in the liver and kidneys, to form active 1,25-dihydroxycholecalciferol. Although UK winter sun provides insufficient UVB for synthesis, storage from summer can supply the deficit [6].

Vitamin D increases calcium reabsorption in the kidneys, and acts via vitamin D-receptors (VDR) on other tissues, including bone, parathyroid gland, and intestine, where it promotes calcium and phosphorus absorption for bone formation and mineralisation [7]. Other functions include

muscle contraction and nerve conduction. Deficiency causes rickets in children - severe cases of which can cause pelvic deformity and reproductive difficulties in females, and osteomalacia and osteoporosis in adults, with resultant heightened risk of falls and fractures. Low levels of vitamin D in winter may have immunological consequences, which may partly explain seasonal fluctuations in viral infections [8]. Vitamin D deficiency may also increase the risk of some cancers, most convincingly colorectal and breast cancers, hypertension, type 2 diabetes, and autoimmune diseases [8]. Vitamin D analogues are prospective anti-cancer agents, having been found to inhibit cancer cell proliferation, prevent angiogenesis and activate apoptosis [9].

A UK cohort study of white adults found vitamin D levels of below-deficiency threshold 25 nmol/L in 15.5% of participants, and below 40 nmol/L in 46.6% [10]. An inner-city hospital study discovered one in four African-Caribbean and one in three Asian adults to have end-of-summer levels below 25 nmol/L [11]. There is concern that recommendations for avoiding sun exposure to reduce skin cancer risk are instead risking vitamin D deficiency, especially in non-white skin types.

Skin cancer and UV

This essay considers those skin cancers for which UV exposure is a significant risk factor: non-melanoma skin cancers - basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs) - and melanomas. UVB radiation causes cross-linking of DNA base pairs, creating genotoxic photoproducts that disrupt DNA replication and transcription and produce mutations in oncogenes and tumour suppressor genes. P53 is particularly important in skin cancer pathogenesis, being present in 90% of SCCs. Interestingly, the UVB tanning response is p53-dependent - targets in the pigmentation pathway may be the basis for future skin cancer prevention [2], which need not affect vitamin D synthesis.

UVA radiation causes cancer indirectly, and is 2-3 times weaker than UVB; absorbed by other chromophores in the skin, it increases generation of DNA-damaging free radicals. UV radiation at the Earth's surface is 95% UVA and 5% UVB, with UVA more abundant farther from the equator [2]. Sunbeds emit high levels of UVA, which photolyses vitamin D [8]: vitamin D synthesis here would be limited, and outweighed by risks of skin cancer.

Strong evidence links non-melanomas to sun exposure, especially exposure resulting in painful sunburn. Chronic UV exposure emerges as the primary cause of SCCs; BCCs seem to be caused by intermittent and chronic exposure; whilst malignant melanoma seems associated with short-term intensive UVR, particularly in childhood [1]. As a result, UK public health initiatives have encouraged people to limit sun exposure, with advice to avoid the hottest sun, cover up and wear sunscreen, and to avoid sunbeds [12]. Some authors, however, have claimed that this advice may be contributing to vitamin D deficiency (e.g. Gillie, 2012).

Skin cancer and vitamin D interactions

A further complication is that vitamin D and cancer pathways may interact. As keratinocytes can produce active vitamin D locally and have VDR, vitamin D can have pro- or anti-skin cancer effects [13]. VDR receptors and vitamin D metabolites may regulate growth characteristics of SCCs, BCCs and melanomas [1], and VDR gene polymorphisms may affect malignant melanoma susceptibility and prognosis [14]. For example, mice without VDR develop increased non-melanomas. In vitro, vitamin D has been found to reduce cyclobutane pyrimidine dimer (CPD) formation from DNA cross-linking caused by UV, improving CPD repair, reducing UVB-induced apoptosis and inducing antioxidants. That said, vitamin D appears to suppress T helper 1 (Th1) responses and so reduces cancer surveillance. In individuals with history of skin cancer there is a relationship between high levels of vitamin D (over 75 nmol/L) and increased risk of BCC and

melanoma (although decreased SCC risk), which may have clinical relevance for skin cancer treatment [13]. However, these findings may be confounded by UV exposure and more research is required, particularly into clinical applications.

Significance

The result of this complex picture is that significant controversy haunts public health recommendations for vitamin D sufficiency. Despite uncertainty around recommended required vitamin D levels, the NHS suggests that below 25 nmol/L is "deficient". Currently, the UK Department of Health recommends supplementation to certain groups at risk: pregnant women, breastfed infants, people aged over 65 and those lacking sun exposure [15]. However, whilst darker skins are mentioned as having higher risk of deficiency, there is no recommendation for supplementation.

Lack of clarity shrouds recommendations for sun exposure. Whilst the NHS website states that *'regularly going out with sunscreen, between the months of April to October, for a few minutes in the middle of the day should provide enough exposure to create sufficient vitamin D*' [15], and there is consensus that sufficient vitamin D synthesis occurs below the threshold of reddening or burning skin, it is not clear whether this information is appropriate for darker skins. Longer sun exposure has no benefit for vitamin D levels [2]. In a 2010 Consensus Vitamin D Position Statement, seven health bodies declared: '*It is impractical to offer a one-size-fits-all recommendation for the amount of sun exposure that people need to make sufficient vitamin D, because this varies according to a number of environmental, physical and personal factors*' [6].

Confusing, sometimes conflicting, information and an energetic media input risks creating public misunderstandings, with adverse health consequences. A BBC news headline from 8th May 2013 (concerning nitric oxide rather than vitamin D) announced: “Sun’s blood pressure benefits ‘may outdo cancer risks’”, accompanied by a picture of a sunbathing couple [16]. While people enjoy sunbathing, share a cultural memory of a ‘healthy tan’, and accord high social value to tanned skin, such reports together with a lack of well-publicised consensus may be used to justify behaviours that increase the risk of skin cancer.

Therefore, the health benefits of vitamin D, when acquired through UV exposure, should be balanced against the risks of skin cancer. Vitamin D requirements have been hard to quantify, and foods are not fortified in the UK. More difficulty exists in clarifying requirements for sun exposure to acquire optimum vitamin D levels, whilst avoiding risky carcinogen-exposure, and especially for darker skins in temperate climates, whilst considering cultural and environmental factors. Many questions remain concerning the association of skin cancer with vitamin D, including disease effects, potential clinical roles, and the balance of the role of supplements and UVR in maintaining healthy vitamin D levels. This is perhaps particularly important for children, who tend to have high rates of vitamin D deficiency [17], but for whom sun exposure may have greater cancer-causing impact.

Overall costs of skin cancer to the NHS, estimated at £71 million in 2002 by research at Imperial College London, are rising in a time of financial pressure, and with an ageing and susceptible population [18]. Better skin cancer prevention, and possible new treatments from better understanding of interaction between vitamin D and skin cancer pathways, will assist dermatological surgery in future treatment, and increase cost-benefits to the population and the profession.

Incomplete and/or conflicting advice may lead to confusion concerning potential risks and benefits of sun-seeking behaviours. Recommendations for sun exposure need to be clear and backed by higher-profile agreement, with specific attention to cancer links, vitamin D sufficiency/deficiency and who is at risk, and the balance between the two. In 1936, in response to observations amongst US Navy personnel of high skin cancer rates against low non-skin cancer incidence, deliberate induction of non-melanoma was advocated to 'vaccinate' against less treatable cancers [19]. Was the preventative mechanism perhaps vitamin D? It is to be hoped that potential benefits of this vitamin can be harnessed without such a pact at the expense of skin health.

Word count (without references) = 1499

References

[1] J. Reichrath, “The challenge resulting from positive and negative effects of sunlight: How much solar UV exposure is appropriate to balance between risks of vitamin D deficiency and skin cancer?,” *Progress in Biophysics and Molecular Biology,* vol. 92, no. 1, pp. 9-16, 2006.

[2] S. Ibrahim and M. Brown, “Tanning and Cutaneous Malignancy,” *Dermatologic Surgery,* vol. 34, no. 4, pp. 460-474, 2008.

[3] WHO, “Skin cancer,” 2013. [Online]. Available: http://www.who.int/uv/faq/skincancer/en/index1.html. [Accessed 29 July 2013].

[4] “Cancer Research UK,” 2013. [Online]. Available: http://www.cancerresearchuk.org/cancer-info/cancerstats/types/skin/. [Accessed 29 July 2013].

[5] S. Ashraf and M. Z. Mughal, “The prevalence of rickets among non-Caucasian children,” *Archives of Diseases of Childhood,* vol. 87, pp. 263-264, 2002.

[6] British Association of Dermatologists, Cancer Research UK, D.iabetes UK, Multiplae Sclerosis Society, National Heart Forum, National Osteoporosis Society and Primary Care Dermatology, “Consensus Vitamin D Position Statement,” 17 December 2010. [Online]. Available: http://www.cancerresearchuk.org/cancer-info/news/archive/cancernews/2010-12-16-Joint-position-statement-issued-to-provide-vitamin-D-clarity-?rss=true. [Accessed 29 July 2013].

[7] B. Lehmann, “The Vitamin D3 Pathway in Human Skin and its Role for Regulation of Biological Processes,” *Photochemistry and Photobiology,* vol. 81, no. 6, pp. 1246-51, 2007.

[8] Yuen and Jablonski, “Vitamin D: In the evolution of human skin cancer,” *Medical Hypotheses,* vol. 74, no. 1, pp. 39-44, 2010.

[9] K. K. Deeb, D. L. Trump and C. S. Johnson, “Vitamin D signalling pathways in cancer: potential for anticancer therapeutics,” *Nature Reviews Cancer,* vol. 7, pp. 684-700, 2007.

[10] E. Hyppönen and C. Power, “Hypovitaminosis D in British adults at age 45y: nationwide cohort study of dietary and lifestyle predictors,” *American Journal of Clinical Nutrition,* vol. 85, no. 3, pp. 860-868, 2007.

[11] L. Ford, V. Graham, A. Wall and J. Berg, “Vitamin D concentrations in an UK inner-city multicultural outpatient population,” *Annals of Clinical Biochemistry,* vol. 43, pp. 468-73, 2006.

[12] NHS, 2013. [Online]. Available: http://www.nhs.uk/Conditions/Cancer-of-the-skin/Pages/Prevention.aspx. [Accessed 29 July 2013].

[13] K. K. Reddy, “Vitamin D Level and Basal Cell Carcinoma, Squamous Cell Carcinoma, and

Melanoma Risk," *Journal of Investigative Dermatology,* vol. 133, pp. 589-592, 2013.

[14] J. A. Halsall, J. E. Osborne, L. Potter, J. H. Pringle and P. E. Hutchinson, "A novel polymorphism in the 1A promoter region of the vitamin D receptor is associated with altered susceptibility and prognosis in malignant melanoma," *British Journal of Cancer,* vol. 91, no. 4, pp. 765-770, 2004.

[15] NHS, 2013. [Online]. Available: http://www.nhs.uk/news/2013/06june/pages/health-claims-about-vitamin-d-examined.aspx. [Accessed 29 July 2013].

[16] B. News, "Sun's blood pressure benefits 'may outdo cancer risks'," 8 May 2013. [Online]. Available: http://www.bbc.co.uk/news/uk-scotland-edinburgh-east-fife-22433359. [Accessed 29 July 2013].

[17] N. J. Shaw and B. R. Pal, "Vitamin D deficiency in UK Asian families: activating a new concern," *Archives of Diseases of Childhood,* vol. 86, pp. 147-149, 2002.

[18] S. Morris, B. Cox and N. Bosanquet, "Cost of skin cancer in England," Tanaka Business School, Imperial College London, 2002.

[19] Peller, "Carcinogenesis as a means of reducing cancer mortality," *Lancet,* vol. 2, pp. 552-556, 1936.

[20] J. Diamond, "Evolutionary Biology: Geography and Skin Cancer," *Nature,* vol. 435, pp. 283-284, 2005.

[21] L. Baldwin and J. Dunn, "Global Controversies and Advances in Skin Cancer," *Asian Pacific Journal of Cancer Prevention,* vol. 14, no. 4, pp. 2155-2157, 2013.

[22] J. H. Davies and N. J. Shaw, "Preventable but no strategy: vitamin D deficiency in the UK," *Archives of Disease in Childhood,* vol. 96, pp. 614-615, 2011.

[23] O. Gillie, "Royal Pharmaceutical Society Blog," 2012. [Online]. Available: http://blog.rpharms.com/england/2012/02/07/vitamin-d-deficiency-in-babies-in-uk/. [Accessed 29 July 2013].

[24] "Consensus Vitamin D Position Statement," 2013. [Online].

[25] WHO, 2013.

[26] S. Morris, B. Cox and N. Bosanquet, "Cost of skin cancer in England," 2002. [Online]. Available: http://www3.imperial.ac.uk/pls/portallive/docs/1/43013.PDF. [Accessed 30 July 2013].