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Review

Ultraviolet radiation: effects on risks of prostate cancer and other internal cancers

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Abstract

Governmental and research agencies worldwide have strongly advocated sun avoidance strategies in an attempt to counter marked increases in skin cancer incidence. Concurrently, there are reports describing widespread Vitamin D_3 deficiency. Because 1,25-dihydroxyvitamin D_3, through interaction with the Vitamin D receptor, exerts pleiotrophic effects, such deficiency might be expected to have clinical consequences. Indeed, various reports indicate that exposure to ultraviolet radiation (UVR) exerts a protective effect on development of some common diseases including internal cancers and multiple sclerosis. We describe studies indicating that modest exposure reduces risk of prostate cancer. The effect of UVR is mediated by skin type; at lower levels of exposure a relative inability to effect skin pigmentation is protective presumably because it allows more efficient Vitamin D_3 synthesis. Polymorphic variants in genes associated with pigmentation including melanocyte stimulating hormone receptor and tyrosinase are also associated with prostate cancer risk. Overall, though preliminary and requiring cautious interpretation, these data indicate that moderate UVR exposure together with characteristics linked with less effective tanning confer reduced prostate cancer risk. Clearly, it is important to define safe levels of UVR that do not result in increased risk of skin cancers such as malignant melanoma.

Keywords: Ultraviolet radiation; Prostate cancer; Vitamin D; Skin type; Polymorphism

Contents

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1. Harmful effects of exposure to sunlight

Humans are repeatedly exposed to sunlight during their lives. Sunlight reaching the Earth's surface comprises ultraviolet radiation (UVR) (wavelength 290–400 nm) and visible light (400–780 nm). UVR has multiple effects in skin. For example, DNA absorbs UVR with formation of products such as cyclobutane-pyrimidine dimers that can give rise to signature mutations of exposure characterised by C → T and CC → TT transitions [1–5]. Such mutations are found in various genes in DNA from human skin cancers and form the molecular basis for the accepted view that inappropriate exposure to UVR increases risk of the common skin cancers, malignant melanoma, squamous cell carcinoma and basal cell carcinoma [1,6].

The public health implications of the association between UVR and skin cancer risk are enormous as more than half of all cancers in Americans occur on the skin. Thus, the lifetime risk of basal cell carcinoma for a Caucasian American born during the 1990s is estimated to be 30% and the annual incidence of malignant melanoma [4] has risen 3–7% in Caucasians over recent years [7]. This is the second highest increase in cancer incidence in the United States. In the United Kingdom, 7000 cases of melanoma were reported in 2000, an increase of 16% in one year and 24% over five years (Cancer Research, UK, http://cancerresearchuk.org/sunsmart/). The link with UVR is compelling. For example, risk in Caucasians in Australia is much higher than in the United Kingdom in spite of shared ancestry. However, while UVR is a critical causative factor, the link between sunlight and melanoma risk is complex. Thus, immigrants reaching Australia before 10 years of age have the same risk as native Australians, while those arriving after 15 years have a lower rate [7]. Indeed, one of the strongest correlates of melanoma development is with childhood sunburning. The evidence for total sun exposure as a risk factor and work-related exposure, that is likely to represent more continuous exposure, is less clear [4,7]. Excess exposure to UVR is also associated with immune suppression, premature aging of the skin and cataract formation [8]. Accordingly, governmental, cancer and scientific agencies including the American Academy of Dermatology, American Cancer Society and Cancer Research, UK, have emphasised the dangers of sunlight and the need to adopt lifestyles that reduce exposure.

2. Beneficial effects of UVR: synthesis of Vitamin D

However, UVR exposure offers health benefits. The importance of adequate exposure was established early in the 20th century with the realization that rickets was endemic in many urban areas because pollution blocked passage of UVR to Earth resulting in inadequate synthesis of Vitamin D [9]. In most societies, sunlight-mediated synthesis of Vitamin D_3 in skin represents the main route of obtaining this Vitamin [10–13].

Vitamin D is formed from 7-Dehydrocholesterol after exposure of skin to UVR. 7-dehydrocholesterol undergoes photolysis to generate the thermolabile intermediate, previtamin D_3 [14]. At normal skin temperature, previtamin D_3 rearranges to form Vitamin D_3. Thus, with regular UVR, Vitamin D_3 can be endogenously produced with no dietary requirement. Indeed, skin has massive synthetic capacity; total body

exposure of 1 minimal erythemal dose is equivalent to an oral dose of 10,000–25,000 IU (daily requirement up to 1000 IU) [14,15]. Vitamin D_3 is without biological activity and enters the circulation to be metabolised to 25-hydroxy Vitamin D_3 in liver and, to the most active metabolite, 1,25-dihydroxy Vitamin D_3. 1α-Hydroxylation occurs mainly in the kidney though catalytic activity is found in other tissues including colon, pancreas, brain and prostate indicating that 1,25-dihydroxy Vitamin D_3 may be synthesized in many tissues (Fig. 1) [15,16].

It was believed that rickets had been eradicated though many current reports show worldwide hypovitaminosis D_3. For example, low serum levels of

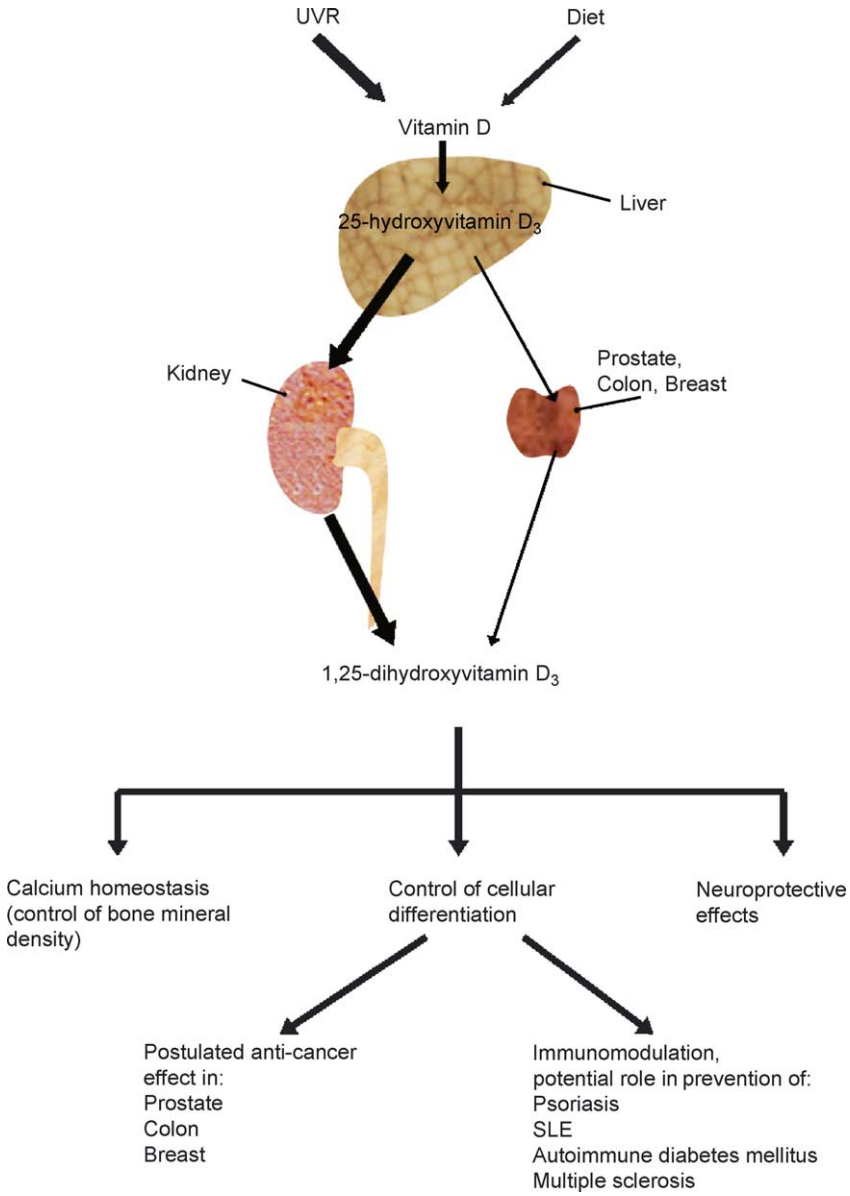

Fig. 1. The synthesis and functions of Vitamin D.

25-hydroxy Vitamin D_3 have been found in Alaskan children, adult Americans of different ethnic backgrounds, elderly Italians and many others [10–13]. This hypovitaminosis presumably results from sun avoidance, a largely indoor lifestyle, failure to eat Vitamin D_3-rich foods (e.g., oily fish) or take supplements and the reduced ability of the skin of elderly people to synthesise Vitamin D.

3. Functions of Vitamin D and the Vitamin D receptor

The classical action of Vitamin D_3 is in calcium homeostatsis and bone mineralisation [17]. The Vitamin acts through the Vitamin D receptor (VDR) (Fig. 2), a nuclear transcription factor, to increase small intestinal absorption of dietary calcium. Hypocalcaemia leads to secondary hyperparathyroidism increasing the production of 1,25-dihydroxyvitamin D_3, which acts via the VDR in osteoblasts to stimulate osteoclastic dissolution of mineralized bone. However, 1,25-dihydroxy Vitamin D_3 through its obligatory binding to the VDR also exerts multiple, systemic effects [17,18]. The VDR gene is located on chromosome 12 and consists of 14 exons. 1,25-Dihydroxyvitamin D_3 diffuses into the cell to effect binding to the VDR resulting in a conformational change in the VDR followed by dimerization with the retinoid X receptor (Fig. 2). Dimerization enables interaction with the Vitamin D response element (VDRE) in target genes, initiating transcription. VDREs are found on bone-related genes and also those related to differentiation and proliferation including p21, TGF-β2, fibronectin, urokinase plasminogen activator and β integrin [17]. Accumulating evidence indicates that 1,25-dihydroxy Vitamin D_3 has important anti-cancer actions on cells expressing the VDR [18]. For example, 1,25-dihydroxy Vitamin D_3 inhibits in vitro proliferation of epithelially derived cancer cells from prostate and colon and maintains the cells in more differentiated state. In addition, Vitamin D analogues inhibit proliferation and induce apoptosis in breast cancer cells in vitro [19]. This effect appears to be related to the ability of VDR-1,25-dihydroxy Vitamin D_3 to arrest cells at G_1 by influencing cell cycle control proteins. 1,25-Dihydroxy Vitamin D_3 also affects down regulation of E2F-driven DNA replication genes [17,18,20]. The Vitamin has immunomodulatory actions as demonstrated by reduced macrophage and lymphocyte function in Vitamin D-deficient rats. 1,25-Dihydroxy Vitamin D_3 functions as a general suppressor of immune function especially of T-helper cells [21].

The finding of widespread Vitamin D_3 deficiency has largely been considered in the context of its adverse effects on bone health in the elderly as exemplified by hip fractures and secondary hyperparathyroidism. However, given the multiplicity of functions it would be surprising if hypovitaminosis was not associated with other clinical phenotypes. Indeed, it might be expected that chronically low levels of exposure would be linked with clinical consequences [22].

4. Associations between UVR exposure and cancer risk

The amount of UVR reaching the Earth's surface varies with the directness of the sun's rays, time of day, time of year, latitude, cloud cover, amount of dust and pollution in the air [23,24]. Thus, through Vitamin D_3-mediated mechanisms it could be speculated that susceptibility and outcome to a variety of diseases might be determined by the level of local exposure and ultimately, serum levels of 25-hydroxy Vitamin D_3. The relative importance of synthesis of 1,25-dihydroxy Vitamin D_3 by target tissues is unknown. Clearly, latitude is relevant. Interestingly, though not widely publicized, several workers have compared disease parameters and extent of exposure in geographically defined areas (ecologic approach) and demonstrated associations between latitude and cancer risk that are interpreted as showing a protective role for sunlight. For example, Garland and Garland [25] reported an inverse link between colon cancer mortality rates in the United States and, UVB radiation and Vitamin D synthesis. Further studies using an ecologic approach also found inverse correlations between exposure and several cancers including those in breast and ovary and non-Hodgkin's lymphoma [26–29]. Such ecologic studies have provided an impetus for further studies on the role of UVR in reducing cancer risk. Case-control studies have also been conducted in breast, colon, ovarian and prostate cancer patients. These also indicate that adequate exposure to UVR and levels of Vitamin D in serum are linked with reductions in risk [29–31]. Tuohimaa et

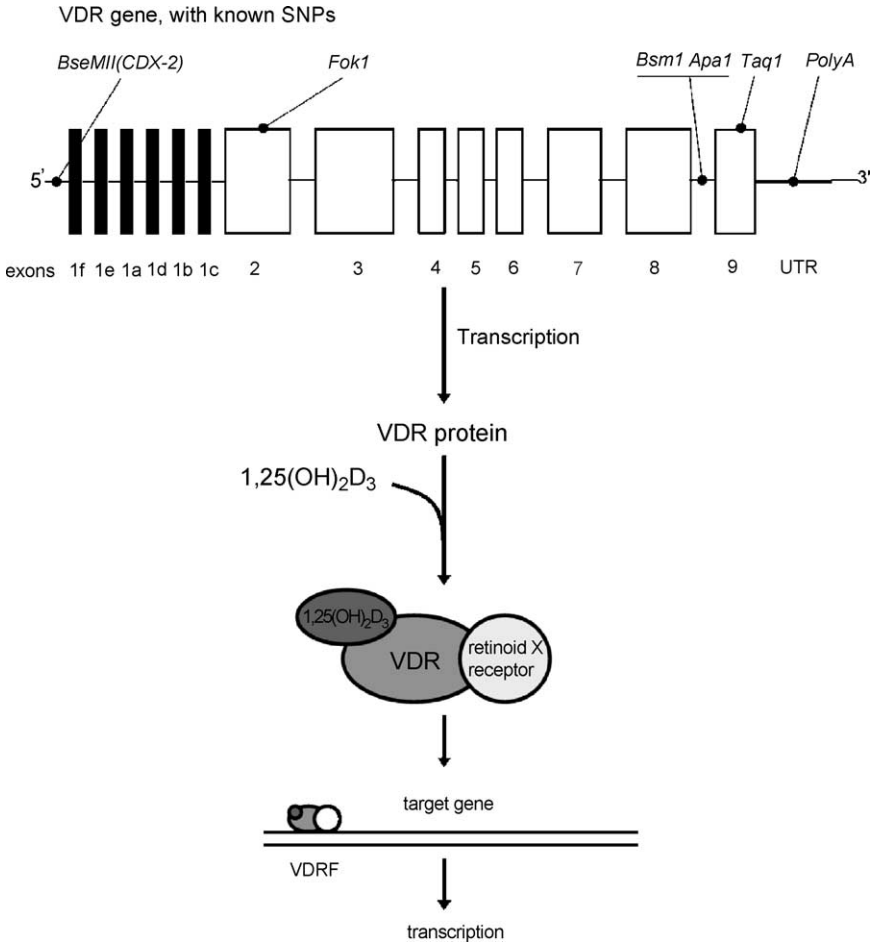

Fig. 2. Genetic polymorphism of the Vitamin D receptor. $1,25(OH)_2D_3$—1,25-dihydroxyvitamin D_3, VDRE—Vitamin D response element.

al. have recently shown both high and low levels of 25-hydroxyvitamin D_3 are associated with increased prostate cancer risk in a Nordic population [32].

5. Prostate cancer risk and exposure to UVR

Prostate cancer is the most prevalent non-cutaneous cancer in United States men and the second leading cause of cancer deaths in men. Its cause is unclear and there is currently no clear preventative strategy. In 1992, Hanchette and Schwartz [28] presented ecologic data from 3073 United States counties showing an inverse association between prostate cancer mortality and UVR. Mortality was significantly lower in the South. These findings are, therefore, of importance as they suggest a public health strategy to reduce the impact of this disease.

Further independent support for these findings came from a case-control study designed to compare parameters of acute and chronic exposure in 210 prostate cancer cases and 155 patients with benign prostatic hypertrophy (BPH) [33]. All the men were Northern European Caucasians resident in North Staffordshire, England (latitude 53.01°N). The BPH patients were chosen as the disease is common and establishing this diagnosis largely excludes the possibility of concurrent prostate cancer [34]. Exposure was assessed using parameters derived from a validated questionnaire [33,35,36]. Table 1 shows these data in men recruited

Table 1
Comparison of exposure UVR parameters in prostate cancer and benign prostatic hypertrophy patients

	Group	BPH		Cancer		Odds ratios		*p*-Values	
		A[a]	B[a]	A	B	A	B	A	B
	Number of subjects	155	135	210	212				
i.	Cumulative exposure (mean weeks)	393	464	355	416	0.998[b]	0.998[b]	0.006	0.004
ii.	Lowest exposure quartile (%)	18.7	14.8	29.0	24.2	3.03	3.21	0.008	0.001
	25–50% exposure quartile (%)	24.5	22.2	25.2	23.2	1.51	1.68	0.182	0.097
	50–75% exposure quartile (%)	27.1	25.2	22.9	24.2	1.18	1.40	0.588	0.263
	Highest exposure quartile (%)	29.7	37.8	22.9	28.4	1.00	1.00	Reference	
iii.	Living abroad for >6 months (%)	32.9	25.9	31.0	25.5	0.71	0.89	0.161	0.661
iv.	Positive childhood sunburn (%)	21.9	17.8	4.3	7.6	0.18	0.42	0.0001	0.014
v.	Sunbathing score (mean)	7.7	7.0	6.2	5.7	0.83[c]	0.79[c]	0.0001	0.0001
vi.	History of regular foreign holidays (%)	34.8	42.2	17.1	25.9	0.41	0.56	0.005	0.016

Variables i–vi were studied in individual logistic regression models with correction for age at diagnosis.
[a] A: patients recruited October 1999–May 2000 [31], B: patients recruited August 2001–April 2002 [37].
[b] Odds ratio per week.
[c] Odds ratio per sunbathing unit.

during October 1999–May 2000 (group A). Thus, cumulative lifetime exposure, a predictor comprising exposure from weekday and weekend activity and estimates of occupational and recreational exposure was significantly protective (odds ratio = 0.998 per week). Of particular interest are the proportions of cancer and BPH patients in each quartile of exposure. Thus, comparison of the odds of having prostate cancer, between the lowest and highest quartiles, resulted in a significant odds ratio (odds ratio = 3.03). Other parameters of exposure were also linked with reduced risk; sunbathing score (never, rarely, occasionally, frequently; scored 1, 2, 3 and 4), regular foreign holidays (average weeks abroad per year) and childhood sunburning (yes/no) were protective. Further, in cases cumulative exposure was associated with age at diagnosis; men with the lowest quartile of exposure developed prostate cancer at a younger age (median 67.7 years) than all other patients (median 72.1 years) ($p = 0.006$, hazards ratio = 1.52) [33].

While these findings support the UVR hypothesis, they were derived from a small, exploratory study with the possibility that observed associations are spurious because of multiple significance testing. Clearly, these initial findings needed confirmation in a separate group. Accordingly, a new group of 212 prostate cancer and 135 BPH patients was recruited during August 2001–April 2002 with a view to re-investigating the observed associations between UVR and prostate cancer risk (group B, Table 1). We found that childhood sunburning, foreign holidays, adult sunbathing and low exposure are predictors for prostate cancer risk [38] indicating the robustness of the original study. Indeed, data from the second study confirmed that men with the lowest quartile of exposure (average less than 1.9 h/day) have an about three-fold greater risk of prostate cancer than men in the highest quartile. Similarly, low levels of sunbathing were linked with a 5.33-fold greater risk of prostate cancer than levels in the highest quartile. Intermediate exposure or sunbathing conferred less protection suggesting a graded effect. Replication of the original findings provides useful support for the UVR hypothesis though it remains possible that the association is idiosyncratic to an area of northern Europe with relatively limited exposure and may not be observed in men living at latitudes that allow continual exposure [33]. Thus, while corresponding data are not available for central England, studies in Edmonton, Canada, which is on a similar latitude to North Staffordshire (52°N), showed that Vitamin D synthesis ceased by mid-October and did not resume until mid-April. In Los Angeles (34°N) and Puerto Rico (18°N) Vitamin D synthesis continued all year [37].

While the semi-quantitative nature of questionnaire-derived exposure data makes definition of an adequate level/duration of exposure difficult, these findings support the view that regular short-term exposure to UVR results in reduced prostate cancer risk. They are

compatible with the known relationship between exposure and Vitamin D synthesis. Thus, exposure to bright sunlight for only 15 min appears sufficient for adequate synthesis of Vitamin D [14,37]. Interestingly, Vitamin D synthesis does not increase linearly with length of exposure; at the equator, 15% of cutaneous 7-dehydrocholesterol is converted into previtamin D_3 after exposure for 30 min or 8 h. This may be a mechanism to limit UVR-mediated Vitamin D production. Adult sunbathing may be important in determining prostate cancer risk because it involves exposure of larger areas of the body, some of which, such as the trunk will generally be the less pigmented. Further, exposure of the trunk and legs to sub-erythemic doses of UVR results in greater increases in serum Vitamin D levels than does exposure of the head, neck or arms [37].

6. What factors determine exposure to UVR and are they related to prostate cancer risk?

The finding of an association between UVR and prostate cancer risk prompts questions regarding factors that determine individual patterns of exposure and inter-individual differences in host response to a quantum of exposure. Skin colour and ability to elicit a pigmentary response to UVR are determinants of these issues. In particular, ability to mount a pigmentation response to sunlight will influence cutaneous Vitamin D synthesis since increased melanin production reduces UVR-mediated previtamin D_3 synthesis [37]. A dark epidermis protects sweat glands from UVR-induced injury insuring integrity of thermoregulation and reducing UV-induced photolysis of folate, a metabolite essential for development of the embryonic neural tube and spermatogenesis. During early human migrations, varying degrees of de-pigmentation presumably occurred allowing UVR-induced synthesis of previtamin D_3 in more limited sunlight [39]. Variations in skin colour are adaptive and in general, the gradation of skin coloration appears to be a compromise between protection from UVR and adequate synthesis of Vitamin D.

There has been much interest in defining ability to tan or burn as they mediate the adverse effects of UVR. In Caucasians, the widely used Fitzpatrick scale assesses these characteristics [40] though can be criticised because there is no simple inverse correlation between burning and tanning [41,42]. Subjects with skin type 1 cannot tan effectively. Subjects with type 2 usually burn and tan with difficulty, those with type 3 may suffer mild burns but have average tanning ability while those with type 4 rarely burn and easily tan. It might be expected that men who readily tan are at higher risk of prostate cancer because they synthesise Vitamin D less readily than those who cannot effectively pigment. However, many (but not all) individuals with sun sensitive skin avoid UVR. Thus, 22% of subjects with highly sensitive skin who were outdoors on the preceding weekend reported being sunburnt [43]. The relationship between prostate cancer risk, UVR and ability to tan is likely, therefore, to be complex and it is not clear if skin type 1 is a risk factor because of sun avoidance or protective because of more effective Vitamin D synthesis. We investigated this association in 453 men with sporadic prostate cancer and 312 men with BPH. This group comprised patients from the studies of Luscombe et al. [33] and Bodiwala et al. [38]. We further speculated that the impact of skin type on risk is related to the level of exposure to UVR.

We used a recursive partitioning approach (HelixTree software from Golden Helix, www.goldenhelix.com) to determine if the protective influence of skin type 1 on risk was more evident in men with low levels of cumulative exposure per year or sunbathing [37,38]. Recursive partitioning allows prediction of a dependent variable on the basis of a number of predictors. The Helix Tree algorithm partitions predictors (cumulative exposure per year, sunbathing score, skin type) so that more homogeneous groups, with respect to prostate cancer or BPH status, are obtained. Thus, in the first partition, the algorithm lists the predictors in the order of their Bonferroni-corrected *p*-values. We selected the most significant predictor to partition men into nodes comprising increasing proportions of cancer or BPH patients (Fig. 3). The algorithm then effects further partitioning of subjects in each node. These analyses showed that in men who never or very rarely sunbathed, those with skin types 2–4 were at significantly increased risk relative to those with type 1. This increased risk was also observed in men with intermediate levels of sunbathing, though the impact was less than in men with lower levels. In men with higher levels of sunbathing, skin type did not mediate risk. These

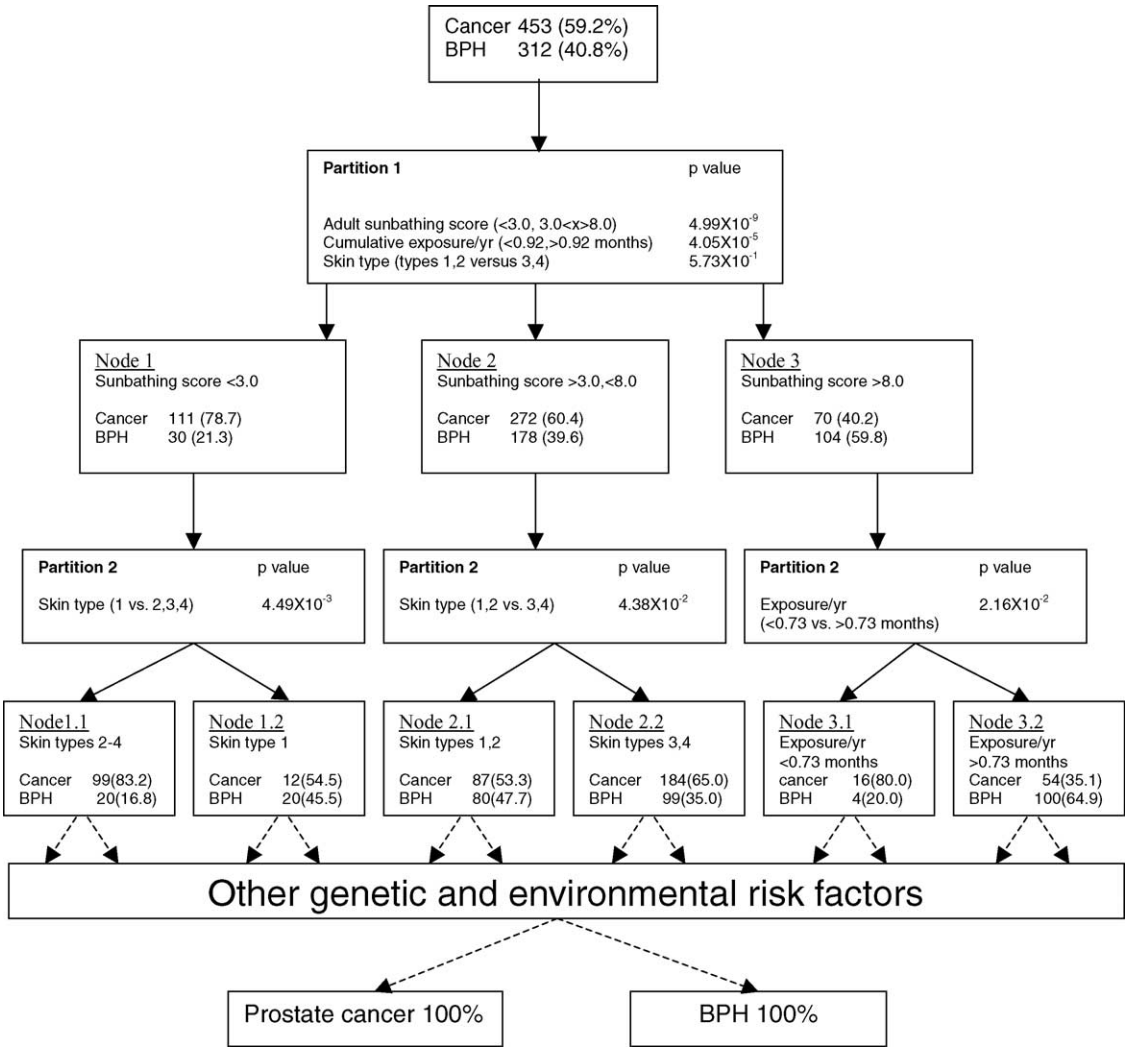

Fig. 3. Recursive partitioning model to identify associations between UVR exposure parameters, skin type and prostate cancer risk. Variables included skin type, cumulative exposure per year and adult sunbathing score. Percentages of patients are shown in parentheses.

findings suggest that at low levels of exposure, inability to pigment is advantageous as it allows some Vitamin D synthesis [44,45]. More deeply pigmented men require more UVR to ensure synthesis of sufficient Vitamin D [46].

7. A role for genetic polymorphisms

Many studies have attempted to identify polymorphic genes associated with sporadic prostate cancer risk [47,48]. Generally, candidate genes have been selected on the basis of their perceived roles in the pathogenesis of the cancer; these include insulin-like growth factor, prostatic specific antigen as well as genes that mediate steroid metabolism (*androgen receptor*, *5α reductase*) and detoxication of xenobiotics (cytochrome P450 *CYP17*, *CYP3A4*, *CYP2D6*) and by-products of oxidative stress (glutathione *S*-transferase *GSTT1*, *GSTM1*, *GSTP1*). The finding that skin type is associated with prostate cancer risk presents a rationale for further candidates.

Skin type is a polygenic trait and studies showing associations with polymorphic variants in the *melanocortin-1 receptor* (*MC1R*) [49] and *p53* [50] genes suggest that these and other pigmentation-related genes are candidates. Melanin largely determines skin colour and the rate-limiting steps in its synthesis are catalysed by *tyrosinase* (*TYR*) under the influence of melanocyte stimulating hormone that acts via the *MC1R*. Both *TYR* and *MC1R* are polymorphic [49,51–53]. For example, over 30 variant *MC1R* alleles have been identified in Caucasian and Asian populations [49]. Similarly, *TYR* is highly allelic with more than 90 alleles identified [51]. Clearly, the *VDR* is also a potentially important candidate.

The first studies investigating the possibility that polymorphism in these genes was implicated in susceptibility to internal cancers focused on prostate cancer [54]. In initial studies, we investigated the A → C change in exon 1 (codon 192) of *TYR*. While this change has not been shown to have functional consequences, the A1 and A2 alleles have similar frequencies (0.44 and 0.56 in cases) and are useful markers. Five allelic sites in the *MC1R* were assessed for associations with prostate cancer: Arg151Cys, Arg160Trp, Val92Met, Asp294His and Asp84Glu. Arg151Cys, Arg160Trp and Asp294His are linked with red hair, Val92Met is linked with skin type and Asp84Glu has been associated with malignant melanoma risk in one but not other studies [49,52,53]. Polymorphisms in *TYR* (codon 192 variants) and MC1R were associated with prostate cancer risk [54]. Homozygosity for *MC1R* Arg^{160} was associated with increased risk (OR = 2.18) while homozygosity for the *TYR* A2 allele was linked with reduced risk (OR = 0.42).

A number of single nucleotide polymorphisms (SNP) have been identified in the VDR gene (Fig. 2). The 3′ region contains *Bsm1*, *Apa1* intronic sites and a *Taq* 1 site in exon 9 and a poly A repeat in the 3′ untranslated region. In Caucasians, the *Taq1* site is in linkage disequilibrium with the *Bsm1*, *Apa1* and polyA sites [17,48]. In the 5′ region of the gene, a *Fok1* restriction site (C/T substitution) exists in exon 2, the *Fok1* f allele results in the translation of a polypeptide comprising 427 amino acids, while the *Fok* F allele encodes a polypeptide comprising 424 amino acids. Further, in the 5′ region of the gene an A/G substitution in the cis element of the promoter that interacts with caudal related homeodomain transcription factor (*CDX-2*) [55]. The F allele has been reported to be more transcriptionally active than the f allele [17,55,56]. *Bsm1*, *Apa1* and a poly(A) tail microsatellite variants may also be functionally significant because the length of the poly(A) repeat affects mRNA stability. The *CDX*-2 polymorphism may also have functional implications [55,56]; transcriptional activity of the promoter with the G allele is 70% that of the A allele, and in small bowel *CDX*-2 has been shown to regulate *VDR* expression. Various groups have determined if prostate cancer risk is associated with *VDR* polymorphisms. The results of these studies have given contradictory results [48]. There are many reasons for the observed intra study heterogeneity: many studies have lacked power and studies have been undertaken with different racial groups. A meta-analysis has been recently published in an attempt to draw firmer conclusions from the multitude of molecular epidemiology studies on the subject [48]. The evidence from 17 separate studies was assessed, investigating the effect of the *Taq1*, poly A, *Bsm1* and *Fok1* polymorphisms on cancer risk. The analysis did not show any statistically significant differences in prostate cancer risk. In agreement, we did not identify associations between risk and the *VDR Taq* or *Fok* variants. Interestingly, we found an increased risk of metastatic disease with the ff genotype but this is not linked with advanced stage or grade [57].

8. Is the impact of polymorphic genes mediated by the extent of exposure to UVR?

The finding of associations between UVR and prostate cancer that are mediated by skin type and polymorphic genes associated with sun-sensitive phenotypes suggests that pathogenesis of prostate cancer in men with low levels of exposure to UVR is different to that in men with higher levels [37,38]. Thus, levels of UVR exposure below the median value are associated with prostate cancers that develop because of relative Vitamin D deficiency.

We speculated that the level of UVR exposure is a surrogate for long-term serum Vitamin D levels. Thus, stratifying cancer and BPH patients into low and high exposure groups based on cumulative UVR exposure

per year might uncover any effect *MC1R*, *TYR* and *VDR* variants have in men with different Vitamin D levels (Fig. 4). We used the median value for cumulative exposure/year to stratify patients into low and high exposure groups as it allowed the maximum number in both groups [58,59]. We found that the protective effect of *TYR* genotypes found in the total group reflects an association with risk in subjects with the highest quartile of exposure. *VDR Fok1* ff (odds ratio = 2.91) genotypes were also associated with prostate cancer risk in men with UVR exposure levels above the median (1100 h/year). Thus, *VDR* variants are not associated with risk in the relatively low exposure group. It is possible that if the functional differences between the VDR genotypes are small relative to the consequences of low Vitamin levels, the impact of the polymorphisms may be masked. By contrast, men with exposure above the median are expected to synthesize adequate Vitamin D (Fig. 4). Thus, the functional consequences of the polymorphisms may be sufficiently great in the presence of adequate levels of the Vitamin, to influence prostate cancer risk. These data show for the first time, that allelism in genes linked with skin pigment synthesis is linked with cancer risk in an exposure-dependent manner.

9. Conclusion

We believe that the hypothesis that UVR exerts a protective effect on the development of prostate cancer is compatible with available data. Firstly, associations between exposure patterns and disease risk have been reported. Studies in prostate cancer cases have been replicated. Secondly, as required by the hypothesis, the impact of UVR is mediated by skin type as a surrogate for pigmentation efficiency. Thirdly, polymorphic genes associated with ability to effect a pigmentary response to UVR have been linked with prostate cancer risk and outcome. The impact of some allelic variants is mediated by extent of exposure. Further support for the view that UVR exposure can be beneficial through a Vitamin D_3-mediated mechanism comes from independent studies in multiple sclerosis (MS). Thus, MS prevalence increases with latitude. Further, sun exposure and Vitamin D administration are associated with reduced risk and disease symptoms [60,61]. Interestingly, recent studies have reported associations between polymorphisms in genes associated with skin pigmentation and MS risk [62]. Associations between prostate cancer risk and serum Vitamin D concentrations showing that low levels and perhaps

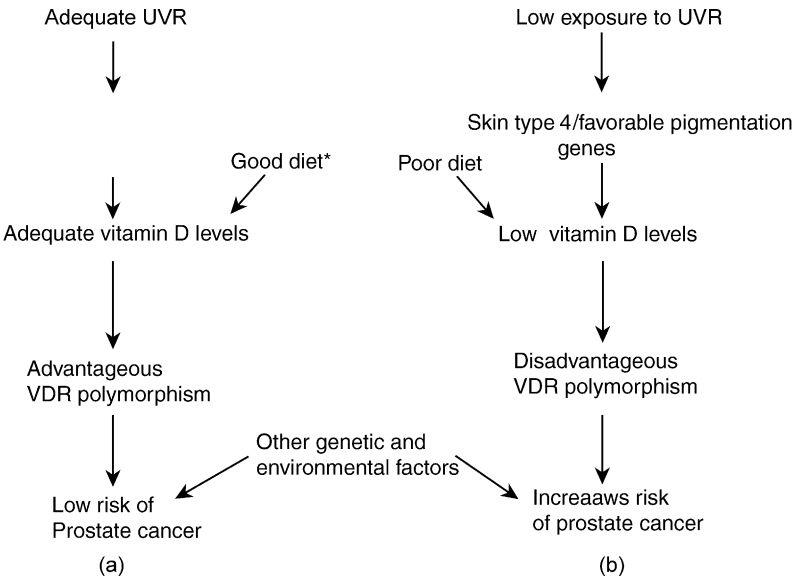

Fig. 4. Low (a) and high (b) risk phenotypes for prostate cancer with reference to UVR exposure, skin type and Vitamin D synthesis. (*) Vitamin D containing foods, such as oily fish and milk.

unexpectedly, high levels confer increased risk suggest the link between the Vitamin and risk is complex [63,64]. Ecologic studies in other diseases also indicate a protective role for UVR [65,66]. Indeed, Grant [66] has proposed that in the United States, as many as 45,000–50,000 premature deaths occur each year because of inadequate Vitamin D. It has been suggested that it is appropriate to re-consider our attitude to sunlight [65].

However, we believe that caution is needed in the interpretation of available data. Perhaps because the Public Health implications are potentially so important it essential that advice regarding the extent of exposure that is safe is compatible with current concerns regarding skin cancer risk. Thus, definition of a level and/or pattern of UVR that results in synthesis of sufficient Vitamin D but does not increase risk of the harmful consequences of exposure is needed. Importantly, intermittent exposure may be more harmful in the context of certain skin cancers. Thus, excess exposure, particularly the burning linked with increased skin cancer risk, can be avoided [5]. However, ensuring that even the relatively limited amount of exposure required for Vitamin D synthesis is obtained may not be easy. More deeply pigmented individuals require more exposure to ensure synthesis of sufficient Vitamin D and it is clear that many people spend little time outdoors. Further, many people use sunscreens that block UVR and reduce Vitamin D_3 production. Thus, while the data presented are consistent with the hypothesis, it is limited and much of it requires confirmation in different study groups. This comment is particularly relevant in the context of the molecular epidemiological data since few reported significant associations have been replicated [67,68]. Reasons given include population stratification, disease heterogeneity, small sample sizes and failure to exclude chance as the reason for the finding of significance. Clearly, proper assessment of the role of interactions between UVR and polymorphic genes in determining disease risk requires studies that confirm existing data and include further relevant genes and fuller assessment of available sites and haplotypes.

The concept that UVR exposure can protect against internal cancers and other common diseases has attracted much interest with articles appearing in the specialised and general press [69–71]. Dermatological bodies have expressed considerable concern. Resolving this discrepancy requires further studies and an open consideration of the data [72]. In our view, it is too early to advocate deliberate exposure (such as increased sunbathing) as a public health approach because such a message may be misconstrued and have an adverse impact on efforts to reduce the incidence of skin cancer. Nonetheless, the available data on the beneficial effects of UVR should not be ignored and if increased exposure to UVR is finally considered too dangerous an approach, perhaps increasing Vitamin D intake could be considered.

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