ANTICANCER RESEARCH *38*: 1111-1220 (2018)

PROCEEDINGS OF THE JOINT INTERNATIONAL SYMPOSIUM «VITAMIN D IN PREVENTION AND THERAPY» and «BIOLOGIC EFFECTS OF LIGHT»

June 21-23, 2017

Schlossberg Hotel, Homburg/Saar, Germany

Organized by

J. Reichrath[1], Th. Vogt[1], M. Friedrich[2] and M.F. Holick[3]

[1]Department of Dermatology, Venerology and Allergology, The Saarland University Hospital, Homburg/Saar, Germany, [2]Klinik fór Frauenheilkunde und Geburtshilfe des Helios Klinikums Krefeld, Germany, and [3]Section of Endocrinology, Diabetes and Nutrition, Department of Medicine, Boston University Medical Center, Boston, MA, U.S.A.

Local Organizing Committee

K. Heyne[1], J. Reichrath[1], R. Saternus[1], C. Schiekofer[1], L. Schilling[1], Th. Vogt[1]

Supported by Deutsche Forschungsgemeinschaft (DFG)

Preface

Both vitamin D and optical radiation exert potent pluripotent effects on human health. Recent scientific progress concerning the underlying mechanisms has led to promising new strategies for the prevention and treatment of many diseases such as autoimmune, infectious and cardio-vascular diseases, skin cancer and other malignancies. To summarize our present knowledge on this topic and to stimulate new research initiatives, a joint international symposium entitled "Vitamin D in Prevention and Therapy" and "Biologic Effects of Light", that was organized by J. Reichrath, Th. Vogt, M. Friedrich and M.F. Holick, and that was supported by the Deutsche Forschungsgemeinschaft (DFG), was held June 21-23, 2017 in Homburg/Saar, Germany.

This meeting was specially designed to offer scientists and clinicians a platform to discuss the latest developments in this intriguing research area. Plenary and Keynote lectures as well as Round Table Discussions gave an update on carefully selected "hot topics", including vitamin D, skin cancer prevention, UVA radiation and cellular homeostasis, photocarcinogenesis, and photochemical internalization (PCI).

Of particular interest were round table discussions with the audience chaired by M.F. Holick, J. Reichrath and R. Vieth (June 22) and by K. Berg, S. Emmert and J. Reichrath (June 23) in which selected experts in the field were engaged with live polling using multiple choice questions prepared and asked by the chair persons and an anonymous direct-recording electronic voting system.

Another highlight of this meeting was the award of the prestigious Arnold Rikli-Prize (that was established in 1989 to honor outstanding science related to the use of optical radiation for human health) to Prof. Bernhard Zastrow. Arnold Rikli (1823-1906) was a Swiss physician and natural healer living in Bled, today a small village in Slovenia close to the Austrian border. He proposed various therapies, mostly based on exposing the body to sun and air and strongly recommended that the health of his patients and the general population should benefit from "mother Nature" including the sun. Prof. Zastrow received the Arnold Rikli-Prize for his outstanding work in photobiology at the Charité in Berlin in the field of free radicals, near infrared radiation and sunscreens demonstrating a "Free Radical Threshold Value" as a new "universal body constant" and defining the evolutional development of a "Free Radical Ground State".

The science presented at this meeting convincingly demonstrated that analyzing the effects of ultraviolet, visible and infrared radiation on human health and the underlying mechanisms has developed in recent years into a fascinating research area. Some of the relevant findings and conclusions of this meeting are published in this issue of Anticancer Research. It is likely that this research activity will lead to the establishment of photopharmacology as a novel approach for the prevention and treatment of a wide variety of acute and chronic diseases including skin cancer and other malignancies, metabolic bone disease associated with chronic kidney disease, hypertension and cardiovascular disease, depression and neurocognitive decline and autoimmune diseases.

J. Reichrath
Th. Vogt
M. Fiedrich
M.F. Holick

ANTICANCER RESEARCH *38*: 1111-1120 (2018)
doi:10.21873/anticanres.12330

Review

A Critical Appraisal of the Recent Reports on Sunbeds from the European Commission's Scientific Committee on Health, Environmental and Emerging Risks and from the World Health Organization

JÖRG REICHRATH[1,2], PELLE G. LINDQVIST[3], FRANK R. DE GRUIJL[4], STEFAN PILZ[5,6], SAMANTHA M. KIMBALL[7,8], WILLIAM B. GRANT[9] and MICHAEL F. HOLICK[10]

[1]*Center for Clinical and Experimental Photodermatology, The Saarland University Hospital, Homburg, Germany;*
[2]*Department of Dermatology, The Saarland University Hospital, Homburg, Germany;*
[3]*Department of Obstetrics and Gynecology, Karolinska Institute, Karolinska University Hospital, Huddinge, Sweden;*
[4]*Department of Dermatology, Leiden University Medical Center, Leiden, the Netherlands;*
[5]*Division of Endocrinology and Diabetology, Department of Internal Medicine, Medical University of Graz, Graz, Austria;*
[6]*Department of Epidemiology and Biostatistics, EMGO Institute for Health and Care Research, VU University Medical Center, Amsterdam, the Netherlands;*
[7]*Department of Research, Pure North S'Energy Foundation, Calgary, Canada;*
[8]*St. Mary's University, Calgary, Canada;*
[9]*Sunlight, Nutrition and Health Research Center, San Francisco, CA, U.S.A.;*
[10]*Boston University Medical Center, Boston, MA, U.S.A.*

Abstract. *The European Commission's Scientific Committee on Health, Environmental and Emerging Risks and the World Health Organization recently published reports which concluded that a large proportion of melanoma and non-melanoma skin cancer is attributable to sunbed use, and that there is no need to use sunbeds as there are no health benefits and they are not needed to achieve an optimal vitamin D level. The overall conclusion from both bodies was that there is no safe limit for UV irradiance from sunbeds. We are, however, deeply concerned that these assessments appear to be based on an incomplete, unbalanced and non-critical evaluation of the literature. Therefore, we rebut these conclusions by addressing the incomplete analysis of the adverse health effects of UV and sunbed exposure (what is 'safe'?) and the censored representation of beneficial effects, not only but especially from vitamin D production. The stance taken by both agencies is not sufficiently supported by the data and in particular, current scientific knowledge does not support the conclusion sunbed use increases melanoma risk.*

Correspondence to: Professor Dr. med. J. Reichrath, Department of Dermatology, The Saarland University Hospital, Kirrbergerstr. 100, 66421 Homburg, Germany. Tel: +49 068411623802, e-mail: Joerg.reichrath@uks.eu

Key Words: SCHEER report on sunbeds, WHO report on sunbeds, solarium, melanoma, sunbed, melanoma risk, tanning, indoor tanning, review.

When preparing their policies and proposals relating to consumer safety, public health and the environment, both the World Health Organization (WHO) and the European Commission rely on scientific committees/commissions, collaborating centers and non-governmental organizations that should be independent and should provide them with sound scientific advice and draw their attention to new and emerging problems. In November 2016, the European Commission's Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) adopted a "Final Opinion on Biological effects of ultraviolet radiation relevant to health with particular reference to sunbeds for cosmetic purposes" (1) and in June 2017, the World Health Organization (WHO) published a report entitled "Artificial

Tanning Devices: Public Health Interventions to Manage Sunbeds" (2). In agreement with the WHO report, the SCHEER report concluded that: (i) sunbed use is responsible for a noticeable proportion of both melanoma and non-melanoma skin cancer (NMSC) and for a large percentage of melanomas arising before the age of 30 years; (ii) sunbed exposure has little health benefit; (iii) there is no need to use sunbeds to achieve an optimal vitamin D level; and (iv) because of evidence of the carcinogenic effects of sunbed exposure and of the nature of skin cancer induction, there is no safe limit for UV irradiance from sunbeds. While these reports were purportedly based on the best available scientific evidence, we are deeply concerned about their scientific quality and obvious lack of objectivity, most likely owing to an infusion with the laudable zeal to combat alarming increases in skin cancer. Both publications show an implicit tendency toward an unbalanced view and must be criticized because of many scientific misinterpretations and shortcomings. The main conclusions are not sufficiently supported by the data presented nor by our present scientific knowledge. Notably, both reports ignore (i) meta-analyses that show no association of sunbed use with increased melanoma risk in Europe; (ii) epidemiological and animal studies that show no increase in melanoma risk following chronic and sub-erythemal UV exposure; (iii) beneficial health effects of UV radiation; and (iv) consequences of vitamin D deficiency.

Critical Analysis of SCHEER and WHO Reports

The overall conclusion of the SCHEER report states "There is strong evidence from meta-analyses and individual studies of an increased risk of melanoma with ever use of sunbeds." [p. 43 in (1)]. This immediately exemplifies the misleading inherent bias as this statement should at least have read "There is weak evidence…of an overall marginally increased risk of melanoma associated with ever-use of sunbeds (including one time and habitual intensive users)". Importantly, the direct causality implied is by no means proven. This statement is not in accordance with generally accepted principles of evidence-based medicine (3). None of the supporting evidence demonstrates causation [the gold standard to prove this would be a randomized, controlled trial (RCT)]. Our present scientific knowledge on this topic is based on observational studies (case–control and cohort studies) that demonstrate associations that are confounded by other known factors and that do not demonstrate causation (4-55). Several meta-analyses of poor quality consolidate the observational study data and compound the flaws of these studies (44, 47, 48). For example, Boniol *et al*. (44) report a summary relative risk (SRR) of 1.20 [95% confidence interval (CI) = 1.08-1.34] for the association of ever-exposure to UV radiation from sunbeds with melanoma risk (based on 27 studies). Overall the quality of the entire evidence is poor due to lack of interventional studies and severe limitations of case–control and cohort studies that include unobserved or unreported confounding (56). Notably, many limitations of the studies these reports rely on (3-56) do not result in an undirected bias but will inevitably cause overestimation of the association of sunbed use with melanoma risk. For example, dermatological phototherapy is often included when only sunbed use should be assessed [*e.g*. Landi *et al*. (20)], and in many studies, subgroups of individuals with presumably high UV exposure in the past (*e.g*. individuals with history of 'non-melanoma skin cancer' or 'dermatological conditions') are excluded from controls but not cases (control selection bias). Additionally, it should be noted that studies available are characterized by high heterogeneity and by difficulties in adjusting for important confounding factors, including solar UV and lifestyle: only a minority of studies report odds ratios (ORs) adjusted for the same confounding factors, 12 studies not for a single confounder (56). Moreover, because individual confounders were assessed using different interrogations, these studies are only partly comparable limiting the ability to interpret results of a combined estimate. and these results should not be considered reliable (56). It has to be emphasized that one has to distinguish between associations, as reported in these case–control/cohort studies and meta-analyses, and causation. In this context, the same results and risk estimates as given in Boniol *et al*. (44) and Colantonio *et al*. (47) could well be obtained in the following scenario, as indicated elsewere (56). Sunbed use has no effect on melanoma risk, lifestyle factors such as extensive sunbathing in the summer as a sun worshipper or an 'unhealthy lifestyle' (*e.g*. alcohol, smoking use), do increase melanoma risk with true OR=1.2 (it has been reported previously that sun worshippers and individuals with an 'unhealthy lifestyle' go more frequently to tanning salons (57)). Many of the confounding factors, including extensive sunbathing in the summer and unhealthy lifestyle, have not been adequately and systematically considered in studies performed to date. For example, the comparison of sunbed users to non-users is confounded by their lifestyle habits, with typical sunbed users found to be females who tend to smoke cigarettes and drink alcohol more frequently than non-users, as well as eating less healthy food (57).

The WHO report states "…and the first use of sunbeds before the age of 35 increases the risk of developing melanoma by 59% (6)" [p. 12 in (2)]. This is not correct. As reported elsewhere (56), the report by Boniol *et al*. (44), that this statement refers to, and the IARC report (46) have to be criticized for defining "first use in younger age" as first use before the age of 36 years, but include studies that consider first use prior to ages 25 to 30 years (7, 26, 39). Moreover, some studies (30, 31) restricted their investigation to melanoma cases diagnosed before the age of 36 years however, this could have resulted in the exclusion of older cases and controls that may have been exposed at a younger age (21).

In strong contrast to the WHO (2) and SCHEER (1) reports, we therefore postulate (due to lack of interventional studies and severe limitations including unobserved or unrecorded confounding) that for main outcomes reported (association of ever exposure, first exposure at younger age and high/low exposure to UV radiation from a solarium with melanoma risk) (44, 46, 47), and according to generally accepted principles of evidence-based medicine (*e.g.* recommendations of the Oxford Centre for Evidence-based Medicine (3)), the resulting evidence levels and grades of recommendation are not "strong", as inaccurately stated in the SCHEER report (which used a highly questionable classification of evidence levels) (1), but are very weak (*e.g.* level 3a– for systematic reviews of case–control studies with heterogeneity, and grade of recommendation D for outcome "ever" *vs.* "never" use of a solarium). In conclusion, our present scientific knowledge does not support the notion that sunbed use *per se* may increase melanoma risk.

Available Evidence Overlooked by SCHEER and WHO Reports

Criticism on inadequate epidemiological studies and analysis thereof in the "Draft summary record" of the public hearing on sunbeds held on April 12, 2016 in Luxemburg published by the European Commission gave a rather revealing explanation: "The SCENIHR representatives acknowledged that there is an insufficient number of studies on European populations, but explained that this left them with no choice but to use the best data from published peer-reviewed scientific studies available to date ……" [first paragraph on p4 (58)]. There is not an "insufficient number of studies" but insufficient evidence from a large number of EU studies. It has to be recognized that the "best data from published peer-reviewed scientific studies available to date" do not show a statistically significant association of sunbed use ("ever" *vs.* "never") with melanoma risk in Europe [*e.g.* meta-analysis by Colantonio *et al*. 2014 (47)]. The lack of association in this subgroup analysis for Europe is very unlikely to be caused by a lack of power because the number of participants in studies performed in Europe is much greater as compared with studies from America that still show an association in subgroup analyses. It is unclear to us why this very important meta-analysis finding is completely ignored in this "Draft summary record" and in the "Final Opinion".

Experimental animal models, including genetically engineered mice, the *Xiphophorus* hybrid fish, the South American opossum, and human skin xenografts, constitute important vehicles for elucidating the relevance of UV in melanomagenesis. Both the SCHEER and WHO reports underappreciate the large body of evidence from epidemiological and animal studies that demonstrates no increase in melanoma risk following chronic (moderate) UV exposure (59-66). As an example, important information was obtained analyzing UV-inducible melanomagenesis in the hepatocyte growth factor/scatter factor (HGF/SF) transgenic mouse (59-61). Using this model, it was demonstrated that dermal melanomas arise in untreated mice with a mean age of onset of approximately 21 months, a latency that was not overtly altered in response to chronic sub-erythemal, or skin non-reddening UV irradiation (59-61). In contrast, erythemal doses to 3.5-day-old-neonatal HGF/SF mice induced cutaneous melanoma with significantly reduced latency (59-61). It should be noted that UV-induced murine melanomas frequently resemble their human counterparts with respect to histopathological appearance and graded progression. Many other studies also support the concept that sub-erythemal exposure to UV doses not only does not increase melanoma risk, but may even be protective (61-66). Occupational exposure to UV radiation was associated with a reduced risk of melanoma in a European population with lightly pigmented skin (66). It also should be noted that neither the SCHEER (1) nor the WHO (2) report discusses the fact that relevant UV signature mutations have not been reported in the B-rapidly accelerated fibrosarcoma (B-RAF) gene nor in other important drivers of melanomagenesis.

It further underlines the unbalanced view of the SCHEER and WHO reports, that they conceal the large body of evidence demonstrating beneficial health effects of UV radiation (*e.g.* 67-127). As an example, a large cohort study reported a longer life expectancy amongst participants with active sun exposure habits, which was related to a decrease in cardiovascular disease (CVD) and non-cancer-related mortality (67). The SCHEER report also misinterprets important findings of that study, stating that the investigation showed an increased risk of death due to cancer amongst participants with active sun exposure habits. This is not true. In this large cohort study, the risk of cancer death was non-significantly decreased (67). However, due to greater survival in those with CVD and those with non-CVD/non-cancer disease, the percentage of cancer death was increased. Furthermore, low sun exposure as a risk factor for all-cause death was comparable in magnitude to smoking, and women with active sun exposure habits were found to live 1 to 2 years longer as compared to those with the lowest sun exposure habits.

Two cohort studies have reported on a relation between personal sunbed use and all-cause mortality (67, 70). Both studies found 30-40% lower all-cause mortality associated with sunbathing vacations (67, 70). In contrast, Yang *et al*. report all-cause mortality risk practically doubled [hazard ratio (HR)=1.9, 95% confidence interval (CI)=1.3-2.7] amongst those in the upper extreme, *i.e.* >12 times per year of sunbed use (70). In the study of Lindqvist *et al*., all users of sunbeds (namely mostly those using a sunbed <12-times per year, *i.e.* sensible users) were at 13% lower risk of all-

cause mortality (HR=0.87, 95% CI=0.8-0.98) (67). Furthermore, the SCHEER report (1) states erroneously that the study population was not a representative sample of the Swedish population, yet the sample was drawn by computerized randomization from the population registry and is a representative sample comprising 20% of the south Swedish female population of the selected age groups.

The most known and well-documented beneficial health effects of UV radiation are mediated *via* vitamin D (see following paragraph). However, other factors might be involved, indicating that preventing and treating vitamin D deficiency may not account for all beneficial effects of solar or artificial UV exposure. Melatonin is involved in the circadian system, with there being a higher level during the night than in the daytime. Light information from the retina influences the production of melatonin *via* the suprachiasmatic nuclei of the hypothalamus. A mutation of the melatonin receptor affecting the melatonin system (*MTNR1B*) is known to be related to increased risk of type 2 diabetes, through the inhibition of insulin release. Thus, the increased susceptibility to type 2 diabetes mellitus noted among women with low sun exposure habits might at least partly be due to interference with the melatonin system (127). Hypertension is a major determinant of CVD. Experimental and observational data support the notion that lack of UVB radiation may be involved in the pathogenesis of hypertension (79, 80) and CVD (75) by (i) suppression of the renin–angiotensin–aldosterone system, (ii) a direct effect on endothelial cells, and effects on (iii) calcium metabolism and (iv) blood pressure, all of which might explain the lower all-cause death risk with increasing sun exposure. Solar UVA radiation induces the release and increases the cutaneous production of NO, resulting in a sustained reduction in blood pressure and has been suggested to act in a cardioprotective manner. Both high acute and chronic stress levels have a role in the activation of coagulation factors and may increase the risk of CVD, high blood pressure and thromboembolism. The finding that UV radiation induces β-endorphin synthesis, which may attenuate stress levels and have a cardioprotective and thromboprophylactic effect, is of note (77, 132). Moreover, epidemiological evidence provides support for solar UVB protection against a number of cancer types, including breast, colorectal, lung, ovarian, pancreatic and prostate cancer (72).

The SCHEER and WHO reports do not adequately consider the large body of evidence demonstrating the negative health consequences of vitamin D deficiency (*e.g.* 72, 78, 86-126). In fact, one of the leading theories of the evolution of skin pigmentation is that it is a compensatory mechanism for vitamin D production in low UVB environments (71). Populations with lighter skin tones (maximally depigmented skin) are those inhabiting environments with the lowest annual and summer peak levels of UVB. During hominin evolution, depigmented and tannable skin evolved numerous times. Facultative pigmentation, or tanning, developed in populations where levels of UVB varied strongly by season (71). It has been estimated that at present, although oral vitamin D supplements are easily available, approximately one billion people worldwide are vitamin D-deficient or insufficient (88). This epidemic causes serious health problems that are still widely under-recognized (*e.g.* 88-91) Apart from well-documented problems in bone and muscle function, there are associations between vitamin D deficiency and increased incidence of or unfavourable outcome for a broad variety of independent acute and chronic diseases, including type 2 diabetes and various types of malignancies (*e.g.* colon, skin, and breast cancer), autoimmune, infectious, neurocognitive and cardiovascular diseases (*e.g.* 72, 78, 86-126). Caini and co-workers provided evidence through meta-analysis that higher levels of vitamin D are associated with reduced risk of non-melanoma skin cancer [summary relative risk of 1.64 (95% CI=1.02-2.65] for highest *vs.* lowest level] (125). Mechanistically, vitamin D acts as an antiproliferative agent and modulates cell growth and development in many tissues (124). Furthermore, vitamin D has profound effects on immune system activity and has been found to have a protective effect against many autoimmune and inflammatory diseases, particularly those of the central nervous system (123).

A recent meta-analyses demonstrated the benefit of vitamin D supplementation in preventing respiratory tract infections (118). In pregnancy, a reduced risk of preterm delivery was found to be associated with vitamin D supplementation (110, 121), as well as of asthma and wheezing in children born to mother's taking adequate vitamin D during pregnancy (119).

A large meta-analysis assessed the beneficial and harmful effects of vitamin D supplementation in the prevention of mortality in healthy adults and adults in a stable phase of disease (114). In that study, 56 randomized trials with 95,286 participants provided usable data on mortality. The age of participants ranged from 18 to 107 years. Most trials included women older than 70 years. The mean proportion of women was 77%. Forty-eight of the trials randomly assigned 94,491 healthy participants. Of these, four trials included healthy volunteers, nine included postmenopausal women and 35 included older people living on their own or in institutional care. The remaining eight trials randomly assigned 795 participants with neurological, cardiovascular, respiratory or rheumatoid diseases. Vitamin D was administered for a weighted mean of 4.4 years. More than half of the trials had a low risk of bias. All trials were conducted in high-income countries. Forty-five trials (80%) reported the baseline vitamin D status of participants based on serum 25-hydroxyvitamin D level. Participants in 19 trials had vitamin D adequacy (at or above 20 ng/ml). Participants in the remaining 26 trials had vitamin D insufficiency (less

than 20 ng/ml). Vitamin D reduced mortality in all 56 trials when analyzed together [5,920/47,472 (12.5%) *vs.* 6,077/47,814 (12.7%); RR=0.97, 95% CI=0.94 to 0.99, p=0.02; I^2=0%). 'Worst-best case' and 'best-worst case' scenario analyses demonstrated that vitamin D was associated with a dramatic increase or decrease in mortality, respectively Trial sequential analysis supported the findings regarding vitamin D_3, with the cumulative Z-score breaking the trial sequential monitoring boundary for benefit, corresponding to 150 people treated over 5 years to prevent one additional death. Vitamin D_3 statistically significantly reduced cancer mortality (RR=0.88, 95% CI=0.78 to 0.98), p=0.02; I^2=0%; 44,492 participants; four trials) (114).

The SCHEER and WHO reports purport that using a sunbed is not an efficient way to generate vitamin D and that there are no health benefits associated with sunbed use beyond cosmetic outcomes, yet numerous publications support both. Sunbeds using UVB radiation lead to sufficient vitamin D production to significantly increase serum 25(OH)D concentration within 8-12 weeks (81-84) independent of ethnicity (85). Furthermore, Tangpricha *et al*. (86) reported 90% higher concentrations of 25(OH)D in those who used sunbeds regularly in comparison with controls. The sunbed users had significantly higher bone mass density and Z scores at the total hip than did non-users (86).

Conclusion

The generally accepted principles and ethics of medical research require that all available results are systematically collected and presented in an objective and impartial manner. This does not appear to be the case in the SCHEER (1) and WHO (2) reports, as the authors/contributors seem to have decided *a priori* on their position with respect to sunbed use and selectively emphasized the results they believed to support their position.

SCHEER should provide the European Commission with the scientific advice it needs when preparing policy for the European population. However, one should keep in mind that the conclusions of the SCHEER report (1) are based on data that do not reflect the present situation in Europe, while the conclusions of both reports are based on historical data that do not reflect the present situation in Europe or in other countries. Many studies included individuals with skin type I, who in Europe are at present not allowed to use a sunbed. Moreover, many studies included data obtained on technical devices that are no longer allowed to be used in Europe. It is well known that regional differences, including impact of confounding factors (*e.g.* solar UV exposure), technical differences of UV-emitting devices and differences in their operation, strongly influence the association of ever-exposure to UV radiation from sunbeds with melanoma risk (4-56). As mentioned above, it is alarming that this SCHEER report (1) conceals the important finding, namely that meta-analyses of studies performed in Europe do not show an association of ever-exposure to UV radiation from sunbeds with increased melanoma risk (47). Because of the high number of participants in European studies, this result is most likely not due to a lack of power, but reflects regional differences concerning impact of confounding factors, including solar UV exposure, technical differences of UV-emitting devices, and differences in their use (47).

Moreover, reductions of melanoma mortality rates during the past decades do not support the hypothesis that UV radiation from sunbeds may have increased melanoma risk. While melanoma death rates had more than doubled in light-skinned populations between 1955 and 1985, reduction in melanoma mortality rates have been observed from 1985-1990 in Australia, the United States and in many European countries. Furthermore, the authors of an article analyzing the imminent inexorable decline in light-skinned populations concluded that independently from screening or treatment, death from malignant melanoma is likely to become an increasingly rare event (128). It has been suggested that better detection methods have been in use to detect melanoma earlier, which is also a possible reason for the increased risk that has been observed (129).

In conclusion, both the SCHEER (1) and WHO (2) reports claim to assess health effects of sunbed use. Unfortunately, however, as such they are partially unbalanced and inaccurate. Both documents mainly assess negative health effects of UV exposure, conceal the large body of evidence demonstrating beneficial health effects of UV radiation, and major conclusions drawn are not sufficiently supported by current scientific knowledge. It should be emphasized that the main conclusions drawn by the SCHEER (1) and WHO (2) reports are not in accordance with generally accepted principles of evidence-based medicine, they not only are not in line with recommendations of the Oxford Centre for Evidence-based Medicine (3), but, as outlined in this critical appraisal, also do not fulfil the criteria proposed by Bradford Hill for examining causality in a biological system (strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment and analogy) (130). Other researchers added the ruling out of confounding factors and bias (131). With this unscientific approach, both the SCHEER (1) and WHO (2) reports are not adequate and do not properly summarize current knowledge on comparing beneficial and adverse effects of UV exposure from sunbeds.

References

1 https://ec.europa.eu/health/sites/health/files/scientific_committees/scheer/docs/scheer_o_003.pdf

2 http://apps.who.int/iris/bitstream/10665/255695/1/9789241512596-eng.pdf?ua=1

3 htpp://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/

4 Autier P, Dore JF, Schifflers E, Cesarini JP, Bollaerts A, Koelmel KF, Gefeller O, Liabeuf A, Lejeune F and 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 *61(6)*: 749-755, 1995.

5 Bataille V, Winnett A, Sasieni P, Newton Bishop JA and Cuzick J: Exposure to the sun and sunbeds and the risk of cutaneous melanoma in the UK: a case-control study. Eur J Cancer *40(3)*: 429-35, 2004.

6 Bataille V, Boniol M, De Vries E, Severi G, Brandberg Y, Sasieni P, Cuzick J, Eggermont A, Ringborg U, Grivegnée AR, Coebergh JW, Chignol MC, Doré JF and Autier P: A multicentre epidemiological study on sunbed use and cutaneous melanoma in Europe. Eur J Cancer *41(14)*: 2141-2149, 2005.

7 Chen YT, Dubrow R, Zheng T, Barnhill RL, Fine J and Berwick M: Sunlamp use and the risk of cutaneous malignant melanoma: a population-based case-control study in Connecticut, USA. Int J Epidemiol *27(5)*: 758-765, 1998.

8 Clough-Gorr KM, Titus-Ernstoff L, Perry AE, Spencer SK and Ernstoff MS: Exposure to sunlamps, tanning beds, and melanoma risk. Cancer Causes Control *19(7)*: 659-669, 2008.

9 Cust AE, Armstrong BK, Goumas C, Jenkins MA, Schmid H, Hopper JL, Kefford RF, Giles GG, Aitken JF and Mann GJ: Sunbed use during adolescence and early adulthood is associated with increased risk of early-onset melanoma. Int J Cancer *128(10)*: 2425-2435, 2011.

10 Dunn-Lane J, Herity B, Moriarty MJ and Conroy R: A case control study of malignant melanoma. Ir Med J *86(2)*: 57-59, 1993.

11 Elliott F, Suppa M, Chan M, Leake S, Karpavicius B, Haynes S, Barrett JH, Bishop DT and Newton-Bishop JA: Relationship between sunbed use and melanoma risk in a large case-control study in the United Kingdom. Int J Cancer *130(12)*: 3011-3013, 2012.

12 Elwood JM, Williamson C and Stapleton PJ: Malignant melanoma in relation to moles, pigmentation, and exposure to fluorescent and other lighting sources. Br J Cancer *53*: 65-74, 1986.

13 Farley C, Alimi Y, Espinosa LR, Perez S, Knechtle W, Hestley A, Carlson GW, Russell MC, Delman KA and Rizzo M: Tanning beds: A call to action for further educational and legislative efforts. J Surg Oncol *112(2)*: 183-187, 2015.

14 Fears TR, Sagebiel RW, Halpern A, Elder DE, Holly EA, Guerry D 4th and Tucker MA: Sunbeds and sunlamps: who used them and their risk for melanoma. Pigment Cell Melanoma Res *24(3)*: 574-581, 2011.

15 Garbe C, Weiss J, Kruger S, Garbe E, Büttner P, Bertz J, Hoffmeister H, Guggenmoos-Holzmann I, Jung EG and Orfanos CE: The German melanoma registry and environmental risk factors implied. Recent Results Cancer Res *128*: 69-89, 1993.

16 Han J, Colditz GA and Hunter DJ: Risk factors for skin cancers: a nested case–control study within the Nurses' Health Study. Int J Epidemiol *35*: 1514-1521, 2006.

17 Holly EA, Aston DA, Cress RD, Ahn DK and Kristiansen JJ: Cutaneous melanoma in women. I. Exposure to sunlight, ability to tan, and other risk factors related to ultraviolet light. Am J Epidemiol *141(10)*: 923-933, 1995.

18 Holman CD, Armstrong BK, Heenan PJ, Blackwell JB, Cumming FJ, English DR, Holland S, Kelsall GR, Matz LR and Rouse IL: The causes of malignant melanoma: results from the West Australian Lions Melanoma Research Project. Recent Results Cancer Res *102*: 18-37, 1986.

19 Kaskel P, Lange U, Sander S, Huber MA, Utikal J, Leiter U, Krähn G, Meurer M and Kron M: Ultraviolet exposure and risk of melanoma and basal cell carcinoma in Ulm and Dresden, Germany. J Eur Acad Dermatol Venereol *29(1)*: 134-142, 2015.

20 Landi MT, Baccarelli A, Calista D, Pesatori A, Fears T and Tucker MA, Landi G: Combined risk factors for melanoma in a Mediterranean population. Br J Cancer *85(9)*: 1304-1310, 2001.

21 Lazovich D, Vogel RI, Berwick M, Weinstock MA, Anderson KE and Warshaw EM: Indoor tanning and risk of melanoma: a case-control study in a highly exposed population. Cancer Epidemiol Biomarkers Prev *19(6)*: 1557-1568, 2010.

22 MacKie RM, Freudenberger T and Aitchison TC: Personal risk-factor chart for cutaneous melanoma. Lancet *2*: 487-490, 1989.

23 Naldi L, Gallus S, Imberti GL, Cainelli T, Negri E and La Vecchia C: Sunlamps and sunbeds and the risk of cutaneous melanoma. Italian Group for Epidemiological Research in Dermatology. Eur J Cancer Prev *9(2)*: 133-134, 2000.

24 Nielsen K, Masback A, Olsson H and Ingvar C: A prospective, population-based study of 40,000 women regarding host factors, UV exposure and sunbed use in relation to risk and anatomic site of cutaneous melanoma. Int J Cancer *131(3)*: 706-715, 2012.

25 Osterlind A, Tucker MA, Stone BJ and Jensen OM: The Danish case-control study of cutaneous malignant melanoma. II. Importance of UV-light exposure. Int J Cancer *42(3)*: 319-324, 1988.

26 Swerdlow AJ, English JS, MacKie RM, O'Doherty CJ, Hunter JA, Clark J and Hole DJ: Fluorescent lights, ultraviolet lamps, and risk of cutaneous melanoma. BMJ *297(6649)*: 647-650, 1988. Erratum in: BMJ *297(6657)*: 1172, 1988.

27 Ting W, Schultz K, Cac NN, Peterson M and Walling HW: Tanning bed exposure increases the risk of malignant melanoma. Int J Dermatol *46(12)*: 1253-1257, 2007.

28 Veierod MB, Adami HO, Lund E, Armstrong BK and Weiderpass E: Sun and solarium exposure and melanoma risk: effects of age, pigmentary characteristics, and nevi. Cancer Epidemiol Biomarkers Prev *19(1)*: 111-120, 2010.

29 Walter SD, King WD and Marrett LD: Association of cutaneous malignant melanoma with intermittent exposure to ultraviolet radiation: results of a case–control study in Ontario, Canada. Int J Epidemiol *28*: 418-427, 1999.

30 Westerdahl J, Ingvar C, Masback A, Jonsson N and Olsson H: Risk of cutaneous malignant melanoma in relation to use of sunbeds: further evidence for UV-A carcinogenicity. Br J Cancer *82(9)*: 1593-1599, 2000.

31 Westerdahl J, Olsson H, Masback A, Ingvar C, Jonsson N, Brandt L, Jönsson PE and Möller T: Use of sunbeds or sunlamps and malignant melanoma in southern Sweden. Am J Epidemiol *140(8)*: 691-699, 1994.

32 Wolf P, Quehenberger F, Mullegger R, Stranz B and Kerl H: Phenotypic markers, sunlight-related factors and sunscreen use in patients with cutaneous melanoma: an Austrian case-control study. Melanoma Res *8(4)*: 370-378, 1998.

33 Zanetti R, Rosso S, Faggiano F, Roffino R, Colonna S and Martina G: A case-control study of melanoma of the skin in the

province of Torino, Italy. Rev Epidemiol Sante Publique *36(4-5)*: 309-317, 1988.
34 Zivkovic MV, Dediol I, Ljubicic I and Situm M: Sun behaviour patterns and perception of illness among melanoma patients. J Eur Acad Dermatol Venereol *26(6)*: 724-729, 2012.
35 Beitner H, Norell SE, Ringborg, Wennersten G and Mattson B: Malignant melanoma: aetiological importance of individual pigmentation and sun exposure. Br J Dermatol *122(1)*: 43-51, 1990.
36 Gallagher RP, Elwood JM and Hill GB: Risk factor for cutaneous malignant melanoma: the Western Canada Melanoma Study. Recent Results Cancer Res *102*: 38-55, 1986.
37 Holly EA, Kelly JW, Shpall SN and Chiu SH: Number of melanocytic nevi as a major risk factor for malignant melanoma. J Am Acad Dermatol *17(3)*: 459-468, 1987.
38 Klepp O and Magnus K: Some environmental and bodily characteristics of melanoma patients. A case–control study. Int J Cancer *23(4)*: 482-486, 1979.
39 Schmitt J, Seidler A, Heinisch G and Sebastian G: Effectiveness of skin cancer screening for the age group 14 through 34 years. J Dtsch Dermatol Ges *9*: 608-617, 2011.
40 Ferrucci LM, Vogel RI, Cartmel B, Lazovich D and Mayne ST: Indoor tanning in businesses and homes and risk of melanoma and nonmelanoma skin cancer in 2 US case-control studies. J Am Acad Dermatol 71(5): 882-887, 2014.
41 Veierod MB, Weiderpass E, Thörn M, Hansson J, Lund E, Armstrong B and Adami HO: A prospective study of pigmentation, sun exposure, and risk of cutaneous malignant melanoma in women. J Natl Cancer Inst 95(20): 1530-1538, 2003.
42 Walter SD, Marrett LD, From L, Hertzman C, Shannon HS and Roy P: The association of cutaneous malignant melanoma with the use of sunbeds and sunlamps. Am J Epidemiol *131(2)*: 232-243, 1990.
43 Zhang M, Qureshi AA, Geller, AC, Frazier L, Hunter DJ and Han J: Use of tanning beds and incidence of skin cancer. J Clin Oncol *30(14)*: 1588-1593, 2012.
44 Boniol M, Autier P, Boyle P and Gandini S: Cutaneous melanoma attributable to sunbed use: systematic review and meta-analysis. BMJ *345*: e4757, 2012.
45 El Ghissassi F, Baan R, Straif K, Grosse Y, Secretan B, Bouvard V, Benbrahim-Tallaa L, Guha N, Freeman C, Galichet L and Cogliano V: WHO International Agency for Research on Cancer Monograph Working Group. A review of human carcinogens – part D: radiation. Lancet Oncol *10(8)*: 751-752, 2009.
46 IARC Working Group on Artificial 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 *120*: 1116-1122, 2007.
47 Colantonio S, Bracken MB and Beecker J: The association of indoor tanning and melanoma in adults: systematic review and meta-analysis. J Am Acad Dermatol *70*: 847-857, 2014.
48 Wehner MR, Chren MM, Nameth D, Choudhry A, Gaskins M, Nead KT, Boscardin WJ and Linos E: International prevalence of indoor tanning: a systematic review and meta-analysis. JAMA Dermatol *150*: 390-400, 2014.
49 Gallagher RP, Spinelli JJ and Lee TK: Tanning beds, sunlamps, and risk of cutaneous malignant melanoma. Cancer Epidemiol Biomarkers Prev *14(3)*: 562-566, 2005.
50 Hirst N, Gordon L, Gies P and Green AC: Estimation of avoidable skin cancers and cost-savings to government associated with regulation of the solarium industry in Australia. Health Policy *89(3)*: 303-311, 2009.
51 Swerdlow AJ and Weinstock MA: Do tanning lamps cause melanoma? An epidemiologic assessment. J Am Acad Dermatol *38(1)*: 89-98, 1998.
52 Boniol M, Autier P, Boyle P and Gandini S: Cutaneous melanoma attributable to sunbed use: systematic review and meta-analysis. BMJ *345*: e8503 (correction), 2012.
53 Grant WB: Critique of the IARCs meta-analyses of the association of sunbed use with risk of cutaneous malignant melanoma. Dermato-Endocrinology *1*: 294-299, 2009.
54 Moan JE, Baturaite Z, Grigalavicius M and Juzeniene A: Sunbed use and cutaneous melanoma in Norway. Scand J Public Health *41(8)*: 812-817, 2013.
55 Adam SA, Sheaves JK, Wright NH, Mosser G, Harris RW and Vessey MP: A case-control study of the possible association between oral contraceptives and malignant melanoma. Br J Cancer *44(1)*: 45-50, 1981.
56 Burgard B, Schöpe J, Holzschuh I, Schiekofer C, Reichrath S, Wagenpfeil S, Pilz S, Ordonez-Mena J, März W, Vogt Th and Reichrath J: Solarium use and risk for malignant melanoma: evidence medicine-based systematic review and meta-analysis. Anticancer Res, in press.
57 Schneider S and Krämer H: Who uses sunbeds? A systematic literature review of risk groups in developed countries. J Eur Acad Dermatol Venereol *24(6)*: 639-648, 2010.
58 http://ec.europa.eu/health/scientific_committees/emerging/docs/ev_20160412_mi_en.pdf
59 Jhappan C, Noonan FP and Merlino G: Ultraviolet radiation and cutaneous malignant melanoma. Oncogene *22(20)*: 3099-3112, 2003.
60 Noonan FP, Zaidi MR, Wolnicka-Glubisz A, Anver MR, Bahn J, Wielgus A, Cadet J, Douki T, Mouret S, Tucker MA, Popratiloff A, Merlino G and De Fabo EC: Melanoma induction by ultraviolet A but not ultraviolet B radiation requires melanin pigment. Nat Commun *3*: 884, 2012.
61 Reichrath J and Rass K: Ultraviolet damage, DNA repair and vitamin D in nonmelanoma skin cancer and in malignant melanoma: an update. Adv Exp Med Biol *810*: 208-233, 2014.
62 Elwood JM, Gallagher RP, Hill GB and Pearson JC: Cutaneous melanoma in relation to intermittent and constant sun exposure. Int J Cancer *35*: 427-433, 1985.
63 Elwood JM and Jopson J: Melanoma and sun exposure: an overview of published studies. Int J Cancer *73(2)*: 198-203, 1997.
64 Gass R, Bopp M: Mortality from malignant melanoma: epidemiological trends in Switzerland. Schweiz. Rundsch Med Prax *94(34)*: 1295-1300, 2005.
65 Kennedy C, Bajdik CD, Willemze R, De Gruijl FR, Bouwes Bavinck JN, Leiden Skin Cancer Study: The influence of painful sunburns and lifetime sun exposure on the risk of actinic keratosis, seborrheic warts, melanocytic nevi, atypical nevi and skin cancer. J Invest Dermatol *120(6)*: 1087-1093, 2003.
66 Grant WB: Role of solar UV irradiance and smoking in cancer as inferred from cancer incidence rates by occupation in Nordic countries. Dermatoendocrinol *4(2)*: 203-211, 2012.
67 Lindqvist PG, Epstein E and Landin-Olsson M: Avoidance of sun exposure is a risk factor for all-cause mortality: results from the Melanoma in Southern Sweden cohort. J Intern Med *276*: 77-86, 2014.

68 Lindqvist PG, Epstein E, Nielsen K, Landin-Olsson M, Ingvar C and Olsson H: Avoidance of sun exposure as a risk factor for major causes of death: a competing risk analysis of the Melanoma in Southern Sweden cohort. J Intern Med *280(4)*: 375-387, 2016.

69 Yang L, Veierød MB, Löf M, Sandin S, Adami HO and Weiderpass E: Prospective study of UV exposure and cancer incidence among Swedish women. Cancer Epidemiol Biomarkers Prev *20(7)*: 1358-1367, 2011.

70 Yang L, Lof M, Veierød MB, Sandin S, Adami HO and Weiderpass E: Ultraviolet exposure and mortality among women in Sweden. Cancer Epidemiol Biomarkers Prev *20(4)*: 683-690, 2011.

71 Jablonski NG and Chaplin G: Colloquium paper: human skin pigmentation as an adaptation to UV radiation. Proc Natl Acad Sci USA *11(107)Suppl 2*: 8962-8968, 2010.

72 Moukayed M and Grant WB: The roles of UVB and vitamin D in reducing risk of cancer incidence and mortality: a review of the epidemiology, clinical trials and mechanisms. Rev Endocr Metab Disord *18*: 167-182, 2017.

73 Hart PH, Gorman S and Finlay-Jones JJ: Modulation of the immune system by UV radiation: more than just the effects of vitamin D? Nat Rev Immunol *11*: 584-596, 2011.

74 Juzeniene A and Moan J: Beneficial effects of UV radiation other than *via* vitamin D production. Dermatoendocrinol *4*: 109-117, 2012.

75 Scragg R: Seasonality of cardiovascular disease mortality and the possible protective effect of ultra-violet radiation. Int J Epidemiol *10*: 337-341, 1981.

76 Nayha S: Cold and the risk of cardiovascular diseases. A review. Int J Circumpolar Health *61*: 373-380, 2002.

77 Lindqvist P, Epstein E and Olsson H: Does an active sun exposure habit lower the risk of venous thrombotic events? A D-lightful hypothesis JTH *7*: 605-610, 2009.

78 Schottker B, Jorde R, Peasey A, Thorand B, Jansen EH, Groot Ld, Streppel M, Gardiner J, Ordóñez-Mena JM, Perna L, Wilsgaard T, Rathmann W, Feskens E, Kampman E, Siganos G, Njølstad I, Mathiesen EB, Kubínová R, Pająk A, Topor-Madry R, Tamosiunas A, Hughes M, Kee F, Bobak M, Trichopoulou A, Boffetta P, Brenner H, Consortium on Health and Ageing: Network of Cohorts in Europe and the United States: Vitamin D and mortality: meta-analysis of individual participant data from a large consortium of cohort studies from Europe and the United States. BMJ *348*: g3656, 2014.

79 Krause R, Buhring M, Hopfenmuller W, Holick MF and Sharma AM: Ultraviolet B and blood pressure. Lancet *352*: 709-710, 1998.

80 Oplander C, Volkmar CM and Paunel-Gorgulu A: Whole body UVA irradiation lowers systemic blood pressure by release of nitric oxide from intracutaneous photolabile nitric oxide derivates. Circ Res *105*: 1031-1040, 2009.

81 Weber B, Bachmann CC, Braun R, Abraham AG, Serra AL and Hofbauer GFL: 25-Hydroxyvitamin-D3 serum modulation after use of sunbeds compliant with European Union standards: A randomized open observational controlled trial. J Am Acad Dermatol *77(1)*: 48-54, 2017.

82 Orlova T, Moan J, Lagunova Z, Aksnes L, Terenetskaya I and Juzeniene A: Increase in serum 25-hydroxyvitamin-D_3 in humans after sunbed exposures compared to previtamin D_3 synthesis *in vitro*. J Photochem Photobiol B *122*: 32-36, 2013.

83 Thieden E, Jørgensen HL, Jørgensen NR, Philipsen PA and Wulf HC: Sunbed radiation provokes cutaneous vitamin D synthesis in humans – a randomized controlled trial. Photochem Photobiol *84(6)*: 1487-1492, 2008.

84 Moan J, Lagunova Z, Cicarma E, Aksnes L, Dahlback A, Grant WB and Porojnicu AC: Sunbeds as vitamin D sources. Photochem Photobiol *85(6)*: 1474-1479, 2009.

85 Hakim OA, Hart K, McCabe P, Berry J, Francesca R, Rhodes LE, Spyrou N, Alfuraih A and Lanham-New S: Vitamin D production in UK Caucasian and South Asian women following UVR exposure. J Steroid Biochem Mol Biol *164*: 223-229, 2016.

86 Tangpricha V, Turner A, Spina C, Decastro S, Chen TC and Holick MF: Tanning is associated with optimal vitamin D status (serum 25-hydroxyvitamin D concentration) and higher bone mineral density. Am J Clin Nutr *80(6)*: 1645-1649, 2004.

87 Reichrath J: The challenge resulting from positive and negative effects of sunlight: how much solar UV exposure is appropriate to balance between risks of vitamin D deficiency and skin cancer? Prog Biophys Mol Biol *92*: 9-16, 2006.

88 Holick MF: Vitamin D deficiency. N Engl J Med *357*: 266-281, 2007.

89 Grant WB, Garland CF and Holick MF: Comparisons of estimated economic burdens due to insufficient solar ultraviolet irradiance and vitamin D and excess solar UV irradiance for the United States. Photochem Photobiol *81*: 1276-1286, 2005.

90 Holick MF: Sunlight "D"ilemma: risk of skin cancer or bone disease and muscle weakness. Lancet *357*: 4-6, 2001.

91 Mason RS and Reichrath J: Sunlight vitamin D and skin cancer. Anticancer Agents Med Chem *13*: 83-97, 2013.

92 Kelishadi R, Salek S, Salek M, Hashemipour M and Movahedian M: Effects of vitamin D supplementation on insulin resistance and cardiometabolic risk factors in children with metabolic syndrome: a triple-masked controlled trial. J Pediatr (Rio J) *90(1)*: 28-34, 2014.

93 Samefors M, Östgren CJ, Mölstad S, Lannering C, Midlöv P and Tengblad A: Vitamin D deficiency in elderly people in Swedish nursing homes is associated with increased mortality. Eur J Endocrinol *170(5)*: 667-675, 2014.

94 Perna L, Schöttker B, Holleczek B and Brenner H: Serum 25-hydroxyvitamin D and incidence of fatal and nonfatal cardiovascular events: a prospective study with repeated measurements. J Clin Endocrinol Metab *98(12)*: 4908-4915, 2013.

95 Zeichner SB, Koru-Sengul T, Shah N, Liu Q, Markward NJ, Montero AJ, Glück S, Silva O, Ahn ER: Improved clinical outcomes associated with vitamin D supplementation during adjuvant chemotherapy in patients with HER2(+) nonmetastatic breast cancer. Clin Breast Cancer *15(1)*: e1-e11, 2015.

96 Uhmann A, Niemann H, Lammering B, Henkel C, Hess I, Nitzki F, Fritsch A, Prüfer N, Rosenberger A, Dullin C, Schraepler A, Reifenberger J, Schweyer S, Pietsch T, Strutz F, Schulz-Schaeffer W and Hahn H: Antitumoral effects of calcitriol in basal cell carcinomas involve inhibition of hedgehog signaling and induction of vitamin D receptor signaling and differentiation. Mol Cancer Ther *10(11)*: 2179-2188, 2011.

97 Kasiappan R, Sun Y, Lungchukiet P, Quarni W, Zhang X and Bai W: Vitamin D suppresses leptin stimulation of cancer growth through microRNA. Cancer Res *74(21)*: 6194-6204, 2014.

98 Khaw KT, Luben R and Wareham N: Serum 25-hydroxyvitamin D, mortality, and incident cardiovascular disease, respiratory disease, cancers, and fractures: a 13-y prospective population study. Am J Clin Nutr *100(5)*: 1361-1370, 2014.
99 Liao Y, Huang JL, Qiu MX and Ma ZW: Impact of serum vitamin D level on risk of bladder cancer: a systemic review and meta-analysis. Tumour Biol *36(3)*: 1567-1572, 2015.
100 Bikle DD: Vitamin D receptor, a tumor suppressor in skin. Can J Physiol Pharmacol *93(5)*: 349-354, 2015.
101 Bikle DD, Oda Y, Tu CL and Jiang Y: Novel mechanisms for the vitamin D receptor (VDR) in the skin and in skin cancer. J Steroid Biochem Mol Biol *148*: 47-51, 2014.
102 Sidhu PS, Teske K, Feleke B, Yuan NY, Guthrie ML, Fernstrum GB, Vyas ND, Han L, Preston J, Bogart JW, Silvaggi NR, Cook JM, Singh RK, Bikle DD and Arnold LA: Anticancer activity of VDR-coregulator inhibitor PS121912. Cancer Chemother Pharmacol *74(4)*: 787-798, 2014.
103 Jiang YJ and Bikle DD: LncRNA: a new player in 1α,25(OH)(2) vitamin D(3)/VDR protection against skin cancer formation. Exp Dermatol *23(3)*: 147-150, 2014.
104 Jiang YJ and Bikle DD: LncRNA profiling reveals new mechanism for VDR protection against skin cancer formation. J Steroid Biochem Mol Biol *144 Pt A*: 87-90, 2014.
105 Bikle DD and Jiang Y: The protective role of vitamin d signaling in non-melanoma skin cancer. Cancers (Basel) *5(4)*: 1426-1438, 2013.
106 Rossdeutscher L, Li J, Luco AL, Fadhil I, Ochietti B, Camirand A, Huang DC, Reinhardt TA, Muller W and Kremer R: Chemoprevention Activity of 25-Hydroxyvitamin D in the MMTV-PyMT Mouse Model of Breast Cancer. Cancer Prev Res (Phila) *8(2)*: 120-128, 2015.
107 Yang HF, Zhang ZH, Chang ZQ, Tang KL, Lin DZ and Xu JZ: Vitamin D deficiency affects the immunity against *Mycobacterium tuberculosis* infection in mice. Clin Exp Med *13(4)*: 265-270, 2013.
108 Coussens AK, Wilkinson RJ, Hanifa Y, Nikolayevskyy V, Elkington PT, Islam K, Timms PM, Venton TR, Bothamley GH, Packe GE, Darmalingam M, Davidson RN, Milburn HJ, Baker LV, Barker RD, Mein CA, Bhaw-Rosun L, Nuamah R, Young DB, Drobniewski FA, Griffiths CJ and Martineau AR: Vitamin D accelerates resolution of inflammatory responses during tuberculosis treatment. Proc Natl Acad Sci USA *109(38)*: 15449-15454, 2012.
109 Salahuddin N, Ali F, Hasan Z, Rao N, Aqeel M and Mahmood F: Vitamin D accelerates clinical recovery from tuberculosis: results of the SUCCINCT Study [Supplementary Cholecalciferol in recovery from tuberculosis]. A randomized, placebo-controlled, clinical trial of vitamin D supplementation in patients with pulmonary tuberculosis'. BMC Infect Dis *13*: 22, 2013.
110 Salamon H, Bruiners N, Lakehal K, Shi L, Ravi J, Yamaguchi KD, Pine R and Gennaro ML: Cutting edge: Vitamin D regulates lipid metabolism in Mycobacterium tuberculosis infection. J Immunol *193(1)*: 30-34, 2014.
111 Wong GL, Chan HL, Chan HY, Tse CH, Chim AM, Lo AO and Wong VW: Adverse effects of vitamin D deficiency on outcomes of patients with chronic hepatitis B. Clin Gastroenterol Hepatol *13(4)*: 783-90, 2015.
112 Lungchukiet P, Sun Y, Kasiappan R, Quarni W, Nicosia SV, Zhang X and Bai W: Suppression of epithelial ovarian cancer invasion into the omentum by 1α,25-dihydroxyvitamin D_3 and its receptor. J Steroid Biochem Mol Biol *148*: 138-47, 2015.
113 Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, Orav JE, Stuck AE, Theiler R, Wong JB, Egli A, Kiel DP and Henschkowski J: Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. BMJ *339*: b3692, 2009.
114 Bjelakovic G, Gluud LL, Nikolova D, Whitfield K, Wetterslev J, Simonetti RG, Bjelakovic M and Gluud C: Vitamin D supplementation for prevention of mortality in adults. Cochrane Database Syst Rev *1*: CD007470, 2014.
115 Heyne K, Heil TC, Bette B, Reichrath J and Roemer K: MDM2 binds and inhibits vitamin D receptor. Cell Cycle *14(13)*: 2003-2010, 2015.
116 Reichrath J, Reichrath S, Heyne K, Vogt T and Roemer K: Tumor suppression in skin and other tissues *via* cross-talk between vitamin D- and p53-signaling. Front Physiol *5*: 166, 2014.
117 Reichrath J, Zouboulis CC, Vogt T and Holick MF: Targeting the Vitamin D Endocrine System (VDES) for the management of inflammatory and malignant skin diseases: an historical view and outlook. Rev Endocr Metab Disord *17(3)*: 405-417, 2016.
118 Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, Dubnov-Raz G, Esposito S, Ganmaa D, Ginde AA, Goodall EC, Grant CC, Griffiths CJ, Janssens W, Laaksi I, Manaseki-Holland S, Mauger D, Murdoch DR, Neale R, Rees JR, Simpson S Jr., Stelmach I, Kumar GT, Urashima M and Camargo CA Jr.: Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. BMJ *356*: i6583, 2017.
119 Litonjua AA, Carey VJ, Laranjo N, Harshfield BJ, McElrath TF, O'Connor GT, Sandel M, Iverson RE, Lee-Paritz A, Strunk RC, Bacharier LB, Macones GA, Zeiger RS, Schatz M, Hollis BW, Hornsby E, Hawrylowicz C, Wu AC and Weiss ST: Effect of prenatal supplementation with vitamin D on asthma or recurrent wheezing in offspring by age 3 years – the VDAART randomized controlled trial. JAMA *315*: 362-370, 2016.
120 McDonnell SL, Baggerly KA, Baggerly CA, Aliano JL, French CB, Baggerly LL, Ebeling MD, Rittenberg CS, Goodier CG, Mateus Nino JF, Wineland RJ, Newman RB, Hollis BW and Wagner CL: Maternal 25(OH)D concentrations ≥40 ng/mL associated with 60% lower preterm birth risk among general obstetrical patients at an urban medical center. PLOS One *12(7)*: e0180483, 2017.
121 Zhou SS, Tao YH, Huang K, Zhu BB and Tao FB: Vitamin D and risk of preterm birth: up-to-date meta-analysis of randomized controlled trials and observational studies. J Obstet Gynaecol Res *43(2)*: 247-256, 2017.
122 Wang H, Chen W, Li D, Yin X, Zhang X, Olsen N and Zheng SG: Vitamin D and chronic diseases. Aging Dis *8(3)*: 346-353, 2017.
123 DeLuca GC, Kimball SM, Kolasinski J, Ramagopalan SV and Ebers GC: The role of vitamin D in nervous system health and disease. Neuropathol Appl Neurobiol *39(5)*: 458-484, 2013.
124 Moukayed M and Grant WB: Molecular link between vitamin D and cancer prevention. Nutrients *5*: 3993-4023, 2013.
125 Caini S, Boniol M, Tosti G, Magi S, Medri M, Stanganelli I, Palli D, Assedi M, Marmol VD and Gandini S: Vitamin D and melanoma and non-melanoma skin cancer risk and prognosis: a comprehensive review and meta-analysis. Eur J Cancer *50(15)*: 2649-2658, 2014.

126 Dutta D, Mondal SA, Choudhuri S, Maisnam I, Hasanoor Reza AH, Bhattacharya B, Chowdhury S and Mukhopadhyay S: Vitamin-D supplementation in prediabetes reduced progression to type 2 diabetes and was associated with decreased insulin resistance and systemic inflammation: an open label randomized prospective study from Eastern India. Diabetes Res Clin Pract *103(3)*: e18-23, 2014.

127 Lindqvist PG, Olsson H and Landin-Olsson M: Are active sun exposure habits related to lowering risk of type 2 diabetes mellitus in women, a prospective cohort study? Diabetes Res Clin Pract *90(1)*: 109-114, 2010.

128 Autier P, Koechlin A and Boniol M: The forthcoming inexorable decline of cutaneous mortality in light-skinned populations. Eur J Cancer *51*: 869-878, 2015.

129 Levell NJ, Beattie CC, Shuster S and Greenberg DC: Melanoma epidemic: a midsummer night's dream? Br J Dermatol *161(3)*: 630-634, 2009.

130 Hill AB: The Environment and Disease: Association or Causation? Proc R Soc Med *58*: 295-300, 1965.

131 Weed DL, Gorelic LS: The practice of causal inference in cancer epidemiology. Cancer Epidemiol Biomarkers Prev *5*: 303-311, 1996.

132 Lindqvist PG and von Känel R: How to avoid venous thromboembolism in women at increased risk – with special focus on low-risk periods. Thromb Res *136(3)*: 513-518, 2015.

Received October 31, 2017
Revised December 5, 2017
Accepted December 18, 2017