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Vitamin D Synthesis May Be Independent of Skin Pigmentation Only with UV of Short Wavelength

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TO THE EDITOR

Bogh *et al.* (2010) found that accumulation of 25-hydroxyvitamin D is not affected by skin pigmentation. I would like to point to a possible explanation to the seeming contradiction between their results and those of many observational investigations, which have found that vitamin D status is better and vitamin D production proceeds more readily in people with fairer skin.

Bogh *et al.* (2010) measured the increase of plasma 25-hydroxyvitamin D caused by unfiltered radiation from Philips TL12 lamps containing very shortwave components, including a significant component at wavelengths <290 nm. Such radiation is efficiently absorbed by 7-dehydrocholesterol (7-DHC, provitamin D_3) in the upper epidermis, outside the most pigmented skin layer. Daylight, on the other hand, contains effectively no radiation below 290 nm. The transmission of the stratum corneum can exceed 90% at 300 nm and increases with wavelength (Philp and Allcock, 1989), so some previtamin D_3-producing radiation, even that of very short wavelength, can reach the outer epidermal layers. The stratum granulosum does not contain much melanin, but some provitamin D_3, which can therefore be converted to previtamin D, even in heavily pigmented individuals.

Compared with light-skinned people living at the same latitude, dark-skinned persons generally have lower vitamin D status. The spring rise in vitamin D status is also lower in dark-skinned people (Harris and Dawson-Hughes, 1998). Exposure of isolated human skin to summer sunlight and exposure *in vivo* of humans to sunbeds simulating sunlight showed that Caucasian skin is more efficient at forming previtamin D_3 than is African American skin (Armas *et al.*, 2007; Chen *et al.*, 2007).

The radiation spectra of the lamps used by Bogh *et al.* (2010) and Armas *et al.* (2007) are shown in Figure 1, together with a daylight spectrum calculated for the conditions of Chen *et al.* (2007) in their daylight experiment. It can be seen that Bogh *et al.* (2010), who did not find any effect of pigmentation, used treatments with a larger proportion of short-wave UV radiation than did Armas *et al.* (2007) and Chen *et al.* (2007), who found such an effect.

Figure 2 shows an absorption spectrum (in relative units) for the previtamin D_3 precursor, 7-DHC, together with transmission spectra for human stratum corneum and epidermis redrawn from Bruls *et al.* (1984). 7-DHC occurs throughout the epidermis (Holick *et al.* (1980) found 58, 393, and 303 ng cm^{-2} in the stratum corneum + granulosum, stratum spinosum, and stratum basale, respectively). Short-wavelength radiation does not penetrate far into the epidermis, but can efficiently convert the 7-DHC in the superficial layers, as

Abbreviation: 7-DHC, 7-dehydrocholesterol (provitamin D_3)

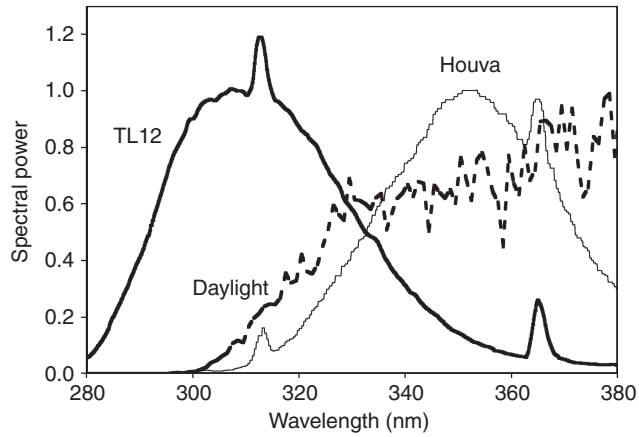

Figure 1. Radiation spectra for Philips TL12, Houva, and daylight in Boston for clear sky at noon on 21 June 2006. The vertical scale is in W m^{-2} nm^{-1} for daylight, arbitrary for lamps. Philips TL12 redrawn from Bogh *et al.*, 2010; Houva redrawn from Morison and Pike, 1984, with permission from Elsevier. Daylight calculated by ''Quick TUV'' (see cprm.acd.ucar.edu/Models/TUV/Interactive_TUV).

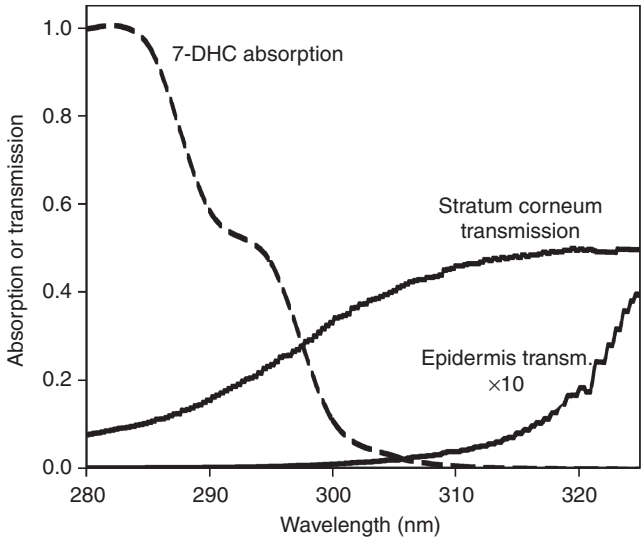

Figure 2. Transmission spectra for unexposed stratum corneum and epidermis (the latter expanded 10x) according to Bruls *et al.* (1984) and absorption spectrum for 7-DHC (provitamin D$_3$) (the latter in arbitrary units).

this radiation is efficiently absorbed by 7-DHC. UVR of longer wavelength is not efficiently absorbed by 7-DHC, but can penetrate deeper and reach more of the 7-DHC present. Therefore, previtamin D$_3$ synthesis induced by daylight or other UVR of longer wavelength is more sensitive to the melanin content of the skin than is that induced by short-wavelength radiation. One can speculate that the rate of synthesis may decrease when the the skin acclimatizes and pigment moves toward the surface, and there is some indication of this (Figure 2 of Armas *et al.*, 2007).

A commonly held view, originating from Murray (1934), is that pale skin has evolved when humans migrated northward out of Africa to areas where UV is less intense, or, in his own words, ''the inhabitants of the interior highlands of the far north not using a fish diet or any other generous source of food vitamin D must needs get most of their antirachitic vitamin from sunlight. If their skins are not sufficiently white to admit large enough amounts of solar radiation for normal bone metabolism, they are subject to rickets''. It is now known that other problems than rickets may arise even with slight vitamin D deficiency. Murray's theory has recently been challenged by Robins (2009), who cites three investigations (Stamp 1975; Lo *et al.*, 1986; Brazerol *et al.*, 1988) in which it was found that vitamin D status is equally improved by UV irradiation irrespective of skin pigmentation, but these seem to be exceptions. Brazerol *et al.* (1988) used FS40 lamps, which emit as much short-wavelength radiation as the TL12 used by Bogh *et al.* (2010); Lo *et al.* (1986) used a FSX72T12 UVB:HO lamp, which has a similar spectrum. Stamp (1975) tested very few individuals, and does not specify the radiation.

CONFLICT OF INTEREST

The author states no conflict of interest.

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I thank Dr Richard L McKenzie for valuable comments and Professor Mary Norval for lingustic corrections, and acknowledge the use of the Quick TUV calculator at 〈http://cprm.acd.ucar.edu/Models/TUV/Interactive_TUV/〉 for calculation of the daylight spectrum.

Statement: The submitted paper is based on an original idea and literature data as described in the paper (except for the absorption spectrum of 7-DHC, which is based on my own measurements).

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Genetic Variants in the *53BP1* Gene and Skin Cancer Risk

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TO THE EDITOR

The conserved p53-binding protein 1 (53BP1) was initially identified as a nuclear protein that interacts with the DNA-binding domain of tumor suppressor p53 and enhances p53-mediated transcription activation (Iwabuchi *et al.*, 1998). The interaction region of 53BP1, BRCT (BRCA1 C-terminus) repeats, are present in several proteins involved in DNA repair and cell cycle control, suggesting a direct role of 53BP1 in the cellular response to DNA damage and maintenance of genomic stability (Rappold *et al.*, 2001; Joo *et al.*, 2002). Recently, studies suggested that 53BP1 is a central mediator of the DNA damage checkpoint signaling (Wang *et al.*, 2002) and it directly participates in the repair for DNA double-strand breaks (Huyen *et al.*, 2004). 53BP1-deficient mice exhibit growth retardation, high-radiation sensitivity, and tumor development features that are indicative of a defective DNA damage response (Ward *et al.*, 2003). 53BP1 has been shown to constitutively have an important role in the etiology of human cancer (DiTullio *et al.*, 2002). It is plausible that sequence variation in the regulatory and coding regions of the *53BP1* gene might affect its transcription and protein structure thus, its biological function in checkpoint signaling and DNA repair, leads to susceptibility to cancers.

In this study, we hypothesized that that common genetic variants of *53BP1* were associated with risk of skin cancer. We comprehensively surveyed common genetic variation of the *53BP1* gene using two complementary approaches, including putatively functional single nucleotide polymorphisms (SNPs) and choosing tagging-SNPs in the *53BP1* gene locus (introns and exons as well as 20 kb upstream and 20 kb downstream of the coding region). We performed a skin cancer case-control study of Caucasians nested within the Nurses' Health Study to evaluate whether these common genetic variants are associated with the risks of non-melanoma skin cancers (squamous cell carcinoma (SCC) and basal cell carcinoma (BCC)) along with melanoma risk. We further investigated the association of these genetic variants with pigmentary phenotypes (hair color, skin color, tanning ability, and the number of moles). The nested case-control study consisted of 218 incident melanoma cases, 285 incident SCC cases, 300 incident BCC cases, and 870 age-matched controls. A detailed description of the selection and characteristics of cases and controls was published previously (Han *et al.*, 2005).

We included four putatively functional SNPs that have been identified in the promoter and coding regions of *53BP1* (http://egp.gs.washington.edu): rs1869258, rs560191, rs689647, and rs2602141. Using genotype data from the 90 CEU samples in the HapMap project, we further selected four tagging-SNPs by the Tagger program ($r^2 > 0.8$): rs3862138, rs17782975, rs2242069, and rs999047 (Supplementary Figure S1 online and Supplementary Table S1 online). We genotyped the eight SNPs by the 5′ nuclease assay (TaqMan) in 384-well format, using the ABI PRISM 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA). The distributions of genotypes for the eight SNPs were in Hardy–Weinberg equilibrium among controls. Because the three SNPs (rs1869258, rs560191, and rs2602141) are in high linkage disequilibrium (each pair-wise $r^2 > 0.9$, Supplementary Table S2 online), we anticipated that these three SNPs would show similar effects on pigmentary phenotypes and skin cancer risk.

We evaluated the main effect of the selected polymorphisms across the three types of skin cancer using unconditional logistic regression (Table 1). In the analyses controlling for the age, we found that three SNPs (rs689647, rs2242069, and rs999047) were consistently associated with a significantly decreased risk of BCC (additive odds ratio and 95% confidence interval: 0.69 (0.50–0.95), 0.68 (0.51–0.90), and 0.66 (0.48–0.91), respectively). These three SNPs are in moderate linkage disequilibrium (pair-wise r^2 between 0.27 and 0.70, Supplementary Table S2 online).

Abbreviations: BCC, basal cell carcinoma; SCC, squamous cell carcinoma; SNP, single nucleotide polymorphism