

In: *Solar Radiation and Human Health*
Espen Bjertness, editor.
Oslo: The Norwegian Academy of Science and Letters, 2008.

Sun beds and sunscreens - friends or foes?

Johan Moan^{1,2} and Alina Carmen Porojnicu¹

¹*Norwegian Radium Hospital,* ²*University of Oslo, Oslo, Norway*

Correspondence: Johan Moan, Department of Radiation Biology, Rikshospitalet - Radiumhospitalet
Medical Centre, Montebello, 0310 Oslo, Norway.
Email: johan.moan@fys.uio.no Telephone: +47 22934268 Fax: +47 22934270

Abstract

When absorbed, a photon of a given energy has the same chemical and biological effect whether it comes from the sun or from an artificial, man-made source like a sun bed. If the spectrum and intensity of a sun bed are the same as those of the sun, the biological effects will be exactly the same. The main difference between radiation from sun and sun beds is that sun beds emit less visible light. This may affect the relative efficiency of photoreactivation, a process through which ultraviolet (UV) -induced DNA damage is repaired. Sun creams do not only reduce the intensity of the radiation reaching living skin tissue, but also changes the spectrum of the radiation, since they are mainly designed to reduce erythemogenesis, which is induced mainly by UVB radiation (280-320 nm). However, other biological effects, such as generation of melanomas, skin ageing and photosensitization associated with endogenous and exogenous dyes, may be caused also by UVA radiation (320-400nm) and even by visible light.

Solar UV radiation is the main source of vitamin D in humans, and most sun beds are equally efficient vitamin D producers. However, both sun and sun beds can cause skin cancer. Notably, intense, intermittent exposures, yielding sunburns, are carcinogenic, while more regular, moderate exposures are less so. The positive effect of such exposures, mainly related to vitamin D photosynthesis, may be much more important than the negative effects. Considerations of skin colours of populations living at different latitudes, as well as modern experimental and epidemiological work, clearly urge us to focus more on the positive effects of UV radiation from sun and sun beds.

The spectral region related to a given biological effect is given by the action spectrum of that particular effect. The action spectra of erythema, melanogenesis

and non-melanoma skin carcinogenesis are very similar and are all centred in the UVB region. Thus, it is the total exposure and the exposure pattern that determine which of the three effects is the dominating one. Sun creams are made to reduce or eliminate erythema and carcinogenesis risks. Then it is evident that they also reduce or eliminate vitamin D production, which has been experimentally proven. Reports in the literature on the effect of sun beds and sun creams on the risk of skin cancer are conflicting: Positive as well as negative effects have been demonstrated. Thus, so far no firm conclusions can be drawn with respect to the overall and dominating impact.

Health authorities frequently recommend that people should avoid midday sun and postpone their sun exposure to the afternoon. This is probably not the best recommendation to make, since moderate midday sun exposure gives maximal amounts of vitamin D at minimal melanoma risks.

Introduction

Sun beds are lamps constructed with the aim to emit radiation giving similar effects in human skin as solar radiation does. Sunscreens are made to play an opposite role: to reduce or eliminate the effect of ultraviolet radiation (UV) from the sun on human skin. Since the use of both sun beds and sunscreens has increased over many decades, their health effects should be continuously and critically investigated. Before attempting to answer the questions in the title, we will briefly review what is known about positive and negative effects of solar radiation on humans.

Any discussion on this topic should be based on action spectra of the biological effects. Such spectra show the wavelength dependency of the effects, and are almost inevitably needed whenever different radiation sources are to be compared with respect to biological effects. This is so because practically all radiation sources have different or varying spectra: the spectrum of the sun changes with solar elevation, ozone layer thickness, latitude, altitude, cloud cover and ground albedo. The spectra of sun beds are also widely different and change with hours of use. UVB ($\lambda = 280\text{-}320\text{ nm}$) is 10-1000 times more biologically active than UVA ($\lambda = 320\text{-}400\text{ nm}$), depending on the wavelengths chosen for comparison. In fact, the division between UVB and UVA is usually set at 320 nm, because DNA absorbs practically no radiation with longer wavelengths than 320nm, and DNA is thought to be the main chromophore for adverse effects in human skin. Other important chromophores, such as urocanic acid and 7-dehydrocholesterol, have similar spectra.

Two basic and undeniable facts should be kept in mind: Humans have developed and lived in solar radiation throughout their entire history, most of the time

without sunscreens and even without clothes. Their first home place is believed to be under the Equator, in Africa, where the solar radiation was, and still is, very strong. Those living under high fluences of solar radiation (i.e. close to the Equator) have dark skin; skin containing the natural, brown sunscreen melanin. Whether some forms of melanin, pheomelanins, can also act as photo sensitizers has to be considered and further studied. As humans moved away from the Equatorial areas and towards less sunny places, their skin gradually turned white, in fact whiter the further away from the tropics they live and the longer they have stayed there.

Negative health effects of solar radiation

Skin cancer

The most important adverse effect of exposure to solar radiation is induction of skin cancer. There are three major forms of skin cancer: squamous cell carcinoma (SCC) arising mainly in keratinocytes in the epidermis, basal cell carcinoma (BCC) arising in dividing, basal cells on the border between the epidermis and the dermis, and cutaneous malignant melanoma (CMM) arising in melanocytes residing close to the basal layer. In Norway there are now about 9000 BCCs, 1300 SCCs and 1100 CMMs diagnosed each year (1). The survival rates of SCC and BCC are higher than 97%, while that of CMM is much lower. The five year survival rates of CMM have increased from about 50% and 60% in 1958 to about 78% and 90% in 2000 in men and women, respectively (1), supposedly due to earlier diagnosis and improved treatment. Nevertheless, about 260 Norwegians die from CMM every year, amounting to about 2.5 % of the total number of total cancer deaths. About 4.7 % of new cancer cases are CMMs (1).

Until about 1990 the incidence rates of all skin cancer forms increased with a doubling time of about 15 years (2). After 1990, however, the incidence rates of CMM have flattened out, and for younger people even decreased (see below). Solar radiation is the main cause of SCC and BCC. We have estimated that even in the Nordic countries more than 80% of the incidences are caused by the sun: Latitude variations and body localization patterns constitute the basis for this conclusion (2). The incidence rates are about three times higher in the south of Norway than in the north, where the annual fluence of UVB is 50% lower. The relative tumor density of SCC and BCC (here defined as the annual incidence rate divided by the skin area under investigation) is much higher on head and neck (heavily exposed areas) than on trunk and limbs. This pattern has not changed significantly over time. Although it has been claimed that intermittent exposure, leading to sunburn, is especially carcinogenic for all three skin cancer forms (3,4), most authors are of the opinion that the risk of SCC increases with accumulated dose (5,6). Mice get SCCs from UVB exposure, and experiments

with these animals generally support that the rates increase with accumulated dose (7). However, mice get neither BCCs nor CMMs (8). The dose dependency of BCC generation is less clear than that of SCC, but also in this case the accumulated dose seems to be important. An intermittent exposure pattern may be more BCC generating than a more constant one. Several reports indicate that CMM generation is mainly related to intermittent exposure and sunburns (9,10).

The relationship between CMM and sun exposure is extremely complicated, and, therefore, vigorously debated. We have earlier listed the main arguments for and against a relationship (11,12). Our work indicates that intermittent sun exposure has a high CMM-generating potential (2). In agreement with this, a large review (13) of published data on CMM (29 studies on sun exposure and 21 on sunburn) indicates a significant, positive association (OR 1.71, 95 % CI: 1.54-1.9) between CMM and intermittent exposure and a reduced risk for heavy occupational exposure (OR 0.86, 95% CI 0.77-0.96). Sunburn was found to be a risk factor for all ages. This is in agreement with the early statement of Holman et al. (14) that when the total sun exposure increases, the CMM risk first increases, reaches a plateau and then decreases with further exposure. Thus, farmers and fishermen, supposedly heavily exposed without sunscreens in all seasons, have a surprisingly low chance to get CMM compared with white collar workers. It is tempting to propose that a constant sun induced tan or skin thickening acts protectively. That the exposure pattern is of great importance is evident from our studies of relative tumor densities of CMM on different body localizations: For younger women the relative tumor density on the lower limbs is higher than that on the face and younger men get more CMMs per cm² on the back than on the much more exposed face and neck (2). A rather strong indication that sun exposure is a main CMM-causing factor is that practically no Norwegian women got CMMs on the breasts before the top-less fashion came (2,12).

Many scientists find it surprising that, as we have moved from agricultural occupations to more office work, the CMM incidence rates have increased. This may support the role of intermittent, vacational UV exposures as particularly melanomagenic factors. Similarly, people working under fluorescent light tubes have an increased CMM risk (15,16). This may simply be related to indoor versus outdoor work, since such tubes emit very low fluence rates of UV.

Skin ageing (17,18)

It is well known and proven that UVB exposure leads to accelerated elastosis and skin ageing. UVA seems to act similarly, and, related to its larger penetration depth, gives deeper effects and acts more on dermal structures.

Eye damage (19-21)

Photokeratitis (snow blindness) and cataract formation are accelerated by UVB exposure. The former is a transient damage to corneal cells, while the latter is mainly persistent cross linking, aggregation and “whitening” of lens proteins.

Immunological impairments (22,23)

This is a controversial topic: On one hand UVB reduces the number of melanocytes and Langerhans cells and makes mouse skin unable to reject transplanted skin tumors, but newer research shows that moderate UV exposures stimulates the immune system in skin in a positive way (24).

Positive health effects of solar radiation**Immune effects**

The positive effects of moderate UV exposures on the immune system may largely be related to vitamin D formation. As long as this photoproduct is retained in the skin, it certainly acts immunomodulatory in a positive way (24). Recent research indicates that this is the biological basis for the positive effect of UV on skin tuberculosis (lupus vulgaris) (Finsen’s Nobel price in 1903) and the effect of sun-sanatory treatment of tuberculosis before the time of BCG vaccination (25-28). The balance of positive versus negative immune effects of UVB is probably related to dose- and exposure patterns. The reason why practically no influenza epidemics start in the summer season may, in addition to direct vitamin D effects, be caused by more general immune effects generated by solar radiation in skin (29). Before about 1930 positive health effects of solar radiation were strongly focused on. An editorial in *The Lancet* in 1932 expressed that the health effects of sun exposure were so large and important that governments should consider arranging areas for nude sunbathing! (30). Then, the medical societies and governments realized that solar radiation caused skin cancer, and the anti-sun campaigns slowly gained power and momentum. Peller’s observation that “skin cancer appeared to protect against other cancers”, published in *The Lancet* in 1936 (31), did not help much in creating a balanced view. In fact, Peller was wrong; it is not the skin cancer itself that acts protective, but the sun exposure through its vitamin D generation.

Positive effects related to vitamin D photosynthesis

Many of the following positive effects are related to interactions of vitamin D with the immune system. Most researchers in the field state that “solar radiation is the most important source of vitamin D for humans” (see Hollick M.F., Zittermann A., Reichrath J. in this book). Large population groups have an inadequate vitamin D status, primarily caused by lack of outdoor activities and sun-shielding by clothes or creams. What an “inadequate vitamin D status” really means is being debated by nutritionists, dermatologists and photo -

biologists. It seems clear that “recommended intake doses”, as well as values for “optimal calcidiol levels” in serum, should be substantially increased (see other chapters in this book). The fear of “vitamin D intoxication” may be extremely exaggerated.

Documented health effects of an optimal vitamin D status are numerous, and only an incomprehensive list will be given here: protection against a number of internal cancers (32-35), improved prognosis of a number of cancers (36-42), prevention of rickets, prevention of osteoporosis (the increase of incidence of this disorder may have two reasons: inadequate vitamin D intake, and increased protein intake which leads to increased calcium excretion (43)), prevention of osteomalacia (soft bone, chronic pain), reduction of risk of arthritis (44,45), reduction of development of muscle weakness and undefined chronic pain (46-51) control of psoriasis and eczema (52), reduction of hypertension, high blood cholesterol and cardiovascular diseases (53-55), reduction of diabetes type 2 incidence rates (56-58) and prevention of influenza epidemics (29). Sun exposure is beneficial also for autoimmune diseases: diabetes type 1, multiple sclerosis (see Kampmann M, chapter in this book) and rheumatoid arthritis (44,45). Finally, there are more or less well founded speculations concerning obesity, Parkinson’s disease, fibromyalgia, and Crohns disease (59-62).

Effects on circadian rhythms

This topic is treated in two other chapters of this book, and we will just mention that the “light governed”, or, more correctly stated, the “darkness-generated” hormone melatonin is interacting with many other hormonal systems, some of which are closely linked to cancer progression. Therefore, it has been proposed that solar radiation may play a role in cancer progression also through its interaction with circadian mechanisms (63). Night-working persons are more prone to get cancer than day-working people, an observation that may be related to effects of the visible part of solar radiation on hormonal systems, via receptors in the eye and signals to the pineal organ via the suprachiasmatic nuclei.

Action spectra

Since UVB is 10-1000 times more biologically efficient than UVA per incident photon, and since there is much more UVA than UVB in solar radiation, action spectra need to be known with great accuracy in the UVA range. For instance, so called UVA sun beds emit very little UVB, but it is still this small fraction that causes erythema, melanogenesis and vitamin D synthesis (64). For humans only three relevant action spectra are known with accuracy: those for erythema generation (65), melanogenesis (66) and vitamin D photosynthesis (67) (Figure 1). Those for elastosis, (68), immediate pigment darkening (IPD) (69) and

photoisomerization of urocanic acid are known with some accuracy (70). Concerning photo carcinogenesis, the action spectrum of SCC in mice (7) and that of CMM in a fish called *Xiphophorus* (71) are known. As shown in figure 1, the spectra of erythema, melanogenesis and SCC are very similar. The chromophore in the UVB range is believed to be DNA, since the spectra are almost identical with the absorption spectrum of DNA when the latter is corrected for scattering and absorption in the epidermis. DNA does not absorb UVA, so another chromophore must be acting in this wavelength region. One possibility might be porphyrins, although they are present only in trace amounts, so the question is unsolved. The urocanic acid isomerization spectrum is similar

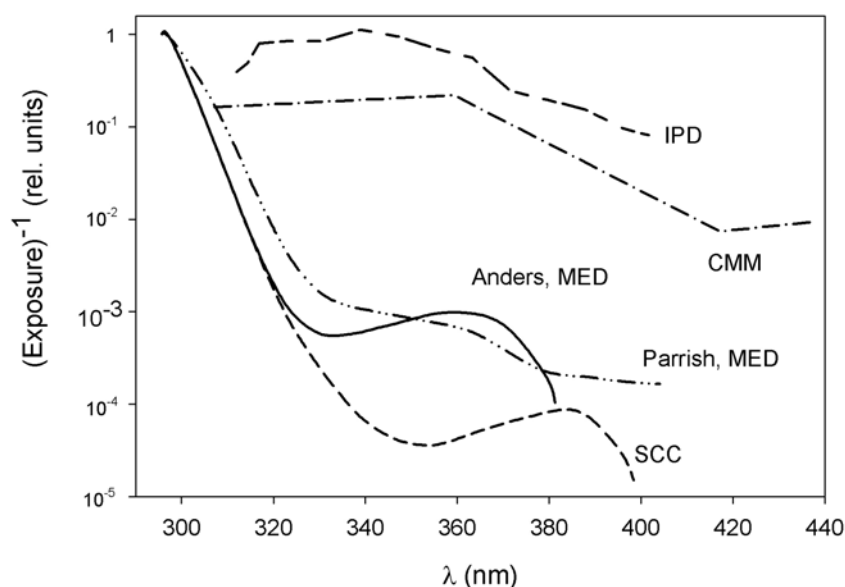


Figure 1. Action spectra for erythema (MED), melanogenesis, CMM in *Xiphophorus*, SCC in mice, immediate pigment darkening (IPD). That for vitamin D generation is similar to the SCC spectrum, but lacks the UVA peak.

to the two above mentioned spectra in the UVB range, making it hard to decide whether DNA or urocanic acid is the main chromophore for immune effects. The vitamin D action spectrum is also similar to the mentioned spectra but lacks the UVA peak. It has been measured in human skin up to about 310 nm, but can also be calculated from the absorption spectrum of 7-dehydrocholesterol, the chromophore for photosynthesis of the vitamin D precursor previtamin D. Using known absorption and scattering characteristics of epidermis and assuming that the most important site of formation of vitamin D is the lower epidermis, one gets a calculated action spectrum for vitamin D formation which is blue-shifted compared with the measured spectrum. This may be due to competing photoreactions of previtamin D and vitamin D. In any case, the long-wavelength part (>300 nm) of the spectrum is not known with sufficient accuracy to allow exact comparisons of the vitamin D generating potential of UVA sources,

although one can be almost sure that UVA alone produces negligible amounts of vitamin D. The elastosis spectrum is also similar to the erythema spectrum, while the IPD spectrum has a much larger UVA contribution than the other discussed spectra. The CMM spectrum resembles the IPD spectrum (Figure 1) and has also a surprisingly large UVA and even a visible light contribution, much larger than that of the SCC spectrum. This has been assumed to be caused by melanin absorption, since it is known that pheomelanin is photoactive and can generate free radicals upon light or UV exposure (72). We have proposed that melanin inside melanosomes acts as a photo carcinogen, while melanin in the upper skin layers acts as a sunscreen; the radicals formed there being unable to reach living and dividing cells during their lifetime (72).

Conclusions from spectral analysis

If the fish CMM spectrum is relevant for humans, large consequences will follow: UVA sun beds are more, rather than less, dangerous than UVB-weighted sun beds, and sunscreens, most of which have a much stronger absorption in UVB than in UVA, can efficiently prevent sunburn and vitamin D formation but not CMM induction. The inefficiency of sunscreens in CMM prevention (see below) may indicate that UVA plays a significant role in CMM generation. The latitude dose gradient is steeper for UVB than for UVA due to the fact that the ozone layer absorbs UVB, but not UVA (72). For instance, the annual UVB dose in South Australia is almost a factor of three larger than the corresponding dose in South Norway, while the annual UVA dose is only about 30% larger in Australia (72). This gives us an opportunity to evaluate the role of UVA and UVB for SCC, BCC and CMM on the basis of epidemiological data for Norway and Australia. The incidence rates of SCC and BCC have almost identical latitude gradients, and are 10-20 times more frequent in Australia than in Norway, while CMM is only a factor 1.7 more frequent in Australia than in Norway (72). This strongly indicates that UVA plays a larger role for CMM than for the non-melanoma skin cancers in humans. Furthermore, it suggests that the action spectra for BCC and SCC are similar, i.e. mainly UVB weighted, just as the spectra for erythema and vitamin D photosynthesis are.

Since UVB is almost absent from late September to early March in North Europe, including UK, there is no sunburn risk and no vitamin D formation in this period. This is supported by experiments (73). Similarly, during a summer day the UVA/UVB ratio is smallest around noon. Thus, if one wants to get maximally of vitamin D at a minimal CMM risk, midday midsummer is the best time for sun exposure. The general recommendation to avoid midday sun and rather sunbathe in the afternoon may be totally wrong! Of course, one should always limit the exposure time to avoid erythema.

The action spectra tell that as skin gets thicker and more pigmented during the summer season and the melanin moves upwards in the skin, the erythema risk, as well as the efficiency of vitamin D photosynthesis, decreases. The CMM risk, however, will not decrease to the same extent, and neither does immediate pigment darkening.

Of importance for our topic is that all sunscreens that reduce erythema and non-melanoma skin cancer risk, also reduce vitamin D formation and melanogenesis. One might construct a sun bed with a UVA spectrum giving pigmentation, at least IPD, but the erythema risk would exist and the CMM risk would probably be very large. However, people with naturally dark skin (skin types IV-VI) might benefit slightly from such UVA sun beds, as long as the CMM risk is not taken into account (74).

Sunscreens - epidemiological and clinical investigations

Practically all of the following results can be predicted by the spectral evaluations above. Since these two approaches, epidemiological investigations and spectral evaluations, are so different in nature, agreements between them should be given strong emphasis.

Sunscreens, properly applied, practically eliminate vitamin D photosynthesis in skin (75,76). It may be true, however, that they are rarely applied in recommended amounts (2 mg/cm^2), and that they, therefore, allow some vitamin D photosynthesis. However, most sunscreen campaigns strongly stress that “correct amounts of high SPF (≥ 15) should be applied, and frequently reapplied, during sun exposure”.

Such campaigns have led to an enormous increase of sunscreen sale: In USA the sale increased from 18 million dollars in 1972 to 640 million dollars in 2005 (77). In spite of this, the CMM incidence rate among Caucasians in USA has increased from 6.3/100 000 in 1973 to 16.5/100 000 in 1997 (78). In Norway the CMM rate increased from about 6/100 000 in 1970 to about 16/100 000 in 1990 (1).

Several reviews and meta-analyses of epidemiological investigations on the relationship between sunscreen use and CMM have been published (79-84). Most of these analyses conclude that no protective role of sunscreens can be demonstrated. This is true for the first analysis (from 1970ies) as well as for those carried out after 2000, so improvements of the sunscreens have not been documented so far. Many of the individual studies show that those applying sunscreens regularly had significantly higher risks of CMM than others (84,85). Several hypotheses for this have been discussed (85). The most frequently

mentioned one is that sunscreen use may tempt people to stay longer in the sun and thus get large UVA doses to the deeper part of their skin. Autier et al (80) showed that use of sunscreens increased the duration of recreational sun exposure of young Europeans. Another hypothesis is that the phenomenon is due to the fact that sunscreens reduce vitamin D photosynthesis in skin (75,76), and that sunscreen users have lower calcidiol levels than others and also lower bone mass density.

As with CMM, BCC incidence rates, and even nevi counts, seem to be higher rather than lower among sunscreen users (75,76,86-91). However, sunscreen use seems to decrease the risk of actinic keratosis (a SCC precursor) and SCC (92,93). Some sunscreens contain ingredients that penetrate into the circulation, notably that of small children with thin skin (94-96). Aromatic compounds might, in principle, be carcinogenic, and should be thoroughly checked before launched for human use that might involve systemic effects. Sun-induced mutagenicity of a common sunscreen ingredient has been clearly demonstrated (97). The physical sunscreens (TiO_2 , ZnO and FeO_2) were introduced because they were thought to be chemically inert and just scatter UV radiation. However, they are made in small particles (100-400nm) and may penetrate the stratum corneum. As long as they are outside living skin, their scattering properties are beneficial. However, inside skin they may act photo-catalytically and even lead to increased space irradiance of UV in certain skin layers. Some sunscreen products inhibit inducible nitric oxide synthesis (98). UV induced erythema is partly due to the synthesis of NO in the skin. NO is also an important regulator in the induction of cell-mediated immune responses in skin. NO synthesis in macrophages seems to delay progression of UV induced mouse tumours (99). In correspondence with this, some sunscreens are made to act even when applied after UV exposure (see references in (98)). It should also be kept in mind that sunscreens seem to reduce radical formation in skin much less efficiently than they reduce erythema (100). This might be important in the case of CMM, for which UVA seems to be important, since UVA is thought to act partly via radical formation. Psoralen-containing suncreams are quite efficient in reducing erythema without reducing pigmentation (79). UVB filters seemed to inhibit the carcinogenic properties of psoralens, and it was proposed that such creams might be a good alternative for people who wanted cancer protection and at the same time a good tan (101,102). However, according to the review of Autier et al (79) the assumed good properties of psoralen containing sunscreens have not been epidemiologically proven.

Sunscreens seem to protect against photoimmunosuppression (103), although the immune protection factor is less than the erythema protection factor (103,104). This may indicate that UVA is involved in the immunosuppression. Growth of CMMs transplanted to UV exposed mice is believed to be caused by immunosuppression. Sunscreens fail to protect well against such growth (105).

Benign melanocytic lesions, so called acquired nevi, increase in number with age, and are to a large extent caused by UV exposures, notably intermittent, burning ones. Such lesions are believed to be strong risk factors for CMM (106). Oppositely, congenital nevi, which are rare, seem to be markers for persons with decreased CMM risk (107). Since acquired nevi are associated with CMM in 50% of the cases, one might suggest that such nevi are CMM precursors (108-110). Two important arguments for sunscreens are that they appear to reduce development of acquired nevi (111) and inhibit mutations (in p53) which are believed to be involved in skin carcinogenesis (112).

Sun beds

UVA and UVB sun beds (See references in (113))

UVA acts deeper than UVB. UVB-tanning is dispersed throughout the epidermis, while UVA-tanning is principally confined to the basal layer. Some investigators believe that due to this, UVB provides a better protection against later UV-induced erythema than UVA. UVB-exposure leads to epidermal thickening. Both UVA and UVB alter the morphology of Langerhans cells and induce antigen presenting cells and suppressor T cells. On the other hand, there is suppression of natural killer cell activity. UVA induces immediate erythema and tanning, while UVB acts in a more delayed manner. Vascular occlusion prevents UVA-tanning, indicating that oxygen is needed in the initial step. This is probably due to the fact that DNA does not absorb UVA, which, therefore, acts through a radical or photosensitization process. A practical consequence of this is that skin in contact with the tanning bed, and therefore oxygen depleted, does not pigment significantly.

Conclusions based on spectra

There is nothing magic about artificial UV radiation, and no rational reason exists why radiation from such sources should be more dangerous than radiation from the sun. The effects totally depend on spectra and fluence rates. The fluence rate of UVB from sun beds is similar to, or slightly larger than that of UVB in solar radiation (114). It was believed that UVA gave a safer tanning than UVB, which was considered more carcinogenic. This was based on action spectra for melanogenesis in persons with dark skin of type V (74). Sun beds with rather large UVA fluence rates were then constructed. Thus, the UVA/UVB ratio is often larger for sun beds than for solar radiation at noon at low and mid latitudes (114). For low solar elevation, however, this ratio in solar radiation is large, even larger than that in sun beds. The magnitude of fluence rates may play a role for carcinogenesis. It seems that a UV dose given at a low fluence rate is more carcinogenic than the same dose given at a high fluence rate. This would be in favour of sun beds. A high UVA/UVB ratio, as found in newer sun beds and in solar radiation at low solar elevation, is disadvantageous

if the fish CMM action spectrum applies to humans. There is also another argument for decreasing this ratio, i.e. for producing sun beds with relatively more UVB, namely the physical efficiency of vitamin D photosynthesis. The action spectrum for this effect is exclusively in the UVB region (67). More than that: Due to complex back reactions and photoproduct degradation, only 15-20% of the 7-dehydrocholesterol in human skin can be converted to previtamin D by solar radiation, while as much as 65% can be converted by semi-monochromatic radiation around 290 nm (67). Small doses of such radiation would give plenty of vitamin D and good tanning at a moderate CMM risk. The visible light contribution of a source is another important issue, since visible light is able to repair DNA damage through photoreactivation. The cyclobutyl pyrimidine dimers removed in photoreactivation are believed to represent an important step in photocarcinogenesis (115). Again, the issue is complex, since pyrimidine dimers are also involved in melanogenesis. UVA acts mainly through radical generation, and the damage caused by this component is probably not photorepairable. In conclusion, at the present stage of knowledge one can propose that an optimal sun bed would be one emitting radiation around 290 nm and visible light. This would give an optimal yield of vitamin D at a minimal CMM risk.

Clinical and epidemiological work

Sun beds are more frequently used in the Nordic countries than in Southern Europe (116). Experiments clearly show that moderate and nonerythemogenic sun bed exposures give large contributions of vitamin D to humans (117-119). We carried out such an experiment with 10 exposures below the individual MED (minimal erythema dose) from a commercial sun bed over four weeks, and found an increase of the calcidiol level from 65 nM to about 92 nM. The experiment was carried out in winter time with no vitamin D contribution from the sun. The vitamin D status at the end of the sun bed sessions was similar to that in summer and autumn. This level decayed to the pre-sun bed level in about 6-8 weeks. Surprisingly, intake of the recommended winter dose of vitamin D (200 IU/day) played no role: The decay of calcidiol was as fast in persons supplemented with vitamin D as in those taking no supplements. Our experiments seem to indicate that the recommended vitamin D intake is too small to keep a summer vitamin D level constant in the absence of vitamin D generating radiation.

Some epidemiological investigations indicate that sun beds are CMM-generating (120,121) and refs in (116,122-124)). There has been no variation in the odds ratio over time (116,123-125), so the introduction of UVA sun beds has played no major role. In Norway sun bed use has increased steeply since 1990 (data from the Norwegian sun bed Association) while the CMM incidence rates have decreased rather than increased since 1990 (11). Other investigations show no effect, or even a protective effect of sun beds (see references in (124,125)).

Several review papers and meta analysis of such data have been published (116,123-125). Overall, these analyses indicate a slightly elevated CMM risk for sun bed users, with an odds ratio of 1.1 – 1.5.

When other cancers are brought into consideration the conclusion would be opposite. Our work has shown that the relative survival of breast-, prostate-, colon-, lung cancer and Hodgkin lymphoma is larger for diagnosis and treatment start in the season of high calcidiol levels (summer and autumn) (37-39,41,42). If such high levels could be maintained throughout the year, a large increase in cancer survival would result (126).

Conclusions

Solar radiation, notably UVB, is likely to be the main cause of SCC. The same is probably true for BCC. For CMM, however, no firm conclusion can be drawn. Regular, moderate UV exposures, from sun or sun beds, may act protectively, at least with respect to survival. Intermittent exposures may be significantly CMM generating. The action spectra for BCC, SCC, erythema, elastosis and melanogenesis are similar, with a main peak coinciding with DNA absorption in UVB and a shoulder around 360 nm in UVA. The action spectrum for immediate pigment darkening is more UVA-weighted than the spectra mentioned above. This is also true for the action spectrum of CMM in the fish *Xiphophorus*. Epidemiological data indicate that this spectrum may apply also to humans, although this has not been proven.

Sun beds are likely to act similarly as the sun, although they have a higher UVA contribution than midday summer sun. Epidemiological investigations have given no conclusive answers as to the role of sun beds for humans, although recent meta-analyses indicate that they may increase the CMM risk slightly (odds ratio around 1.15).

Concerning sunscreens, the situation is even more confusing. In the worst case they may be photocarcinogenic and increase the CMM risk. Sun beds give good contributions of vitamin D, since practically all of them emit some UVB (>1%). Sunscreens, properly applied, eliminate vitamin D photosynthesis from any source, sun or sun beds.

Acknowledgements

The present work was supported by Sigval Bergesen D.Y. og hustru Nankis Foundation, by The Research Foundation of The Norwegian Radiumhospital and Helse Sør Health Enterprise.

References

1. Cancer in Norway 2005, in F.Brav (Ed.), 2006.
2. Moan J, Dahlback A. Ultraviolet radiation and skin cancer: Epidemiologic data from Scandinavia. In Bjørn LO, Moan J, Nultsch W, Young AR, eds. *Environmental UV Photobiology*, New York: Plenum Press, 1993: 255-192.
3. Armstrong BK, Kricger A. How much melanoma is caused by sun exposure? *Melanoma Res.* 1993; **3** (6): 395-401.
4. Green A, Battistutta D. Incidence and determinants of skin cancer in a high-risk Australian population. *Int J Cancer* 1990; **46** (3): 356-361.
5. Boukamp P. Non-melanoma skin cancer: what drives tumor development and progression? *Carcinogenesis* 2005; **26** (10): 1657-1667.
6. Salasche SJ. Epidemiology of actinic keratoses and squamous cell carcinoma. *J Am Acad Dermatol* 2000; **42** (1 Pt 2): 4-7.
7. de Gruijl FR, Sterenborg HJ, Forbes PD, Davies RE, Cole C, Kelfkens G, van Weelden H, Slaper H, van der Leun JC. Wavelength dependence of skin cancer induction by ultraviolet irradiation of albino hairless mice. *Cancer Res* 1993; **53** (1): 53-60.
8. de Gruijl FR, Forbes PD. UV-induced skin cancer in a hairless mouse model. *Bioessays* 1995; **17** (7): 651-660.
9. Josefsson AP. Monitoring ultraviolet radiation. In Young AR, Bjørn LO, Moan J, Nultsch W, eds. *Environmental UV photobiology*, New York: Plenum Press, 1993: 73-85.
10. de Gruijl FR, van der Leun JC. Influence of ozone depletion on the incidence of skin cancer: quantitative prediction. In Young AR, Bjørn LO, Moan J, Nultsch W, eds. *Environmental UV photobiology*, New York: Plenum Press, 2007: 89-109.
11. Moan J, Porojnicu AC, Dahlback A. Epidemiology of cutaneous malignant melanoma. In Ringborg U, Brandberg Y, Breitbart EW, Greinert R, eds. *Skin cancer prevention*, New York: Informa Healthcare, 2006: 179-201.
12. Moan J, Porojnicu AC, Dahlback A. Cutaneous malignant melanoma (CMM) epidemiology in Norway. In Reichrath J, eds. *Sunlight, vitamin D and skin cancer*, Landes Bioscience, 2007.
13. Elwood JM, Jopson J. Melanoma and sun exposure: an overview of published studies. *Int J Cancer* 1997; **73** (2): 198-203.
14. Holman CD, Armstrong BK, Heenan PJ. Relationship of cutaneous malignant melanoma to individual sunlight-exposure habits. *J Natl Cancer Inst* 1986; **76** (3): 403-414.
15. Beral V, Evans S, Shaw H, Milton G. Malignant melanoma and exposure to fluorescent lighting at work. *Lancet* 1982; **2** (8293): 290-293.

16. Kennedy AR, Ritter MA, Little JB. Fluorescent light induces malignant transformation in mouse embryo cell cultures. *Science* 1980; **207** (4436): 1209-1211.
17. Rittie L, Fisher GJ. UV-light-induced signal cascades and skin aging. *Ageing Res Rev* 2002; **1** (4): 705-720.
18. Wlaschek M, Tancheva-Poor I, Naderi L, Ma W, Schneider LA, Razi-Wolf Z, Schuller J, Scharffetter-Kochanek K. Solar UV irradiation and dermal photoaging. *J Photochem Photobiol B* 2001; **63** (1-3): 41-51.
19. Young AR. Acute effects of UVR on human eyes and skin. *Prog Biophys Mol Biol* 2006; **92** (1): 80-85.
20. Cullen AP. Photokeratitis and other phototoxic effects on the cornea and conjunctiva. *Int J Toxicol* 2002; **21** (6): 455-464.
21. Balasubramanian D. Ultraviolet radiation and cataract. *J Ocul Pharmacol Ther* 2000; **16** (3): 285-297.
22. Schade N, Esser C, Krutmann J. Ultraviolet B radiation-induced immunosuppression: molecular mechanisms and cellular alterations. *Photochem Photobiol Sci* 2005; **4** (9): 699-708.
23. Ullrich SE. Mechanisms underlying UV-induced immune suppression. *Mutat Res* 2005; **571** (1-2): 185-205.
24. Sigmundsdottir H, Pan J, Debes GF, Alt C, Habtezion A, Soler D, Butcher EC. DCs metabolize sunlight-induced vitamin D3 to 'program' T cell attraction to the epidermal chemokine CCL27. *Nat Immunol* 2007; **8** (3): 285-293.
25. Liu PT, Stenger S, Li H, Wenzel L, Tan BH, Krutzik SR, Ochoa MT, Schaubert J, Wu K, Meinken C, Kamen DL, Wagner M, Bals R, Steinmeyer A, Zugel U, Gallo RL, Eisenberg D, Hewison M, Hollis BW, Adams JS, Bloom BR, Modlin RL. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science* 2006; **311** (5768): 1770-1773.
26. Wang TT, Nestel FP, Bourdeau V, Nagai Y, Wang Q, Liao J, Tavera-Mendoza L, Lin R, Hanrahan JW, Mader S, White JH. Cutting edge: 1,25-dihydroxyvitamin D3 is a direct inducer of antimicrobial peptide gene expression. *J Immunol* 2004; **173** (5): 2909-2912.
27. Martineau AR, Honecker FU, Wilkinson RJ, Griffiths CJ. Vitamin D in the treatment of pulmonary tuberculosis. *J Steroid Biochem Mol Biol* 2007; **103** (3-5): 793-798.
28. Martineau AR, Wilkinson RJ, Wilkinson KA, Newton SM, Kampmann B, Hall BM, Packe GE, Davidson RN, Eldridge SM, Maunsell ZJ, Rainbow SJ, Berry JL, Griffiths CJ. A Single Dose of Vitamin D Enhances Immunity to Mycobacteria. *Am J Respir Crit Care Med* 2007;
29. Cannell JJ, Vieth R, Umhau JC, Holick MF, Grant WB, Madronich S, Garland CF, Giovannucci E. Epidemic influenza and vitamin D. *Epidemiol Infect* 2006; **134** (6): 1129-1140.
30. Dawson L. Naked and unashamed. *Lancet* 1932; 688.

31. Peller S. Carcinogenesis as a means of reducing cancer mortality. *Lancet* 2007; **2**: 552-556.
32. Garland CF, Mohr SB, Gorham ED, Grant WB, Garland FC. Role of ultraviolet B irradiance and vitamin D in prevention of ovarian cancer. *Am J Prev Med* 2006; **31** (6): 512-514.
33. Garland CF, Gorham ED, Mohr SB, Grant WB, Giovannucci EL, Lipkin M, Newmark H, Holick MF, Garland FC. Vitamin D and prevention of breast cancer: pooled analysis. *J Steroid Biochem Mol Biol* 2007; **103** (3-5): 708-711.
34. Giovannucci E. The epidemiology of vitamin D and cancer incidence and mortality: A review (United States). *Cancer Causes Control* 2005; **16** (2): 83-95.
35. Tuohimaa P, Pukkala E, Scelo G, Olsen JH, Brewster DH, Hemminki K, Tracey E, Weiderpass E, Kliewer EV, Pompe-Kirn V, McBride ML, Martos C, Chia KS, Tonita JM, Jonasson JG, Boffetta P, Brennan P. Does solar exposure, as indicated by the non-melanoma skin cancers, protect from solid cancers: Vitamin D as a possible explanation. *Eur J Cancer* 2007; Epub ahead of print.
36. Grant WB, Garland CF, Gorham ED. An estimate of cancer mortality rate reductions in Europe and the US with 1,000 IU of oral vitamin D per day. *Recent Results Cancer Res* 2007; **174:225-34**: 225-234.
37. Moan J, Porojnicu AC, Robsahm TE, Dahlback A, Juzeniene A, Tretli S, Grant W. Solar radiation, vitamin D and survival rate of colon cancer in Norway. *J Photochem Photobiol B* 2005; **78** (3): 189-193.
38. Porojnicu AC, Robsahm TE, Hansen Ree A, Moan J. Season of diagnosis is a prognostic factor in Hodgkin lymphoma. A possible role of sun-induced vitamin D. *Br J Cancer* 2005; **93**: 571-574.
39. Robsahm TE, Tretli S, Dahlback A, Moan J. Vitamin D3 from sunlight may improve the prognosis of breast-, colon- and prostate cancer (Norway). *Cancer Causes Control* 2004; **15** (2): 149-158.
40. Schwartz GG, Hanchette CL. UV, latitude, and spatial trends in prostate cancer mortality: all sunlight is not the same (United States). *Cancer Causes Control* 2006; **17** (8): 1091-1101.
41. Porojnicu AC, Lagunova Z, Robsahm TE, Berg JP, Dahlback A, Moan J. Changes in risk of death from breast cancer with season and latitude : Sun exposure and breast cancer survival in Norway. *Breast Cancer Res Treat* 2007; **102** (3): 323-328.
42. Porojnicu AC, Robsahm TE, Dahlback A, Berg JP, Christiani DC, Bruland OS, Moan J. Seasonal and geographical variations in lung cancer prognosis in Norway. Does vitamin D from the sun play a role? *Lung Cancer* 2007; **55** (3): 263-270.
43. Zemel MB. Calcium utilization: effect of varying level and source of dietary protein. *Am J Clin Nutr* 1988; **48** (3 Suppl): 880-883.

44. Merlino LA, Curtis J, Mikuls TR, Cerhan JR, Criswell LA, Saag KG. Vitamin D intake is inversely associated with rheumatoid arthritis: results from the Iowa Women's Health Study. *Arthritis Rheum* 2004; **50** (1): 72-77.
45. Cantorna MT, Hayes CE, DeLuca HF. 1,25-Dihydroxycholecalciferol inhibits the progression of arthritis in murine models of human arthritis. *J Nutr* 1998; **128** (1): 68-72.
46. Janssen HC, Samson MM, Verhaar HJ. Vitamin D deficiency, muscle function, and falls in elderly people. *Am J Clin Nutr* 2002; **75** (4): 611-615.
47. Bischoff-Ferrari HA, Dietrich T, Orav EJ, Hu FB, Zhang Y, Karlson EW, wson-Hughes B. Higher 25-hydroxyvitamin D concentrations are associated with better lower-extremity function in both active and inactive persons aged > or =60 y. *Am J Clin Nutr* 2004; **80** (3): 752-758.
48. Bischoff-Ferrari HA, Orav EJ, wson-Hughes B. Effect of cholecalciferol plus calcium on falling in ambulatory older men and women: a 3-year randomized controlled trial. *Arch Intern Med* 2006; **166** (4): 424-430.
49. Van Veldhuizen PJ, Taylor SA, Williamson S, Drees BM. Treatment of vitamin D deficiency in patients with metastatic prostate cancer may improve bone pain and muscle strength. *J Urol* 2000; **163** (1): 187-190.
50. Kaur M, Feldman SR, Liguori A, Fleischer AB, Jr. Indoor tanning relieves pain. *Photodermatol Photoimmunol Photomed* 2005; **21** (5): 278.
51. Visser M, Deeg DJ, Lips P. Low vitamin D and high parathyroid hormone levels as determinants of loss of muscle strength and muscle mass (sarcopenia): the Longitudinal Aging Study Amsterdam. *J Clin Endocrinol Metab* 2003; **88** (12): 5766-5772.
52. Holick MF. Vitamin D and the skin:photobiology, physiology and therapeutic efficacy for psoriasis. In Heersche JNM, Kanis JA, eds. *Bone and Mineral Research*, Amsterdam: Elsevier, 1990: 313-366.
53. Grimes DS, Hindle E, Dyer T. Sunlight, cholesterol and coronary heart disease. *QJM* 1996; **89** (8): 579-589.
54. Pell JP, Cobbe SM. Seasonal variations in coronary heart disease. *QJM* 1999; **92** (12): 689-696.
55. Zittermann A, Schleithoff SS, Koerfer R. Putting cardiovascular disease and vitamin D insufficiency into perspective. *Br J Nutr* 2005; **94** (4): 483-492.
56. Hahn S, Haselhorst U, Tan S, Quadbeck B, Schmidt M, Roesler S, Kimmig R, Mann K, Janssen OE. Low serum 25-hydroxyvitamin D concentrations are associated with insulin resistance and obesity in women with polycystic ovary syndrome. *Exp Clin Endocrinol Diabetes* 2006; **114** (10): 577-583.
57. Pittas AG, wson-Hughes B, Li T, Van Dam RM, Willett WC, Manson JE, Hu FB. Vitamin D and calcium intake in relation to type 2 diabetes in women. *Diabetes Care* 2006; **29** (3): 650-656.

58. Di Cesar DJ, Ploutz-Snyder R, Weinstock RS, Moses AM. Vitamin D deficiency is more common in type 2 than in type 1 diabetes. *Diabetes Care* 2006; **29** (1): 174.
59. Gilman J, Shanahan F, Cashman KD. Determinants of vitamin D status in adult Crohn's disease patients, with particular emphasis on supplemental vitamin D use. *Eur J Clin Nutr* 2006; **60** (7): 889-896.
60. Kim JS, Kim YI, Song C, Yoon I, Park JW, Choi YB, Kim HT, Lee KS. Association of vitamin D receptor gene polymorphism and Parkinson's disease in Koreans. *J Korean Med Sci* 2005; **20** (3): 495-498.
61. Al-Allaf AW, Mole PA, Paterson CR, Pullar T. Bone health in patients with fibromyalgia. *Rheumatology (Oxford)* 2003; **42** (10): 1202-1206.
62. Martini LA, Wood RJ. Vitamin D status and the metabolic syndrome. *Nutr Rev* 2006; **64** (11): 479-486.
63. Studzinski GP, Moore DC. Sunlight - can it prevent as well as cause cancer? *Cancer Res* 1995; **55** (18): 4014-4022.
64. Moan J, Johnsen B. What kind of radiation is efficient in solarium, UVA or UVB? *J. Photochem Photobiol B* 1994; **22** (1): 77-79.
65. Anders A, Altheide HJ, Knalmann M, Tronnier H. Action spectrum for erythema in humans investigated with dye lasers. *Photochem Photobiol* 1995; **61** (2): 200-205.
66. Parrish JA, Jaenicke KF, Anderson RR. Erythema and melanogenesis action spectra of normal human skin. *Photochem Photobiol* 1982; **36** (2): 187-191.
67. MacLaughlin JA, Anderson RR, Holick MF. Spectral character of sunlight modulates photosynthesis of previtamin D₃ and its photoisomers in human skin. *Science* 1982; **216** (4549): 1001-1003.
68. Kligman LH, Sayre RM. An action spectrum for ultraviolet induced elastosis in hairless mice: quantification of elastosis by image analysis. *Photochem Photobiol* 1991; **53** (2): 237-242.
69. Irwin C, Barnes A, Veres D, Kaidbey K. An ultraviolet radiation action spectrum for immediate pigment darkening. *Photochem Photobiol* 1993; **57** (3): 504-507.
70. Gibbs NK, Norval M, Traynor NJ, Wolf M, Johnson BE, Crosby J. Action spectra for the trans to cis photoisomerisation of urocanic acid in vitro and in mouse skin. *Photochem Photobiol* 1993; **57** (3): 584-590.
71. Setlow RB, Grist E, Thompson K, Woodhead AD. Wavelengths effective in induction of malignant melanoma. *Proc Natl Acad Sci U. S. A* 1993; **90** (14): 6666-6670.
72. Moan J, Dahlback A, Setlow RB. Epidemiological support for an hypothesis for melanoma induction indicating a role for UVA radiation. *Photochem Photobiol* 1999; **70** (2): 243-247.
73. Webb AR, Kline L, Holick MF. Influence of season and latitude on the cutaneous synthesis of vitamin D₃: exposure to winter sunlight in Boston

- and Edmonton will not promote vitamin D₃ synthesis in human skin. *J Clin Endocrinol Metab* 1988; **67** (2): 373-378.
74. Kollias N, Malallah YH, al-Ajmi H, Baqer A, Johnson BE, Gonzalez S. Erythema and melanogenesis action spectra in heavily pigmented individuals as compared to fair-skinned Caucasians. *Photodermatol Photoimmunol Photomed* 1996; **12** (5): 183-188.
 75. Matsuoka LY, Ide L, Wortsman J, MacLaughlin JA, Holick MF. Sunscreens suppress cutaneous vitamin D₃ synthesis. *J Clin Endocrinol Metab* 1987; **64** (6): 1165-1168.
 76. Matsuoka LY, Wortsman J, Hanifan N, Holick MF. Chronic sunscreen use decreases circulating concentrations of 25-hydroxyvitamin D. A preliminary study. *Arch Dermatol* 1988; **124** (12): 1802-1804.
 77. Moss RW, Another dissident dermatologist, 2005.
 78. Jemal A, Devesa SS, Hartge P, Tucker MA. Recent trends in cutaneous melanoma incidence among whites in the United States. *J Natl Cancer Inst* 2001; **93** (9): 678-683.
 79. Autier P, Dore JF, Schiffers E, Cesarini JP, Bollaerts A, Koelmel KF, Gefeller O, Liabeuf A, Lejeune F, Lienard D. Melanoma and use of sunscreens: an EORTC case-control study in Germany, Belgium and France. The EORTC Melanoma Cooperative Group. *Int J Cancer* 1995; **61** (6): 749-755.
 80. Autier P, Dore JF, Negrier S, Lienard D, Panizzon R, Lejeune FJ, Guggisberg D, Eggermont AM. Sunscreen use and duration of sun exposure: a double-blind, randomized trial. *J Natl Cancer Inst* 1999; **91** (15): 1304-1309.
 81. Weinstock MA. Do sunscreens increase or decrease melanoma risk: an epidemiologic evaluation. *J Invest Dermatol Symp Proc* 1999; **4** (1): 97-100.
 82. Wolf R, Wolf D, Morganti P, Ruocco V. Sunscreens. *Clin Dermatol* 2001; **19** (4): 452-459.
 83. Huncharek M, Kupelnick B. Use of topical sunscreens and the risk of malignant melanoma: a meta-analysis of 9067 patients from 11 case-control studies. *Am J Public Health* 2002; **92** (7): 1173-1177.
 84. Dennis LK, Beane Freeman LE, VanBeek MJ. Sunscreen use and the risk for melanoma: a quantitative review. *Ann Intern Med* 2003; **139** (12): 966-978.
 85. Westerdahl J, Olsson H, Masback A, Ingvar C, Jonsson N. Is the use of sunscreens a risk factor for malignant melanoma? *Melanoma Res* 1995; **5** (1): 59-65.
 86. Beitner H, Norell SE, Ringborg U, Wennersten G, Mattson B. Malignant melanoma: aetiological importance of individual pigmentation and sun exposure. *Br J Dermatol* 1990; **122** (1): 43-51.
 87. Luther H, Altmeyer P, Garbe C, Ellwanger U, Jahn S, Hoffmann K, Segerling M. Increase of melanocytic nevus counts in children during 5

- years of follow-up and analysis of associated factors. *Arch Dermatol* 1996; **132** (12): 1473-1478.
88. Krickler A, Armstrong BK, English DR, Heenan PJ. Does intermittent sun exposure cause basal cell carcinoma? a case-control study in Western Australia. *Int J Cancer* 1995; **60** (4): 489-494.
 89. Harvey I, Frankel S, Marks R, Shalom D, Nolan-Farrell M. Non-melanoma skin cancer and solar keratoses II analytical results of the South Wales Skin Cancer Study. *Br J Cancer* 1996; **74** (8): 1308-1312.
 90. Koh HK, Bak SM, Geller AC, Mangione TW, Hingson RW, Levenson SM, Miller DR, Lew RA, Howland J. Sunbathing habits and sunscreen use among white adults: results of a national survey. *Am J Public Health* 1997; **87** (7): 1214-1217.
 91. Autier P, Dore JF, Cattaruzza MS, Renard F, Luther H, Gentiloni-Silverj F, Zantedeschi E, Mezzetti M, Monjaud I, Andry M, Osborn JF, Grivegne AR. Sunscreen use, wearing clothes, and number of nevi in 6- to 7-year-old European children. European Organization for Research and Treatment of Cancer Melanoma Cooperative Group. *J Natl Cancer Inst* 1998; **90** (24): 1873-1880.
 92. Thompson SC, Jolley D, Marks R. Reduction of solar keratoses by regular sunscreen use. *N Engl J Med* 1993; **329** (16): 1147-1151.
 93. Naylor MF, Boyd A, Smith DW, Cameron GS, Hubbard D, Neldner KH. High sun protection factor sunscreens in the suppression of actinic neoplasia. *Arch Dermatol* 1995; **131** (2): 170-175.
 94. Janjua NR, Mogensen B, Andersson AM, Petersen JH, Henriksen M, Skakkebaek NE, Wulf HC. Systemic absorption of the sunscreens benzophenone-3, octyl-methoxycinnamate, and 3-(4-methyl-benzylidene) camphor after whole-body topical application and reproductive hormone levels in humans. *J Invest Dermatol* 2004; **123** (1): 57-61.
 95. Benson HA. Assessment and clinical implications of absorption of sunscreens across skin. *Am J Clin Dermatol* 2000; **1** (4): 217-224.
 96. Hayden CG, Roberts MS, Benson HA. Systemic absorption of sunscreen after topical application. *Lancet* 1997; **350** (9081): 863-864.
 97. Knowland J, McKenzie EA, McHugh PJ, Cridland NA. Sunlight-induced mutagenicity of a common sunscreen ingredient. *FEBS Lett* 1993; **324** (3): 309-313.
 98. Chiang TM, Sayre RM, Dowdy JC, Wilkin NK, Rosenberg EW. Sunscreen ingredients inhibit inducible nitric oxide synthase (iNOS): a possible biochemical explanation for the sunscreen melanoma controversy. *Melanoma Res* 2005; **15** (1): 3-6.
 99. Yim CY, Bastian NR, Smith JC, Hibbs JB, Jr., Samlowski WE. Macrophage nitric oxide synthesis delays progression of ultraviolet light-induced murine skin cancers. *Cancer Res* 1993; **53** (22): 5507-5511.

100. Haywood R, Wardman P, Sanders R, Linge C. Sunscreens inadequately protect against ultraviolet-A-induced free radicals in skin: implications for skin aging and melanoma? *J Invest Dermatol* 2003; **121** (4): 862-868.
101. Young AR, Magnus IA, Davies AC, Smith NP. A comparison of the phototumorigenic potential of 8-MOP and 5-MOP in hairless albino mice exposed to solar simulated radiation. *Br J Dermatol* 1983; **108** (5): 507-518.
102. Young AR, Potten CS, Chadwick CA, Murphy GM, Cohen AJ. Inhibition of UV radiation-induced DNA damage by a 5-methoxypsoralen tan in human skin. *Pigment Cell Res* 1988; **1** (5): 350-354.
103. Poon TS, Barnetson RS, Halliday GM. Prevention of immunosuppression by sunscreens in humans is unrelated to protection from erythema and dependent on protection from ultraviolet a in the face of constant ultraviolet B protection. *J Invest Dermatol* 2003; **121** (1): 184-190.
104. Kelly DA, Seed PT, Young AR, Walker SL. A commercial sunscreen's protection against ultraviolet radiation-induced immunosuppression is more than 50% lower than protection against sunburn in humans. *J Invest Dermatol* 2003; **120** (1): 65-71.
105. Wolf P, Donawho CK, Kripke ML. Effect of sunscreens on UV radiation-induced enhancement of melanoma growth in mice. *J Natl Cancer Inst* 1994; **86** (2): 99-105.
106. Green A, MacLennan R, Siskind V. Common acquired naevi and the risk of malignant melanoma. *Int J Cancer* 1985; **35** (3): 297-300.
107. Rivers JK, Frederiksen PC, Dibdin C. A prevalence survey of dermatoses in the Australian neonate. *J Am Acad Dermatol* 1990; **23** (1): 77-81.
108. Skender-Kalnenas TM, English DR, Heenan PJ. Benign melanocytic lesions: risk markers or precursors of cutaneous melanoma? *J Am Acad Dermatol* 1995; **33** (6): 1000-1007.
109. Kruger S, Garbe C, Buttner P, Stadler R, Guggenmoos-Holzmann I, Orfanos CE. Epidemiologic evidence for the role of melanocytic nevi as risk markers and direct precursors of cutaneous malignant melanoma. Results of a case control study in melanoma patients and nonmelanoma control subjects. *J Am Acad Dermatol* 1992; **26** (6): 920-926.
110. Grob JJ, Gouvernet J, Aymar D, Mostaque A, Romano MH, Collet AM, Noe MC, Diconstanzo MP, Bonerandi JJ. Count of benign melanocytic nevi as a major indicator of risk for nonfamilial nodular and superficial spreading melanoma. *Cancer* 1990; **66** (2): 387-395.
111. Gallagher RP, Rivers JK, Lee TK, Bajdik CD, McLean DI, Coldman AJ. Broad-spectrum sunscreen use and the development of new nevi in white children: A randomized controlled trial. *JAMA* 2000; **283** (22): 2955-2960.
112. Ananthaswamy HN, Loughlin SM, Cox P, Evans RL, Ullrich SE, Kripke ML. Sunlight and skin cancer: inhibition of p53 mutations in UV-irradiated mouse skin by sunscreens. *Nat Med* 1997; **3** (5): 510-514.

113. Spencer JM, Amonette RA. Indoor tanning: risks, benefits, and future trends. *J Am Acad Dermatol* 1995; **33** (2 Pt 1): 288-298.
114. Miller SA, Hamilton SL, Wester UG, Cyr WH. An analysis of UVA emissions from sunlamps and the potential importance for melanoma. *Photochem Photobiol* 1998; **68** (1): 63-70.
115. Freeman SE, Hacham H, Gange RW, Maytum DJ, Sutherland JC, Sutherland BM. Wavelength dependence of pyrimidine dimer formation in DNA of human skin irradiated in situ with ultraviolet light. *Proc Natl Acad Sci U. S. A.* 1989; **86** (14): 5605-5609.
116. Gallagher RP, Spinelli JJ, Lee TK. Tanning beds, sunlamps, and risk of cutaneous malignant melanoma. *Cancer Epidemiol Biomarkers Prev* 2005; **14** (3): 562-566.
117. Tangpricha V, Turner A, Spina C, Decastro S, Chen TC, Holick MF. Tanning is associated with optimal vitamin D status (serum 25-hydroxyvitamin D concentration) and higher bone mineral density. *Am J Clin Nutr* 2004; **80** (6): 1645-1649.
118. Chen TC, Lu Z, Perez A, Holick MF. Cutaneous synthesis of vitamin D₃ in response to sun-tanning bed radiation. In Holick MF, Jung EG, eds. *Biologic effects of light*, Berlin: Walter De Gruyter & Company, 1992: 28-33.
119. Shao Q, Chen TC, Holick MF. Sun-tanning bed radiation increases vitamin D synthesis in human skin in vivo. In Holick MF, Kligman AM, eds. *Biologic effects of light*, Berlin: Walter de Gruyter, 1992: 57-61.
120. Bataille V, Winnett A, Sasieni P, Newton Bishop JA, Cuzick J. Exposure to the sun and sunbeds and the risk of cutaneous melanoma in the UK: a case-control study. *Eur J Cancer* 2004; **40** (3): 429-435.
121. Han J, Colditz GA, Hunter DJ. Risk factors for skin cancers: a nested case-control study within the Nurses' Health Study. *Int J Epidemiol* 2006; **35** (6): 1514-1521.
122. Autier P. Perspectives in melanoma prevention: the case of sunbeds. *Eur J Cancer* 2004; **40** (16): 2367-2376.
123. Young AR. Tanning devices--fast track to skin cancer? *Pigment Cell Res* 2004; **17** (1): 2-9.
124. Levine JA, Sorace M, Spencer J, Siegel DM. The indoor UV tanning industry: a review of skin cancer risk, health benefit claims, and regulation. *J Am Acad Dermatol* 2005; **53** (6): 1038-1044.
125. The international agency for research on cancer working group on artificial ultraviolet (UV) light and skin cancer. The association of use of sunbeds with cutaneous malignant melanoma and other skin cancers: A systematic review. *Int J Cancer* 2007; **120** (5): 1116-1122.
126. Moan J, Porojnicu AC. The photobiology of vitamin D-a topic of renewed focus. *Tidsskr Nor Laegeforen* 2006; **126** (8): 1048-1052.