

Review

Sunlight: For Better or For Worse? A Review of Positive and Negative Effects of Sun Exposure

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Abstract

During the last decades new, mainly favorable, associations between sunlight and disease have been discovered, initially ascribed to vitamin D. There is, however, accumulating evidence that the formation of nitric oxide, melatonin, serotonin, endorphin, photodegradation of folic acid, immunomodulation, photoadaptation, and the effect of (sun)light on circadian clocks, are involved as well. After a systematic search in the literature, a summary is given of (recent) research on the health effects of sun exposure and the possibly involved mechanisms.

In the last 200 years our exposure to sunlight has changed radically: from a more continuous to an intermittent exposure. Our exposure to light during the day and to artificial light in the evening and at night has changed as well. The present 'epidemic' of skin cancer is mainly caused by the increase of intermittent sun exposure, coinciding with decrease of chronic exposure. Effects of chronic and occupational exposure appear to be latitude-dependent: risk of skin cancer decreases with increasing latitude. In North-western Europe chronic exposure yields a relatively low risk of melanoma and (to a lesser degree) of basal cell carcinoma and squamous cell carcinoma. There is epidemiological and experimental evidence that chronic exposure to sunlight could contribute to the prevention of colorectal-, breast-, prostate cancer, non-Hodgkin Lymphoma, multiple sclerosis, and metabolic syndrome. The possible consequences of these findings for public health messages on sun exposure are discussed. It is concluded that both too much and too little sunlight may be harmful to our health.

Keywords: skin cancer, colon cancer, breast cancer, non-Hodgkin lymphoma, metabolic syndrome, multiple sclerosis, sunlight, vitamin D, circadian clocks, nitric oxide

1. Introduction

The beginning of the 20th century saw a rise in the advocacy of ultraviolet (UV) exposure both as a prophylactic measure against rickets and infectious disease and as treatment for patients with chronic ulcers, cutaneous and other forms of tuberculosis (1,2,3). These medical opinions played a significant role in the popularity of recreational sunbathing (4).

Decades later an increase in the incidence of skin cancer was noted, starting in northern Australia, with its (sub)tropical climate and its population with a sun-sensitive skin (5-7). In 1992 the WHO concluded that solar UV radiation is the main environmental cause of skin cancer (5).

The positive and negative influence of sun exposure is well-established now for a number of diseases. (Table 1) During the last decades new associations between sunlight and disease (particularly colon-, breast-, prostate cancer, non-Hodgkin lymphoma, multiple sclerosis, and

metabolic syndrome) were discovered, initially ascribed to vitamin D. However, it became evident that vitamin D is not the only potential mechanism of action for these effects of sunlight (11-16).

This review presents the available data on the relationship between sunlight (both ultraviolet rays and visible light) and:

- the risk of skin-, colon-, breast-, prostate cancer, and non-Hodgkin lymphoma,
- the risk of multiple sclerosis, and metabolic syndrome.

Skin pigmentation and skin color are correlated strongly with UV radiation. Since pigmentation is an important factor in regulating the penetration of UV rays into the skin, it has effects on health. Migration, the rise of rapid long-distance transportation, and lifestyle changes have led to a completely different exposure to sunlight, in comparison with our ancestors. The health consequences of this change in exposure are often underestimated

Table 1. Established negative and positive effects of sunlight.

Negative effects	Positive effects
Induction of skin cancer: <ul style="list-style-type: none"> - basal cell carcinoma, - squamous cell carcinoma, - melanoma Photo-ageing Photodermatoses, like: <ul style="list-style-type: none"> - polymorphic light eruption, - solar urticaria, - photo-allergic and -toxic reactions Aggravation of skin diseases like <ul style="list-style-type: none"> - rosacea - Chronic Discoid Lupus Erythematosus Aggravation of eye diseases: <ul style="list-style-type: none"> - cataract - macular degeneration Aggravation of internal disease: <ul style="list-style-type: none"> - Systemic Lupus Erythematosus - Porphyrias 	Prevention and treatment of skin diseases like <ul style="list-style-type: none"> - psoriasis, - eczema, - vitiligo - acne Photosynthesis of vitamin D, important for bone and muscle health Prevention and treatment of seasonal affective disorder

Sources: references 8-10

Table 2. Search strategy.

Subject	Mesh terms
Skin Cancer	Melanoma or basal cell carcinoma or cutaneous squamous cell carcinoma and sunlight or ultraviolet rays or vitamin D or circadian rhythm or circadian clocks or light
Colorectal cancer	Colonic neoplasms or rectal neoplasms or colorectal neoplasms and sunlight or ultraviolet rays or vitamin D or circadian rhythm or circadian clocks or light
Breast cancer	Breast neoplasms and sunlight or ultraviolet rays or vitamin D or circadian rhythm or circadian clocks or light
Prostate cancer	Prostatic neoplasms and sunlight or ultraviolet rays or vitamin D or circadian rhythm or circadian clocks or light
Non-Hodgkin lymphoma	Lymphoma Non-Hodgkin and sunlight or ultraviolet rays or vitamin D or circadian rhythm or circadian clocks or light
Multiple sclerosis	Multiple sclerosis and sunlight or ultraviolet rays or vitamin D or circadian rhythm or circadian clocks or light
Metabolic syndrome	Metabolic syndrome or diabetes mellitus or hypertension and sunlight or ultraviolet rays or vitamin D or circadian rhythm or circadian clocks or light

A literature search was performed in Pubmed from 1 January 2004 until 1 October 2015. The mesh terms used are given in the right column.

(17-20). Therefore this review begins with a brief summary of the present knowledge of the relationship between (the evolution of) skin pigmentation, sun exposure, and health. Finally, the biological mechanisms activated by sunlight will be described.

2. Methods

A systematic search of the literature was performed as described in table 2. Epidemiological, experimental, and clinical studies on colon-, breast-, prostate cancer, non-Hodgkin lymphoma, multiple sclerosis, and metabolic syndrome, were evaluated. All identified titles and abstracts were reviewed by one of the authors (Van der Rhee). The initial inclusion criteria were: studies with original data that met the following demands: investigating

the effect of sunlight on the subjects mentioned above, with a clear description of methodology and containing effect estimates with *P* value or confidence intervals. Further details are described elsewhere (21).

For most of the topics mentioned (skin-, colon-, breast-, prostate cancer, non-Hodgkin lymphoma, and sunlight or vitamin D; metabolic syndrome and vitamin D) systematic reviews and/or meta-analyses were available. The results of these studies are presented. Consequently the original studies were excluded, with the exception of recent studies not yet included in the systematic reviews and meta-analyses. When no systematic reviews or meta-analyses were available, summaries of the literature are provided. Finally, 71 original studies, 21 meta-analyses, 6 systematic reviews, and 17 reviews were included.

3. Results

3.1. Health effects of ultraviolet radiation

3.1.1. Skin color and sunlight. Evolutionary biology and anthropology

The estimated degree of variation in human skin pigmentation is 88%, which is high compared to roughly 10-15% observed for genetic loci on average. Such high phenotypic differentiation, most likely, is the effect of natural selection. The variation in pigmentation markedly correlates with the latitudinal differences in annual UV radiation; therefore it is presumed that UV radiation is the selective force (17-19). UV radiation is highest at the equator and diminishes gradually with increasing latitude on both the Northern and Southern Hemispheres. In the Northern Hemisphere every 10 degrees in latitude the color of the skin gets roughly 8 % lighter (20).

Our skin color is defined by the amount of the pigment melanin. Recently, several locus-specific and genome-wide association studies, searching for signatures of positive selection, have highlighted distinct loci in the pigmentation pathways. One of the most important polymorphisms affecting skin and hair color is the rs16891982*G/C SNP on chromosome 5 in the *SLC45A2* gene (22-24). In African and Asian populations the ancestral 374L allele dominates (23,25). The 374F allele dominates in Europe with a north-south decline (26). For details see Table 3.

Positive natural selection functions on genetic variability in such a way that the fittest individuals have the best chance of surviving and producing more offspring. Apparently a light skin offered the best chances for the European ancestors. The principal theories relating to variation in pigmentation and UV radiation assume that dark skin protects against sunburn and possibly folate deficiency, whereas light skin allows sufficient photosynthesis of vitamin D and other possible effects of sunlight in areas with low UV radiation (17-19,27). The importance of vitamin D as a selective force in

the evolution of skin pigmentation is related to its manifold effects on fitness (18,19,28).

In the context of human evolution, the variation in pigmentation is considered a superb compromise between the positive and deleterious effects of sunlight (18,19). This is an appropriate statement for our ancestors who up to the industrial revolution mainly had outdoor occupations, whereas nowadays the vast majority of the population in developed countries works indoors. Since the Second World War developments such as automobiles, TV, computers, videogames, indoor sports etc. have promoted indoor activities. German and Danish studies revealed that indoor workers on average expose their hands and face to less than 3% of the total available amount of sunlight (29,30).

Simultaneously, the advent of widely available, rapid long-distance transportation promoted the popularity of sun-seeking vacations in areas with an UV index much higher than at home. The exposition pattern to sunlight has definitely changed from a continuous or occupational pattern to a more intermittent pattern.

Not only has the exposure of our skin to UV changed. The exposure of our eyes to bright light during daytime, and to artificial light in the evening and at night has changed as well. Our ancestors rose with the sun and went to bed at sunset. The invention of light bulbs at the end of the 19th century has had a dramatic influence on our pattern of activity and rest. At present we are exposed to numerous sources of bright light from lamps (both indoor and outdoor), television, and computer screens in the evening and at night, while our daytime exposure to (sun)light has diminished considerably (31,32). Moreover, 15-20 percent of the western population is regularly working at night in illuminated surroundings (33).

3.1.2. Skin cancer

Skin cancer results from an interaction between genetic susceptibility and environmental

Table 3. Frequency of the 374F allele of the *SLC45A2* gene in 10 cities across Europe and Africa.

Location (Europe)	Latitude(°)	Frequency of 374F allele	Location (Africa)	Latitude(°)	Frequency of 374F allele
Copenhagen, Denmark	56	0.98	Tangier, Morocco	36	0.61
Brussels, Belgium	50	0.93	Algiers, Algeria	36	0.70
Marseille, France	43	0.89	Tunis, Tunisia	36	0.69
Barcelona, Spain	41	0.86	Nouakchott, Mauritania	20	0.41
Sevilla, Spain	37	0.73	Dakar, Senegal and Africa south of Senegal	=<15	0.00*

The 374F allele is associated with depigmented skin.

*Except inhabitants of European origin.

Sources: references 25 and 26

exposure, mainly to UV. The incidence rates of skin cancer have been increasing worldwide since at least five decades (34,35). Increased risks were shown for those who have red/blonde hair, light eye color, burn easily, and tan poorly (36,37).

Intermittent sun exposure and sunburn, particularly at young age, are considered to be the main risk factors for melanoma, the most lethal form of skin cancer. Intermittent exposure is defined as: recreational activities such as sunbathing, water sports, and vacations in sunny places. Chronic exposure is usually defined as a continuous or more continuous pattern of sun exposure (38). Successive meta-analyses (38-40) found an inverse association between chronic and occupational exposure and melanoma risk. The effect of chronic and occupational sun exposure appeared to be latitude-dependent (41). Chronic and occupational exposure increases melanoma risk in Southern Europe (41), whereas in North-western Europe it is associated with relative low

risks (41-45). In a case-control study performed in the Netherlands, it was found that leisure activities such as sunbathing and vacations in sunny countries increased the risk of melanoma in indoor workers but not in outdoor workers (42).

For basal cell carcinoma (BCC) intermittent exposure is an important risk factor as well (43,44,46,47). A meta-analysis investigating the effect of occupational exposure on the risk of BCC found a pooled odds ratio (OR) of 1.4 (95%CI:1.2-1.7) (48). The data also show that there is a decline in risk from lower to higher latitudes in Europe. The risk is robust in southern countries, whereas studies performed at or above 50 degrees north latitude show no association between occupational sun exposure and BCC risk (48). More recent studies performed in Denmark (44) and Eastern and Central Europe (49), not yet included in this meta-analysis, show a significant decrease in risk of BCC in outdoor workers; in Denmark this

Table 4. Associations between different types of skin cancer and different types of UV exposure.

Type of skin cancer	Type of UV exposure			References
	Intermittent with sunburn	Chronic	Occupational	
Melanoma	Most important risk factor*, uninfluenced by latitude	Risk influenced by latitude. In sunny regions increased risk. In moderate and cold regions: decreased risk*	Risk influenced by latitude. In sunny regions increased risk. In moderate and cold regions decreased risk*	37-44
Basal cell carcinoma	Most important risk factor	Probably modest risk factor. Influence of latitude not studied	Modest risk factor. In Europe influenced by latitude. In southern Europe increased risk, in Northern Europe decreased risk	35,42,45-47
Squamous cell carcinoma	Modest risk factor	Most important risk factor. Influence of latitude not studied	Important risk factor, influenced by latitude: decreasing risk with increasing latitude	35,42,43,49

Intermittent exposure is defined as: recreational activities and vacations in sunny places. Chronic exposure is defined as a continuous or more continuous pattern of sun exposure.

*For melanoma of trunk and limbs, not for head and neck melanoma

effect was even dose-dependent for men working in agriculture.

A meta-analysis of studies on the association between occupational sun exposure and squamous cell carcinoma (SCC) found an increased risk (OR 1.8;95%CI: 1.4-2.2). Meta-regression analyses suggested a decreasing strength of this association with increasing latitude (50). Two Scandinavian studies found no association between occupational exposure and SCC risk (44,51).

In vitro, 1,25-dihydroxyvitamin D inhibits keratinocyte and melanocyte growth and promotes differentiation, factors that are important for skin cancer prevention (52). However, epidemiological studies do not show a consistent relationship between 25-hydroxyvitamin D levels and the risk of skin cancer (52,53). A recent meta-analysis found no

association between the blood levels of 25-hydroxyvitamin D and melanoma risk, and a statistically significant positive association with increasing risk of nonmelanoma skin cancer for high values of 25-hydroxyvitamin D levels was found. An inverse relationship might exist between 25-hydroxyvitamin D blood levels and melanoma thickness at diagnosis and melanoma survival (53-55).

3.1.3. Colorectal-, breast-, prostate cancer, and non-Hodgkin lymphoma

In 1980, the hypothesis was proposed that vitamin D is a protective factor against colon cancer (56). Subsequently, for many types of cancer an inverse association between ambient solar radiation and cancer incidence and mortality rates has been described. For many

Table 5 Associations between UV exposure and colon-, breast-, prostate cancer, non-Hodgkin lymphoma, multiple sclerosis, hypertension and diabetes.

Disease	Influence of sunlight			Reference
	Epidemiology: ecological, case-control and prospective studies. High vs low UV exposure	Animal experiments with UV	Experiments in humans with UV	
Colon cancer	Mainly inverse associations with cancer risk.	Reduction in malignant progression and growth of carcinomas	n.d.	15,16,55-57
Breast cancer	Mainly inverse associations with cancer risk.	Inhibition of tumor outgrowth with xenografts of breast cancer cell lines	n.d.	15,56,57,59
Prostate cancer	Mainly inverse associations with cancer risk	n.d.	n.d.	15,56,57
Non-Hodgkin lymphoma	Mainly inverse associations with lymphoma risk	n.d.	n.d.	15,56-58,135
Multiple sclerosis	Mainly inverse associations with MS risk and mortality	Chronic UV exposure suppresses disease induction and progression	In MS patients depression, fatigue and MRI neurodegeneration inversely associated with sun exposure	11,12,67-80,136
Hypertension	Towards the equator less hypertension. Hypertension shows seasonality. Higher ambient temperature associated with lower blood pressure	n.d.	Regular artificial UV exposure lowers blood pressure significantly.	81-89
Diabetes	Moderate evidence for inverse associations with diabetes risk	In a murine model of obesity UV significantly suppressed weight gain, glucose intolerance, insulin resistance, serum levels of fasting insulin and glucose	Regular artificial UV exposure increases glucagon-stimulated insulin secretion	90-94

n.d.=not done

types of cancer only ecologic studies are available. For colorectal-, breast, prostate cancer, and non-Hodgkin lymphoma (NHL) case-control and prospective studies were performed (15,21,57). A systematic review of 26 case-control and 19 cohort studies on these subjects,

established an inverse association between chronic (not intermittent) sun exposure and colorectal-, breast-, prostate cancer and NHL. The association was consistent and persuasive (15). As to NHL, the larger studies that specifically investigated the risk in NHL

subtypes, found a decreased risk mainly for B cell lymphoma, particularly diffuse large cell and follicular lymphomas, and not for T cell lymphoma (15,58).

Although in many studies the results were corrected for known risk factors, confounding with dietary and lifestyle factors cannot be excluded completely. Animal studies, however, support a causal relationship. Inhibition of tumor outgrowth by UV exposure was found with xenografts of breast cancer cell lines in mice (59). Moderate UV doses can reduce the load of primary intestinal tumors of mice. This reduction could be partly ascribed to the increase of the vitamin D status. However, a reduction in malignant progression and growth of adenocarcinomas could not be attributed to vitamin D, as these effects were only observed with moderate UV exposure and not with dietary supplementation (16).

Virtually all studies on the association between the 25-hydroxyvitamin D serum levels and colorectal cancer risk (15,57,60,61) showed inverse associations. For breast cancer, case-control studies observed inverse associations, but prospective studies found mixed results. A recent dose-response meta-analysis of prospective studies of 25-hydroxyvitamin D suggested an inverse association only in postmenopausal women with a plasma 25-hydroxyvitamin D level lower than 27 ng/mL, with flattening of effects above 35 ng/mL (62).

No epidemiological support was found for a decreased risk of prostate cancer or NHL and higher levels of serum 25-hydroxyvitamin D (15,57,60,61,63).

Animal studies support a causal relationship between vitamin D and the prevention of colon-, breast-, and prostate cancer: supplementation of vitamin D and vitamin D analogues resulted in a lower incidence of tumors and a reduction of tumor outgrowth. Placebo-controlled, randomized vitamin D supplementation trials showed an inverse association for all-cause mortality, but not for cancer risk (64-66). For details see table 6.

3.1.4. Multiple sclerosis

The prevalence of multiple sclerosis (MS) follows a latitudinal gradient (67,68). Case-control-, prospective-, and twin studies on the association between sun exposure and MS in Caucasians found reduced risks or mortality with increasing hours of sun exposure (12,69-76).

Sun exposure and 25-hydroxyvitamin D levels appear to contribute independently to the reduced MS risk (11,12). Studies with an experimental autoimmune encephalomyelitis (EAE) model of MS demonstrated that vitamin D treatment leads to a modest suppression of disease induction and progression, using doses which cause vitamin D toxicity and hypercalcaemia. However, chronic suberythematal UV doses, that caused only a modest increase in serum 25-hydroxyvitamin D, led to a greater disease suppression than vitamin D without side effects (11,77,78).

In MS patients personal reported sun exposure was inversely associated with depression, fatigue scores (79), and MRI measures of neurodegeneration (80), independently of vitamin D.

3.1.5. Metabolic syndrome

Metabolic syndrome is an important determinant of vascular disease, which is the major cause of morbidity and mortality worldwide. Ambient solar radiation was found to correlate well with the prevalence of coronary heart disease mortality rate in the adult population of Western Europe (81). Sun exposure is associated with beneficial effects on blood pressure and the risk of diabetes.

Levels of blood pressure (BP) vary with latitude with less hypertension towards the equator (82). The seasonality of BP, higher values in winter than in summer, was already described more than 50 years ago (83). Ambient temperature and seasonality (reflected by the number of hours between sunrise and sunset)

Table 6 Summary of the results of studies on the association between vitamin D (vit D) and colon-, breast-, prostate cancer, non-Hodgkin lymphoma, multiple sclerosis (MS), hypertension and diabetes.

Disease	Observational studies	Animal experiments	Vitamin D supplementation	References
Colon cancer	Inverse associations with cancer risk	Reduction of incidence and tumor growth	Insufficient evidence	15,16,57,60,61, 64-66
Breast cancer	Mixed results. Inverse associations with cancer risk mainly in postmenopausal women	Reduction of incidence and tumor growth	Insufficient evidence	15,57,59-62,64,65
Prostate cancer	Insufficient evidence	Reduction of incidence and tumor growth	Insufficient evidence	15,57,60,61,64,65
Non-Hodgkin lymphoma	Insufficient evidence	n.d	Insufficient evidence	15,,57,58,61,63-65
Multiple sclerosis (MS)	Inverse associations with MS risk	Vit D enhances immunotolerance and suppresses disease induction and progression	Insufficient evidence	11,12,71,79,80
Hypertension	Inverse associations with hypertension risk	n.d.	Inconclusive evidence	95,100,101,104
Diabetes	Inverse associations with diabetes risk	Vit D enhances immunotolerance and suppresses disease induction	Insufficient evidence	90,93,96-99,102,103

n.d= not done

appear to be independent predictors of BP (84,85). Pregnancy hypertension (86) and preeclampsia (87) show seasonality as well. Both increased sunlight and increased ambient temperature in the month(s) before delivery were associated with decreased rates of pregnancy hypertension. All studies on irradiation of Caucasians with physiological doses (8-20 J/cm²) of ultraviolet A (UVA) reported significant lowering of BP (88-90).

Incidence rates of diabetes mellitus (DM), particularly DM type 1, follow a latitudinal gradient, inverse with the global distribution of ultraviolet rays (91,92). A systematic review reported moderate evidence to support a role of recreational sun exposure in reducing DM type 2 incidence (93). In a small study with

young French adults an UV treatment of 2 weeks was found to increase glucagon-stimulated insulin secretion (94). In a murine model of obesity UV significantly suppressed weight gain, glucose intolerance, insulin resistance, serum levels of fasting insulin, and glucose (95).

Meta-analyses and (systematic) reviews of observational studies indicate that high serum 25-hydroxyvitamin D concentration is associated with a lower risk of hypertension, DM type 2, metabolic syndrome, and cardiovascular disease (96-103).

The evidence that vitamin D supplementation has a positive effect on BP is inconclusive (103,104). There is currently insufficient evidence of a beneficial effect of vitamin D supplementation in diabetes (105,106). A meta-

analysis of observational trials in chronic kidney disease patients, treated with vitamin D or vitamin D analogues, reported a significant reduction of all-cause mortality (relative risk (RR) 0.73; 95% CI 0.65–0.82) and cardiovascular mortality (RR 0.63; 95% CI 0.44–0.92) (107). (Table 6)

3.2. Health effects of visible light

Most organisms exhibit daily rhythms in physiology and behavior, organized by a clock mechanism. The circadian clock consists of a central clock, localized in the hypothalamic suprachiasmatic nucleus (SCN) and peripheral clocks in virtually every tissue and organ system. The SCN clock is mainly entrained and synchronized by light via the retinohypothalamic tract, whereas the peripheral clocks are also regulated by the central SCN pacemaker, directly and indirectly, by virtue of multiple neural, humoral, and other signals from the SCN clock (108-110). The decrease of outdoor jobs, the increase of indoor activities, and the widespread adoption of electrical lighting since the 19th century has led to unnaturally disrupted cycles, with less light during daytime and more light at night. Exposure to unnatural light cycles may increase the risk of cancer (108,111-114), sleep disturbances (115), mood disorders (116,117), MS (118), cardiovascular disease, and metabolic changes (110,119-121). The International Agency for Research on Cancer (IARC) categorized shiftwork that involves circadian disruption as “*probably carcinogenic to humans*” in 2007 (33).

During the day light intensities of 3000 lux or more (e.g. direct or indirect sunlight) are needed to reinforce the circadian rhythm and to influence its phase, while at night light sources of 100 lux or less (comparable to the light of a bedside lamp) can lead to disturbances of the circadian rhythm (121-124).

Genetic association studies support the relation between circadian rhythm and the risk of

several types of cancer, particularly breast cancer, prostate cancer, and NHL (108,125-129). Alterations of the circadian rhythm have been related to modulations of tumor growth in animal models and differences in recurrence rate, stage, and prognosis in human cancers (108).

Shift workers exposed to less bright daylight and experiencing sustained night-time illumination are at increased risk for elevated body mass index, diabetes, and cardiovascular disease (110,119,130,131). Increases in night-time light exposure at home are associated with increased body mass, waist circumference, triglyceride levels, and poor cholesterol balance in elderly individuals (132).

3.3. Biological mechanisms of action of sunlight

3.3.1. DNA damage

A large number of molecules (chromophores) in different layers of the skin interact with and absorb UV (10). Ultraviolet B (UVB) reaches the epidermis where it is absorbed by DNA leading to the formation of photoproducts, primarily cyclobutane pyrimidine dimers (CPDs). They interfere with both replication and transcription and hence are potentially toxic and mutagenic to cells. UVA penetrates more deeply into the skin and exerts DNA damage, mainly through photo-oxidative mechanisms. UV also can induce carcinogenesis by suppressing the immune system (as reviewed in 10,133).

3.3.2. Photoadaptation

Human epidermis adapts to chronic UV exposure by increasing the amount of melanin pigment, epidermal hyperplasia, and thickening of the horny layer. Stronger pigmentation leads to an increased absorption of UVA and UVB, while epidermal thickening mainly increases the absorption of UVB. UVB-induced (delayed) pigmentation results in a protection, which amounts to a sun protection factor of 2 to 3 against DNA damage and burning. The

thickened epidermis and horny layer obstruct transmission of UV to the vulnerable cells of the basal and suprabasal layers. The protecting effect of thickening is found to be of more importance than the increase of pigmentation (134).

Regular exposure to suberythematal doses of solar-simulating artificial UV for 3 weeks decreases the ultraviolet sensitivity for erythema on average by 75%. CPD formation was reduced on average by 60%. More importantly, virtually no CPDs were found in the basal and suprabasal layers. DNA damage of basal and suprabasal cells with their proliferative capacity is likely to have far more consequences than damage of the cells of higher epidermal layers that are already committed to terminal differentiation (135-137).

3.3.3. Immunomodulation

Immunomodulation by UV radiation involves multiple pathways associated with the formation of vitamin D, *cis*-urocanic acid, and oxidation products of DNA, lipids and proteins. These initiate signaling pathways, leading to the release of a number of secondary mediators capable of regulating cell-mediated immunity through multiple mechanisms. UV stimulates T-regulatory cells and secretion of IL-10, reduces levels of the proinflammatory cytokine IL-17, and dampens T-helper (Th-1) immune function (as reviewed in 13). This leads to both local and systemic immunosuppression, thereby eliminating natural defense mechanisms (10,13). On the other hand, they might provide biologically plausible pathways for the reduction of MS, diabetes type 1, and NHL risk (11,13,138-143).

3.3.4. Vitamin D

Most of our vitamin D stems from photosynthesis in the skin. Vitamin D (in its active form: 1,25-hydroxyvitamin D) has been

known for its important role in regulating levels of calcium and phosphate as well as in bone mineralization. Moreover vitamin D appears to be involved in a large number of different pathophysiological processes. Many cell types are known to express vitamin D receptors and to produce 1,25-hydroxyvitamin D. Activation of the vitamin D receptor by 1,25-dihydroxyvitamin D induces or inhibits transcription of a number of genes that influence proliferation, differentiation, invasiveness, metastatic potential, angiogenesis, and apoptosis (as reviewed in 64). Many reviews have been written about the manifold effects of vitamin D (e.g. 28,64). These effects are summarized in table 7.

3.3.5. Nitric oxide

Human skin can be considered as the largest human storage organ for nitric oxide (NO) and NO-derivatives such as nitrite and nitrosothiols. The biological effects of NO are mediated through its reaction with targets, like haem groups, cysteine residues, and iron and zinc clusters. These targets help to explain the multiple roles NO plays, including vasodilatation, immune defense, neurotransmission, apoptosis, and cell motility (as reviewed in 14).

Irradiation with biologically relevant doses UVA induces in the skin release of NO from a pre-formed store and induces NO translocation from the skin to the circulation. This results in a significantly enhanced concentration of plasma nitroso compounds, strongly correlated with vasodilatation, a decreased vascular resistance, and a sustained reduction in BP (89,90). Intravenous slow infusion of NO in healthy volunteers increases plasma levels of nitroso thiols and elicits a simultaneous and significant drop in mean BP (90). Irradiation of Caucasians with physiological doses of UVA (8-20 J/cm²) was found to vasodilate arterial vasculature and to lower BP (88-90).

Independently of vitamin D, UV significantly suppressed weight gain, glucose intolerance, insulin resistance, serum levels of fasting insulin, glucose, and cholesterol in a murine model of obesity. NO reproduced many of these effects of UV (95).

3.3.6. Serotonin and endorphins

In a blinded experiment frequent tanners instinctively prefer a tanning bed with UV to a seemingly identical tanning bed with an acrylic filter in place that prevented the transmission of UV light (i.e. sham light). Sunbed-users feel more relaxed and less tense than non-users. This has been ascribed to an increase in the production of serotonin and endorphins (144).

Serotonin is a neurotransmitter involved not only in mood, but also in cognition, regulation of feeding behavior, anxiety, aggression, pain, sexual activity, and sleep. It is synthesized in many organs such as the intestines, CNS, thyroid gland, ovaries, breasts, and skin and then released into the blood (145). Production of serotonin can be increased by sunlight through the eyes and the skin. Blood samples from internal jugular veins showed that the production of serotonin by the brain was directly related to duration of exposure of the eyes to sunlight, rising rapidly with increased luminosity (146). UVA exposure of the skin of blinded individuals can lead to a slight increase of serum serotonin levels as well (147).

Serotonin was reported to have a risk-lowering effect on diabetes and a risk-increasing effect on hypertension (148-152).

Exposure of keratinocytes to UV radiation leads to production of an opioid β -endorphin. This β -endorphin, released into the blood during UV exposure, may reach the brain in sufficient concentrations to induce mood enhancement and relaxation. Some, but not all, studies in humans have demonstrated increased β -endorphin levels in the blood after UV exposure (14). Administration of the opioid antagonist naltrexone, used for treatment of opioid

dependence, reduced UV preference and even induced withdrawal symptoms in frequent tanners (153).

3.3.7. Circadian clocks

Proper circadian clock function is essential for the coordination of cellular functions in response to light and dark cycles. Exposure to light is the most important stimulus for the circadian rhythm, and an unnatural exposure to light can weaken and/or disturb the circadian rhythm.

The circadian rhythms of both central and peripheral clocks are regulated by feedback loops generated by interplaying clock proteins (108,109). The positive limb of the clock machinery comprises CLOCK and BMAL1, which heterodimerize and induce expression of clock-controlled genes. The cryptochrome (*CRY1* and *CRY2*) and period (*PER1*, *PER2* and *PER3*) families are clock-controlled genes and encode proteins that regulate negatively the circadian machinery (108,109). The circadian clock regulates key aspects of cell growth and survival, including cell cycle, DNA damage responses, and metabolism (108-110). Animal experiments have established convincing links between some clock genes and carcinogenesis, and also between clock genes and metabolic syndrome (108,110).

3.3.8. Melatonin

Melatonin is produced predominantly in the pineal gland, and, in lesser amounts, in the brain and extracranial sites. The melatonin precursor serotonin is normally produced during the day and only converted to melatonin in darkness. Pineal production and release of melatonin is controlled by the biologic clock in the SCN and by exposure to light. It is secreted at a daily rhythm, peaking near the middle of the night, while concentrations remain very low during daytime (145). The phase and amplitude of the nocturnal peak are controlled by exposure to

light. A robust exposure to light during the day increases the amplitude, and the timing of the exposure determines the phase of the nocturnal peak. In contrast, small amounts of light during the evening and at night can reduce circulating melatonin levels (122,123,145,154).

Melatonin has a potent anti-oxidant effect and is potentially anti-metastatic, anti-angiogenic, and capable of the induction of apoptosis and cell-cycle arrest. Animal experiments and studies with cultured cancer cells have shown that melatonin has a potential for inhibition of colon-, breast-, and prostate cancer (155-158). Studies in humans reported an inverse association between high levels of the primary urinary metabolite of melatonin, 6-sulfatoxymelatonin and the risk of prostate cancer in men and breast cancer in women (159-163). In vitro melatonin increases the sensitivity of a rat breast cancer cell line to vitamin D (164).

Melatonin may play a role in the regulation of BP and glucose homeostasis (145,154,165-168).

3.3.9. Folic acid

Folic acid is essential for human health. It is involved in DNA synthesis, DNA repair, and amino acid metabolism, and, consequently, it is especially important in rapidly dividing cells, such as (pre)malignant cells and those present in the embryo and the seminiferous tubules. Deficiency is linked to birth defects and megaloblastic anemia. It may also be a risk factor for some cancers and cardiovascular disease, although the role of folate in these diseases is controversial (14,169,170). UV radiation can degrade folic acid in in-vitro studies, which was confirmed in several human studies (18,19,170-172). Consequently, photodegradation of folic acid may lead to folate deficiency. However, the degree and health consequences of such photodegradation are unknown (169,170). (Table 7)

4. Discussion

The geographic variation in human skin color is one of the best examples of natural selection, resulting in an appropriate adjustment of levels of pigmentation to levels of UV radiation (20). The most well-established explanation assumes that the optimal degree of skin pigmentation is a balance between skin dark enough to protect our cells from too much UV radiation, and yet light enough to permit sufficient penetration of UV rays in order to let them execute their beneficial effects, e.g. the photosynthesis of vitamin D. High ambient UV near the equator led to the evolution of dark photoprotective skin, in which melanin acts as natural sun block. Low UV environments led to depigmented skin (18,19,27).

In the millennia before the industrial revolution, and before fast long-distance travel and migration of lightly pigmented people to sunny climates, the skin color of a population reflected an adequate balance between the advantages and disadvantages of sunlight. In the last two centuries, however, this balance has been disturbed progressively by migration and changes in lifestyle leading to a completely different pattern of exposure to sunlight (18,19).

The 'epidemic' of skin cancer can be considered as the most striking result of this unbalance. Most skin cancers are caused by a mismatch between skin type and geography and/or sun exposure related lifestyle.

Incidence rates of melanoma have continued to rise now for several decades. Rates have been rising steadily in generations born up to the end of the 1940s, followed by a stabilization or decline in rates for more recently born cohorts in Australia, New Zealand, the U.S., Canada, and Norway (34). It is not clear whether this is mainly the result of prevention-campaigns or whether the peak of the epidemic has just been reached; possibly a combination of these two. According to an analysis of the WHO mortality database, mortality rates of melanoma increased in successive generations from 1875 until a peak year (173). Peak years were for subjects born in

Table 7. Summary of the (recently discovered) biological effects of (sun)light

Pathways	Effects of sunlight exposure	Implications
DNA damage	-Mutagenic -Carcinogenic	-Increase of skin cancer risk
Photo-adaptation	-Thickening of the epidermis -Increase of pigmentation	-Protection against DNA damage and burning
Immuno-modulation	-Stimulation of T-reg cells -Secretion of IL-10 -Reduction of IL-17 -Dampening of T-helper (Th-1) immune function	-Immunosuppression (both local and systemic) -Increased risk of (skin) cancer -Possibly decreased risk of MS, diabetes and NHL
Vitamin D synthesis	-Stimulation of photosynthesis in the skin	-Inhibition of proliferation, angiogenesis and metastasis, stimulation of differentiation and apoptosis; possibly decreasing cancer risk and improving prognosis -Enhanced immuno-tolerance: possibly reducing risk of MS, diabetes and NHL - Increased insulin secretion and decreased insulin resistance: possibly reducing risk of diabetes -Maintenance of musculoskeletal health
Nitric oxide (NO) release	-Mobilization of NO from the skin into the circulation	-Vasodilatation, lowering of blood pressure -Decreasing of glucose intolerance and insulin resistance, probably reducing risk of diabetes
Serotonin production	-Increased production	-Mood improvement -Possibly reduction of risk of diabetes -Possibly risk increasing effect on hypertension
Endorphin production	-Possibly increased levels of endorphins	-Mood improvement -Pain relief
Circadian clocks	-Natural exposure to (sun)light reinforces circadian rhythm and prevents rhythm disturbances -Circadian clocks regulate key aspects of cell growth, DNA damage responses and metabolism	-Probably reduction of risk and improvement of prognosis in breast-, prostate cancer and NHL -Probably reduction of risk of weight gain and diabetes -Mood, sleep, and cognition improvement
Melatonin production	-Sufficient exposure to (sun)light increases nocturnal melatonin peak -Melatonin possibly plays a role in the regulation of blood pressure and glucose homeostasis	-Possibly reduction of breast- and prostate cancer risk -Possibly reduction of hypertension and diabetes risk
Folic acid degradation	-Lower levels of folate	-Health consequences unknown

1937–1943 in North America, 1941–1942 in Northern Europe, 1945–1953 in the United Kingdom and Ireland, and 1948 in Western

Europe. After peak years, lifetime risk of melanoma death gradually decreased in successive generations. It is expected that, as

time passes, melanoma deaths will steadily rarefy in younger age groups and concentrate in older age groups (173).

After reviewing in great detail the relationship between skin cancers and sun exposure the WHO in 1992 accepted sun exposure as the main exogenous cause of cutaneous melanoma in humans (5). The available data were: observational studies in humans, experimental induction of skin cancers in animals, and other relevant data. Other relevant data considered were related to the, at that time, limited insights in the effects of UV on immunity and in the mechanisms of UV-associated DNA-damage (5). Randomized controlled trials are not available, since they are considered unfeasible and unethical. Even at present, there is discussion on the value of sunscreens in the prevention of melanoma (174-176).

The strength of the WHO conclusion was debated. The results from epidemiological studies on melanoma were considered inconsistent by some, and the relationship between sunlight exposure and melanoma risk is not a straightforward one, as is illustrated by higher incidence rates of melanoma among indoor than outdoor workers and higher incidences in the north of Europe than in the south (39,40). More convincing answers to a number of questions on effects of sun exposure were still needed at that time. Such questions included whether the pattern of sun exposure is really important, whether it acts independently of the amount of sun exposure, and whether sunburn makes a specific contribution to the risk of skin cancer. At present observational studies support the 'intermittent sun exposure hypothesis' for melanoma: a positive association of the latter with intermittent sun exposure and sunburn, but an inverse association with a continuous pattern of sun exposure (38). This inverse association appeared to be latitude dependent (41,45). Recently it became clear that for risk of BCC and SCC the pattern of exposure and latitude is of importance as well, particularly in Europe. Both

chronic and intermittent exposure increase the risk in southern Europe, while in the north a more continuous pattern of exposure confers a relatively moderate risk (48,50).

Extensive programs for the primary prevention of skin cancer were developed, commencing in Australia in the 1980 decade with the "Slip, Slop, Slap" (Slip on a shirt, Slop on a sunscreen, and Slap on a hat) program, followed by the Sun Smart program. The WHO introduced the UV index: a measure of biologically effective UV radiation, designed to inform the public of UV levels. The Australian prevention programs were adopted and copied by most Western countries. They consist mainly of avoidance of the sun in the middle of the day, the use of sunlight-protective clothing, and more or less continuous use of sunscreens with a SPF of 30 or higher, that protect against UVA and UVB (7). These sun advices are more or less similar all over the world. They are without doubt useful for persons with a sun-sensitive skin living in Australia or other countries with high ambient UV. However, it is questionable whether they should be used in North-western Europe, where chronic exposure and outdoor occupations are associated with a relatively low risk of melanoma and BCC and even SCC (in Scandinavia) (44,48-51).

Regular exposure to UV leads to an almost complete disappearance of DNA damage in the basal and suprabasal layers of the epidermis, where the initiating of skin cancer occurs (135-137). This might explain the 'risk-lowering' effect of regular exposure, whereby photosynthesis of extra vitamin D and/or other effects of (sun)light may contribute to this phenomenon as well. Regular exposure decreases melanoma risk in North-western Europe (with low UV indices and a short "sunny season"), whereas in Southern Europe (with relatively high UV indices and a long "sunny season") it is associated with an increased risk. Compared to inhabitants of Southern Europe, those of North-western Europe have a lesser capability of tanning, but the same capability of

thickening of the epidermis, which attributes more to the protection of the skin to UV (134). Consequently, as has been suggested by Newton-Bishop and co-workers (45), regular exposure might be more important for melanoma risk in high UV environments. Additionally self-selection against outdoor work by fair-skinned people living in regions with high ambient UV could also lower the estimates of melanoma risk in those who had high occupational exposure (41).

With all these recent data in mind it is obvious that a clerk in Scandinavia with skin type 3 (sometimes mild sunburns, moderate tan) needs a different advice than a farmer in Queensland with skin type 1 (always burns, never tans). We contend that sun advices which are more individualized, both per country or climate and skin type, contribute more to human health than the present guidelines.

There are additional reasons to reconsider the present sun advice, particularly for people living in temperate climates. Present generations expose themselves less and in a more intermittent pattern to sunlight, and less to bright light during the day, and more to artificial light in the evening and at night than their ancestors. This change of exposure might not only lead to an increase of skin cancer, but to a decrease of the positive effects of (sun)light as well. These positive effects comprise both the well-established effects and the recently discovered effects. Epidemiological studies suggest that regular exposure to the sun and a natural exposure to light is inversely associated with the risk of colon-, breast-, prostate cancer, NHL, as well as MS, and metabolic syndrome (12,15,21,57,67-76,82-87,91-93,108,110). These associations are generally consistent, but the question is whether they are causal. Reverse causality cannot be excluded completely. Recent animal experiments, however, show that sunlight may indeed prevent breast-, intestinal cancer, MS and metabolic syndrome (11,16,59,95). Experiments in humans show that UV can lower blood pressure and increase

insulin secretion (88-90,94). Insights into the involved mechanisms of action of sunlight are increasing gradually. In addition to the production of vitamin D, immunomodulation, the role of circadian clocks, the formation of nitric oxide, melatonin, and serotonin are important as well. Influence of formation of endorphin and the photodegradation of folic acid is more speculative. These biological effects may function simultaneously and in some instances even re-enforce each other's effect (32,164).

Thus far, the effects of too little sunlight during the daytime were studied separately from the effects of too much artificial light during the night. There is a need of studies on the combined effects of too little sunlight during the day and too much artificial light at night, a situation nowadays so prevalent almost everywhere throughout the world (32). Recent data suggest that decreased sunlight exposure during daytime can negatively affect circadian rhythmicity (177), while sufficient day-time exposure can prevent disruption of the circadian rhythm (178).

The question can be raised whether the present sun-shunning advices benefit our general health; there is no unequivocal scientific proof that they do. We could identify three prospective studies on the influence of sun exposure and sun avoidance on total mortality. Two Scandinavian studies, using personal exposure data, (179,180) found a significant negative association between sun exposure and mortality, while an American study, using ambient residential exposure data (181) found no evidence of a beneficial effect of sunlight.

At present the question "how much sunlight do we need?" is difficult to answer. Even from the viewpoint of skin cancer prevention and the avoidance of vitamin D sufficiency, the answer is complex. Regarding other biological effects of sunlight, such as immunosuppression, NO-, serotonin-, and melatonin synthesis, it is even more difficult to estimate a "healthy sun exposure" (182,183).

The present sun advices most likely lead to a decrease in the risk of skin cancer. It is obvious that excessive sun exposure and sunburn should be avoided. During sun-seeking vacations an adequate protection is needed. It is, however, unlikely that continuous protection during daily life contributes to our health, particularly in countries with a temperate climate. Both too much and too little sunlight may be harmful to our health.

Abbreviations:

BCC, basal cell carcinoma;
 BMAL1, brain and muscle ARNT-like 1;
 BP, blood pressure;
 CLOCK, circadian locomotor output cycles kaput;
 CPD, cyclobutane pyrimidine dimer;

CRY, cryptochrome;
 DM, diabetes mellitus;
 EAE, experimental autoimmune encephalomyelitis;
 IARC, International Agency for Research on Cancer;
 MS, multiple sclerosis;
 NHL, non-Hodgkin lymphoma;
 NO, nitric oxide;
 OCA2, oculocutaneous albinism gene2;
 PER, period;
 SCC, squamous cell carcinoma;
 SCN, suprachiasmatic nucleus;
 SLC45A2, solute carrier family 45 member 2;
 UV, ultraviolet radiation;
 UVA, ultraviolet radiation of wavelength 315-400 nm;
 UVB, ultraviolet radiation of wavelength 280-315 nm;

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