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The relationship between sun exposure and all-cause mortality

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We aimed to conduct a narrative review of the rapid advances in knowledge regarding sun exposure and all-cause mortality. Data support the hypothesis that sun exposure avoidance is a major risk factor for all-cause mortality in adjusted analysis (age, income, education, marital status, smoking, and comorbidity). This was caused by an increased risk of death due to cardiovascular disease (CVD) and noncancer/non-CVD. However, the increased life span among those with high sun exposure naturally results in an increased prevalence of cancer death. In addition, sun exposure increases the incidence, but is related to better prognosis of skin cancer. The new findings indicate that there is a need for modification of guidelines regarding sun exposure. They may also add to our knowledge regarding the increasing incidence of diabetes mellitus and increased mortality among non-Caucasians in western countries. According to the present knowledge, in a low solar intensity region we should aim for sound and safe sun exposure habits, especially for those at increased risk of CVD or noncancer/non-CVD.

Introduction

In 2011, a 30% lower rate of all-cause mortality was reported among those who took a sunbathing vacation at least once a year over the course of three decades.[1] A 15-year prospective follow-up of the Melanoma in Southern Sweden (MISS) cohort of women demonstrated a significant dose-dependent decrease in all-cause mortality with increasing sun exposure habits[2] (Fig. 1) and the mortality rate was doubled (2.0, 95% CI 1.6–2.5) among those avoiding sun exposure compared to the highest sun exposure group (Fig. 2). The population attributable risk (PAR) for mortality for the group avoiding sun exposure was estimated to be 3%. In a 20-year follow-up of the same cohort, analyzed in a competing risk scenario, it was

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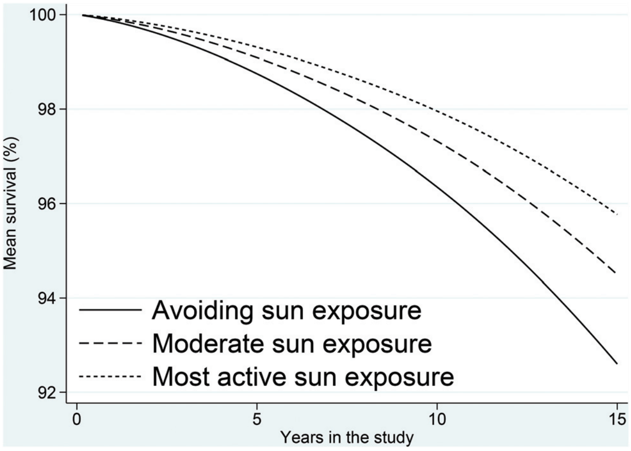

Fig. 1 The Melanoma in Southern Sweden (MISS) cohort included 1000 women from each age from 25 to 64 years, without cancer from the population registry 1990 and 29 518 women entered the study. Adjusted all-cause survival plot of all 29 518 women in the MISS Cohort. Significance of difference $P < 0.001$ among all three sun exposure groups. (Used with permission from Whiley.)[2]

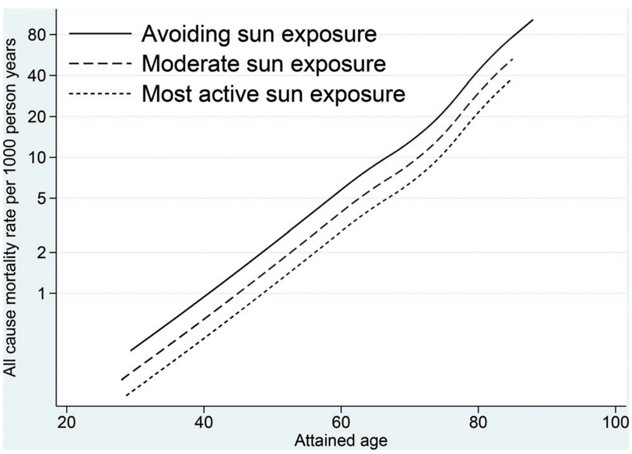

Fig. 2 Mortality rate by sun exposure with attained age as time variable. As compared to the highest sun exposure group, the mortality rate was two-fold higher (2.0, 95% CI 1.6–2.5) amongst avoiders of sun exposure and increased by 40% (1.4, 95% CI 1.1–1.7) in those with moderate exposure. (Used with permission from Whiley.)[2]

shown that the shorter life expectancy of women who avoided sun exposure was mainly due to a dose-dependent significantly increased risk of cardiovascular disease (CVD) and noncancer/non-CVD deaths, compared to the moderate and high sun exposure groups (Fig. 3, top).[3] While the risk of dying in the CVD and noncancer/non-CVD groups decreased with increasing sun exposure, the relative contribution of death due to cancer increased as a result of extended life expectancy (Fig. 3, bottom).[3] Thus, the overall prevalence of death due to cancer increased. In an analysis stratified by smoking, sun exposure habits and age groups, there was a similar risk of death among nonsmokers avoiding sun exposure as for smokers in the highest sun exposure groups (Fig. 4).[3] We interpreted this as suggesting that sun exposure avoidance is a risk factor for all-cause death of the same magnitude as smoking.

Skin cancer and all-cause mortality

Sunlight exposure and fair skin are major determinants of both skin cancer and vitamin D production. Due to similar etiology and prognosis, basal cell carcinoma and squamous cell carcinoma are often grouped as non-melanoma skin cancer (NMSC). NMSC is related to cumulative UV radiation and has a good prognosis. Cutaneous malignant melanoma (MM) is the skin cancer mainly related to increased mortality and is related to episodic overexposure to UV radiation.[4] There seems to be a relationship between higher sun exposure and MM incidence but an inverse relationship to prognosis. High UV exposure increases the incidence, while low sun exposure habits/vitamin D levels have been linked to thicker, more aggressive melanomas with shorter survival times.[5–7] The incidence of MM has shown the greatest increase of all cancers during the last 30 years. The disease is reported to be fatal in approximately 20% of patients. In line with these prior results, we reported that of those contracting MM, 35% of women with low sun exposure and 10% of those with the highest sun exposure habits died during the follow-up period in the MISS cohort, *i.e.* an eight-fold increased risk of all-cause mortality among those with low sun exposure.[3] Further, when grouping women based on skin cancer status (no skin cancer, NMSC, or MM) and sun exposure habits (low sun exposure, moderate exposure, or highest exposure), women with the highest sun exposure habits contracting NMSC had the highest life expectancy, while those avoiding sun exposure and contracting MM had the lowest survival rate.[3] In agreement with our findings, US Navy personnel have been reported to have a 26% reduced all-cause mortality, but a higher risk of skin cancer and a reduced risk of other internal cancers.[8,9]

Are there seasonal/latitudinal differences in CVD or noncancer/non-CVD mortality?

Ultraviolet radiation from the sun can convert 7-dehydrocholesterole into vitamin D3 in the skin, and with a further hydroxylation on position 1 and 25 and in the kidney and liver, the active form of vitamin D3 is formed. This "sunshine vitamin" not only has an effect on calcium metabolism and calcification of the bones but also has extensive effects on the immune system and the activation of T-cells.

Both coronary heart disease (CHD) and cerebrovascular disease show an increased risk during winter/spring compared to summer in countries at higher latitudes.[10–12] There are several noncancer/non-CVD conditions that increase the risk of all-cause mortality. In the UK, the risk of autoimmune diseases has been found to be significantly influenced by the season of birth, suggesting the presence of seasonal risk factors such as gestational UVB exposure.[13] Multiple sclerosis (MS) is an immunopathological autoimmune condition with a positive association with both latitude and seasonal differences.[14] The risk of MS increases approximately three-fold

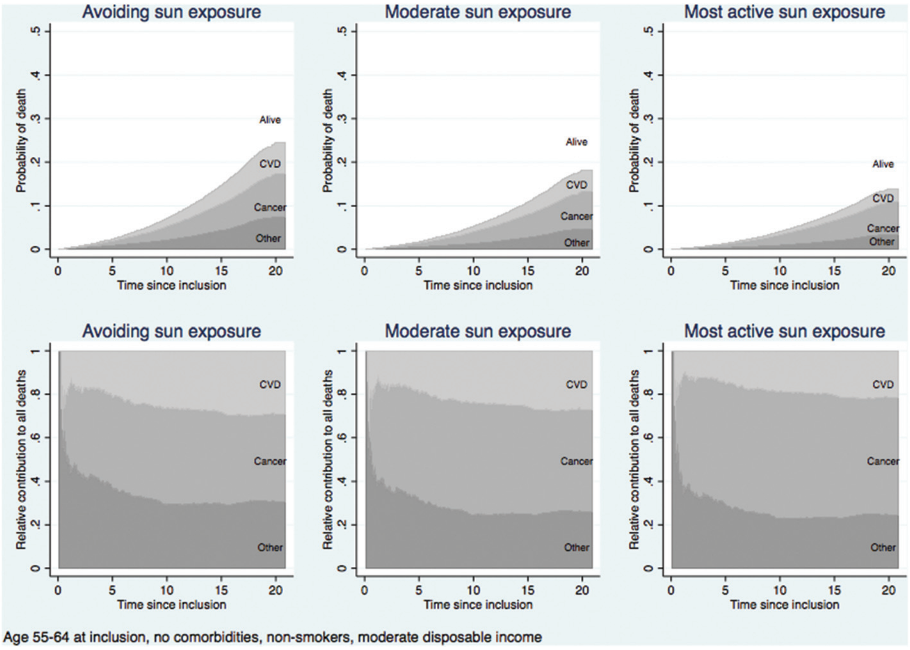

Fig. 3 Probability of death by sun exposure habits in a competing risk scenario. Upper three graphs show death categorized into CVD, cancer and other (noncancer/non-CVD) according to time in years since study inclusion. Bottom three graphs show relative contribution to death be sun exposure habits. As compared to highest sun exposure group, the subdistributional Hazard ratio (sHRs) of CVD mortality among sun exposure avoidance and moderate exposure were (sHR = 2.3, 95% CI 1.8–3.1, and 1.5, 95% CI 1.2–1.8, respectively). The corresponding sHRs for noncancer–non-CVD death were (2.1, 95% CI 1.7–2.8, and 1.57, 95% CI 1.3–1.9), and for cancer (1.4, 95% CI 1.04–1.6, and 1.1, 95% CI 0.9–1.4), respectively.

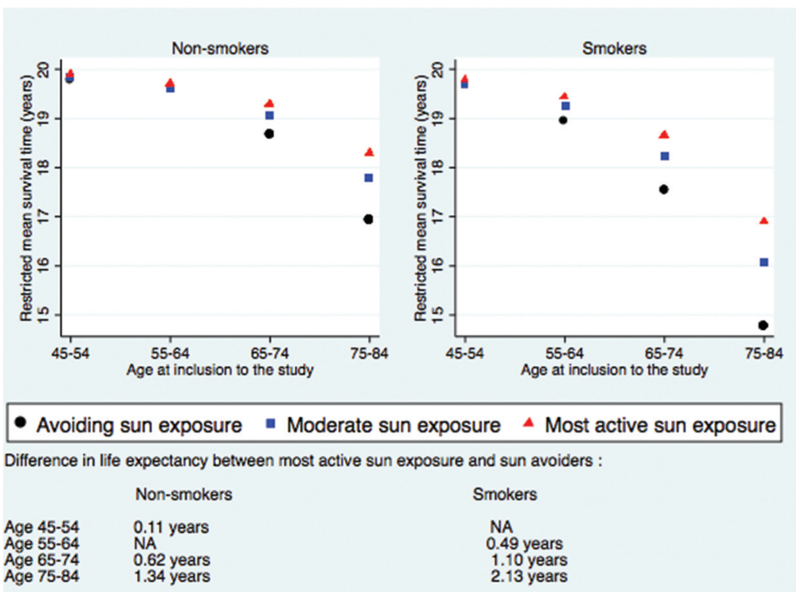

Fig. 4 Mean survival by age groups and sun exposure habits, stratified by smoking status, and calculations of mean difference in life expectancy by age groups amongst smokers and nonsmokers using restricted mean survival, *i.e.*, the area under the curve between two time points based on flexible parametric survival analysis.

among those with low sun exposure habits during their childhood and youth.[15] MS is characterized by Th1 and Th17 expression, and UV radiation has a possible beneficial role for Th1-mediated autoimmune diseases [also type 1 diabetes mellitus (T1DM) and rheumatoid arthritis].[16] Thus, it has been suggested that sun exposure lowers the risk of MS, and that vitamin D deficiency is related to an increased frequency of relapse.[14,17] The incidence of childhood T1DM has been shown to have latitude-dependent occurrence with the nadir close to the equator.[18] In a Danish study, mothers exposed to more sunshine during the third trimester had male offspring with a lower risk of developing T1DM before the age of 15 compared to those who had less sun exposure.[19] Newborns supplemented with vitamin D had an 80% reduced risk of contracting childhood or adolescent T1DM.[20] In Finland the recommended supplementary dose of vitamin D was reduced from 4000 units per d in 1964 to 1000 units per d in 1975, and to 400 units per d in 1992; the incidence of T1DM among those aged below 15 years rose from 20/100 000 to 60/100 000. Thus, when the supplementary dose decreased, the incidence of T1DM increased.[21] A recent Swedish study reported a better association between low temperature rather than low sun exposure and the development of childhood T1DM.[22] In the MISS cohort we showed that there was a dose-dependent reduced risk of incidental type 2 DM (T2DM) with increasing sun exposure and that the decrease in risk was mainly found among non-overweight women.[23] The finding of lower risk of T2DM with higher sun exposure was found to be independent of physical exercise habits.[23] However, since these are observational data, they do not have the same strength as a randomized control trial. Serum levels of vitamin 1,25-OH-D3 are described to be lower in patients with T1DM and T2DM as well as in women with gestational diabetes. The causality of a low level of vitamin D for these diseases is difficult to prove. However, using bi-directional Mendelian randomization analysis, a genetic approach that limits confounding, suggests that a higher BMI leads to lower vitamin D levels, but low vitamin D levels do not lead to increased BMI.[24] In addition, low levels of sun exposure/vitamin D levels might also be a marker for an unhealthy lifestyle that precedes the diagnosis of T2DM, for which we might not control.[23]

Intervention studies in which vitamin D supplementation has been given to risk groups have not convincingly shown a reduced incidence of diabetes.[25] The lack of effects of vitamin D supplementation has led to speculation about other mechanisms connected to low sun exposure. Measurement of circulating vitamin D levels may only provide a surrogate measure of sun exposure.[26]

Since 1,25 vitamin D induces antimicrobial peptide production, such as cathelicidin and β-defensin, when combating infections much research has focused on the role of vitamin D in respiratory tract infections.[27] For example, two RCTs with vitamin D supplementation showed reduced antibiotic consumption in patients with primary immune deficiency (60% reduction) and >70 years of age (50% reduction) compared to the placebo group.[28,29] These observations could be explained by a direct effect of vitamin D. Vitamin D can modulate IL-8 response to infection through the action of IL-10-producing regulatory lymphocytes IL-1.[30,31]

Thus, there seem to be several plausible mechanisms explaining the inverse relationship between sun exposure and both CVD and noncancer/non-CVD death.

Maternal mortality

Eclampsia is a major cause of maternal mortality worldwide. Eclampsia has been shown to be more prevalent during the winter season.[23,32,33] Earlier, it was hypothesized that this was due to cold or humidity, but we recently suggested an alternative interpretation that lack of sun exposure might be the environmental factor causing the increased risk of eclampsia.[23,32,33]

The largest single cause of maternal mortality in western countries is venous thromboembolism. There are no large studies regarding sun exposure and thromboembolism in pregnant women. However, there is a 40% increased risk of venous thromboembolism in the winter season in women.[34] In addition, women with low sun exposure habits in the MISS cohort showed an increased risk of venous thromboembolism.[34]

Perinatal death

The three largest causes of perinatal deaths are prematurity, infection, and asphyxia due to fetal growth restriction.[35,36] Vitamin D deficiency is an inflammatory condition, which in turn is overrepresented in intrauterine fetal death (IUD).[35] Vitamin D sufficiency has an immunomodulatory, anti-inflammatory effect and produces antibacterial proteins (see discussion above), and might be involved in the etiology of both prematurity and infections.[35,37] Both striated and coronary muscle strength are dependent on adequate vitamin D levels. If the fetus is vitamin D deficient, the fetal heart might be more vulnerable to hypoxic stress. Recently, we showed that women with vitamin D deficiency in early pregnancy were more likely to be delivered by emergency cesarean delivery due to suspected fetal distress and at doubled risk of newborn asphyxia.[38]

Possible mechanisms for the lower all-cause mortality among those with active sun exposure habits

Since the results are based on observational data rather than randomized controlled trials (RCTs), possible reversed causation has to be taken into consideration. Compared to women with low sun exposure, women in the highest sun exposure group might be better educated, have higher income, smoke less, exercised more, have a better diet and have had fewer diseases at the inception of the study. In the study we only included women without a diagnosis of cancer, and we adjusted for comorbidity in our analysis. In addition, while omitting the first ten years in the analysis, the HR were similar. This part of the analysis was also adjusted for BMI and physical exercise, which resulted in similar HRs.[2] Further, we adjusted for family income, educational level, smoking habits, and marital status in the survival analysis.[3] The findings that there was a dose dependency in sun exposure to inversed risk of all-cause mortality and the magnitude of the differences indicate a causal relationship and not only an association. The major shortcoming is, however, that we still cannot exclude the possibility that a bias exists between a healthy lifestyle and high sun exposure habits.

A genetic variant in a receptor for the circadian-regulated hormone melatonin (MTNR1B) is associated with increased risk of T2DM.[39] Exposure of light on the retina influences the melatonin production *via* suprachiasmatic nuclei of the hypothalamus. Thus, the melatonin system might, *via* the hypothalamic–pituitary axis, be involved in the lower risk of T2DM among those with active sun exposure habits.[23,40] Disruption of circadian rhythm is well described as having implications for glucose metabolism.[41] Sun radiation could influence other systems such as alpha-melanocyte-stimulating hormone and calcitonin gene-related peptide. The effects of these hormones on immunity and autoimmunity are unknown.

Solar UVA radiation causes decreased blood pressure and cardiovascular morbidity. This might be due to an increase in skin-derived nitric oxide (NO) bioactivity and to the mobilization of NO stores.[42,43] Both high chronic and acute stress levels may activate coagulation and thereby increase the risk of CVD.[44,45] UV radiation might attenuate stress levels by induced β-endorphin synthesis and thus, have a cardioprotective effect.[46] The endorphins also induce mood enhancement, feelings of relaxation and socialization.[47,48] An inborn awarding system to UVB exposure may be interpreted as an evolutionary mechanism indicating that sun exposure is important for our health. Atherosclerosis is a chronic inflammatory disease with cardiovascular dysfunction leading to increased risk of myocardial infarction, stroke and thromboembolism. In atherosclerosis angiotensin II levels are increased and NO levels decreased, which might be normalized by sun exposure. Depletion of sun radiation or low levels of vitamin D alone can probably not induce and propagate autoimmune diseases, but could facilitate a progression of cascade events, initiated by virus or other exogenous factors, towards a manifest disease.

Findings regarding vitamin D and all-cause mortality are heterogenous. In observational studies, low vitamin D levels are related to an increased risk of all-cause mortality, mainly CVD and noncancer/non-CVD death.[49,50] However, randomized controlled trials (RCTs) of studies with vitamin D supplementation have not been able to confirm reduced cardiovascular death.[50] In addition, Mendelian randomization studies have not confirmed that genetically determined vitamin D levels to be is associated with stroke, coronary heart disease, myocardial infarction, or CVD mortality.[50]

Public health implications

Different health issues stand in opposition to each other regarding UV exposure and a careful weighing of both hazards and benefits is required. As compared to northern Australia with strong UV radiation (UV index >6) during most time of the year, while Sweden have low UV intensity (UV index <3) 8 to 9 months of the year, increasing to strong UV radiation only rarely. Even if there are less than 5 days a year with strong sun, we learn not to be out in the sun between 1100 to 1500 to avoid strong UV intensity.[51] Although the use of sun blockers has a very minor position in the present guidelines, the general interpretation of the guidelines is as long as they use sun blockers they can be out for long. An intriguing explanation for the increasing MM incidence in Sweden is that sun exposure advice that urges reliance on sun screen use has resulted in sun UV overexposure, explaining the double risk of MM among sun screen users in Sweden.[52,53] No study has showed that it is safe to be out longer with sun blocker with regards to MM. More importantly, strong recommendation to avoid sun exposure may potentially increase the risk of CVD and noncancer–non-CVD morbidity and death in our population. Thus, national guidelines regarding sun exposure ought to be balanced, taking different health aspects into consideration depending on the regional UV intensity and skin type.

The MISS cohort is comprised of Swedish-born women before 1966, *i.e.* before widespread immigration took place and consists almost entirely of fair-skinned women. If avoidance of sun exposure is a major risk factor for all-cause mortality among Caucasian women, the problem may even be more serious among women who traditionally cover their skin or women with more densely pigmented skin. For example, black women in the US were reported to have a 26% excess all-cause mortality, as compared to Caucasians.[54]

Lifestyle factors and all-cause mortality

Traditionally, overweight, inactivity, and smoking have been the major life style risk factors related to all-cause mortality. Since low sun exposure habit found to be a risk factor in the same range as smoking, we made an estimation of differences in mean life-expectancy.[3] As compared to the highest sun exposure group, avoiders of sun exposure had a 0.6 to 2.1-year shorter life expectancy during study interval. The results need however to be confirmed by other groups and further work has to be done to further reduce the risk of bias. If so, those with high risk for coronary heart disease, stroke, venous thromboembolism or diabetes should be recommended safe sun exposure habits if living in a low UV intense region.[55,56] We know that too little and too much sun exposure is threats to our health. Future research will tell us how to define safe sun exposure habits, particularly if living in a low UV intensity region. Recent research in mice indicate that maternal vitamin D depletion leads to altered DNA methylation in over 500 regions and these differences persisted for two generations.[57,58]

Evolutionary perspective

From an evolutionary perspective, there must be a selection advantage in being less pigmented when living far from the equator; otherwise, differences in skin pigmentation would not have emerged. Fair skin might confer an evolutionary advantage in regions with low solar intensity and thereby increasing longevity. Since two-thirds of modern Western population has Neanderthal DNA which makes their skin fairer, it has been speculated that this might have helped them to adjust for life out of Africa.[59,60] However, a fair-skinned individual, for example emigrating from the UK, would not derive any benefit from light skin in Northern Australia, where heavy pigmented skin is an advantage due to the high solar intensity.

Conclusions

We conclude that the excess mortality rate among those who avoid sun exposure is mainly due to an increased risk of death from CVD and noncancer/non-CVD. We hope our findings add to the ongoing debate regarding the effects of sun exposure on our health. We might be in a position to improve health by implementing appropriate sun exposure habits and guidelines.

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