ANTICANCER RESEARCH *42*: 1671-1677 (2022)
doi:10.21873/anticanres.15644

Review

Sun Exposure - Hazards and Benefits

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Abstract. *There are carcinogenic effects of sun exposure that increase the risk for skin cancer, especially for fair-skinned individuals. Therefore, there are recommendations to avoid sun exposure and to apply sun blockers. A more nuanced and balanced message for sun safety guidelines is now advocated. Despite an increased risk of death due to skin cancer, fair skinned women seem to have an overall survival advantage. In addition, an inverse association between sun exposure and hypertension, thromboembolism, and type 2 diabetes mellitus has been shown. Furthermore, low sun exposure habits result in increased risk of cardiovascular disease (CVD), and non-CVD/ non-cancer mortality among women. There are also data supporting that the prognosis of cancer is improved with increasing levels of vitamin D/ sun exposure. In this narrative review we will provide a brief update of hazards and benefits of sun exposure focused on an updated, balanced, and evidence-based view.*

A US National Cancer Institute sponsored interdisciplinary meeting was gathered in 2016 to improve sun protection guidelines (1). Among other, they called for nuanced messages for at-risk populations, that reducing risk for one disease should not come at the cost of increasing risk for another. They concluded that although harms associated with overexposure of sun outweigh the benefits and should be avoided, the beneficial effects of ultraviolet radiation (UVR) exposure should not be ignored in developing new sun safety guidelines (1).

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Key Words: UV exposure, diabetes mellitus, cancer, melanoma, cardiovascular disease, mortality, review.

MISS Cohort

Our studies are mainly performed within the large melanoma in southern Sweden (MISS) cohort (2). Since 1990, we have followed ~30,000 women with written questionnaires every 10 years. We included ~750 Swedish-born women from each year between 1927 and 1966, without a diagnosis of cancer at inclusion. The women were randomized from the Swedish population registry and comprise 20% of the south Swedish population in the selected age-groups. By means of personal identification number (PIN) it was possible to crosslink data from the National prescription register and National discharge register. The rate of dropouts was neglectable. The few women who emigrated remained in the study until emigration.

Sun exposure habits are related to exercise, body mass index (BMI), skin color, and socio-economic factors. We have therefore adjusted for these variables in order to compensate for confounding factors. We used odds ratio as a measure of risk. Sweden is a country at latitude 55° to 68° North with scarcity of sun, and there are only few days per year when ultraviolet (UV) index is >6 and more than half of the year the UV index is ≤3.

Our studies based on a prospective cohort design will not give causal results, but only hypothesis generating associations that may suggest causality. The finding of dose-dependency, correct temporal and consistency of association's effect, and a plausible relationship in a prospective cohort study increase the likelihood of causality. Similar data as other well-established relationships or experimental research may provide additional support. A prospective cohort study has advantage over retrospective cohort or case-control studies due to the correct baseline status and independence from recall data.

In contrast to most other sun exposure studies, we were not interested in those with highest exposure habits, but instead the group with the lowest habits. We assessed low sun exposure as the possible 4th major lifestyle factor for our health, together with low exercise habits, smoking, and

obesity. In these MISS studies, we categorized sun exposure according to the answer to four selected questions; Do you sunbath during summer? Do you travel south to sun bath? Do you use solarium? Do you sunbath during winter vacations? Women answering no to all of these questions were categorized as having low sun exposure habits, one or two "yes" as moderate sun exposure and "yes" to three or four as greatest sun exposure habits. Self-reported UVR levels have been shown to better predict objectively measured UVR compared to ambient UVR (3).

Skin Cancer and Cancer Mortality

UVR is the most important environmental risk factor for both cutaneous malignant melanoma (MM) and non-melanoma skin cancer (NMSC). The risk factor for NMSC is mainly the cumulative UV exposure and NMSC is rarely a risk factor for death. MM is caused mainly by overexposure to UVR. Sun exposure and solarium are the dominant sources of UV exposure and high UV exposure is estimated to increase the risk of MM up to 2-fold. In our 20-year follow-up, the total incidence of MM was 0.9%, 0.81% for low and 1.1% for greatest exposure (OR=1.34, 95%CI=0.8-2.3) (4).

In the MISS cohort, women who used solarium were at a 20% increased risk of MM [hazard ratio (HR)=1.2, 95%CI=1.0-1.6], but the risk of all-cause mortality was 23% lower (HR=0.77, 95%CI=0.7-0.8) as compared to those that did not use solarium (5). In the MISS study, there was a dose-dependent increase in the risk of death with lower exposure, with a 40% higher risk of cancer-related death in the group with low sun exposure [subHR (sHR)=1.4, 95%CI=1.04-1.6] as compared to those with greatest sun exposure (4).

The incidence of MM is rising 5% annually, while the age standardized total risk of death decreases annually by 2.2% (6). In 2016, the risk for women to be diagnosed with MM in Sweden before the age of 75 was estimated to be 2.3%, comprising 6.6% of all cancers and 2.2% of cancer-related deaths (6). Thus, in terms of cancer mortality, MM is a small contributor to death (6). The mortality rate during the study interval of women who developed MM differed between sun exposure groups, low sun exposure 36%, moderate sun exposure 16%, and greatest sun exposure 11% (4). Thus, women with more active sun exposure habits survived their MM more often. Newton Bishop and co-workers reported the HR for relapse-free survival of MM was 0.79 (95%CI=0.64-0.96; p=0.01) for each 20 nmol/l increase in plasma vitamin D levels (7). An Italian study reported that sun bathing holidays after a diagnosis of MM were related to reduced rates of relapses (HR=0.3, 95%CI=0.1-0.9) (8).

Our results of lower death rate among those with high sun exposure are not new. Already in 1937, Peller and Stephenson reported that soldiers of US Navy, intensively exposed to open air, sun rays, and salt water, had 8-fold higher frequency of skin cancer (MM) and lip cancer, but the death rate among these cases of cancer was 3-fold lower than expected. In addition, they reported a 44% lower incidence of other cancer-related deaths (9).

In agreement with the above, those included in the VITAL trial (n=25871) in the vitamin D arm (2000 U vitamin D daily for 5 years) showed a 25% reduction of death due to cancer (HR=0.75, 95%CI=0.59-0.96), but vitamin D had no effect on incidence (10). Supplementation with 2000 U raised the vitamin D level in the plasma approximately 27 nmol/l from a baseline of ~77 nmol/l. This was followed-up with a meta-analysis of randomized controlled trials (RCT's) with vitamin D supplementation, that showed no effect on cancer incidence, but a 13% reduced risk of cancer death (HR=0.87, 95%CI=0.79-0.96) among those supplemented with vitamin D (11). The authors suggest that we should aim for vitamin D levels of 54-135 nmol/l in the plasma to reduce cancer mortality. Possible mechanisms for this improved prognosis are decreased invasiveness and immunomodulatory effects of vitamin D (12). Since UV is a carcinogen, inappropriate overexposure should be avoided. However, paradoxically, although sun exposure is the major risk factor for MM, the incidence of death due to cancer is lower among those with greatest exposure, possibly due to improved prognosis. Vitamin D seems to be involved in cancer prognosis, but not cancer incidence.

Redheads or Fair Skin

Red hair, freckles, pale skin, and melanocytic nevus are all genetically determined risk factors for MM, occurring most frequently among Irish, Scottish, and Scandinavian populations (13). The reason for prevalent skin risk factors in the North is presumably due to the evolutionary selection of a sun sensitive skin in these countries because of the low UV intensity. However, UVR may not be an important risk factor for MM among those with skin of color (14). In a recent study, we matched 11993 fair (redhead or having freckles) women one-to-one to non-fair white women and adjusted for age, smoking, education, marital status, income, and comorbidity. We aimed to assess whether fair women had a survival advantage and whether they had an over-risk of death due to skin cancer (15). We found that fair women had a 59% increased risk of death due to skin cancer (OR=1.59, 95%CI=1.3-2.0) while having an 8% overall longer life expectancy (OR=1.08, 95%CI=1.002-1.2) (15). The increase in risk for NMSC among fair women in our study was somewhat lower (OR=1.6, 95%CI=1.3-1.9) than previously reported for other populations (OR=2.0, 95%CI=1.7-2.4) (15, 16). The odds of MM were also lower (OR=1.3, 95%CI=1.03-1.65 *vs.* 2.4 95%CI=1.7-3.4, respectively) (15, 17).

Our interpretation is that sun sensitive skin is selected in Northern Europe by evolution and the increased risk of skin cancer is the "cost" for this survival advantage. Our

conclusion is that fair women should not abstain from sunlight, but they do not need as much sun exposure as non-fair women.

Sunscreen Use

Sunscreen users in Sweden have been reported to be at an 80% increased risk of MM (OR=1.8, 95%CI=1.1-2.9) (18). The subgroup of 19% of women who used sunscreen to enable long time exposure to the sun was at an 8-fold increased risk of MM (OR=8.5, 95%CI=1.0-75.8) (18). A plausible explanation of this increased MM risk might be that the application of a sunscreen inhibits the redness of the skin but allows prolonged UV exposure (=overexposure). Further, this subgroup usually applies low sun protection factor (SPF), while those who use sunscreens for other reasons use higher SPF (18). Only one Lóreal sponsored RCT has shown a 50% reduction (n=11 *vs*. n=22) of MM (19), but population-based cohort studies have shown increased risk (20). It has been difficult to assess whether sunscreen-use protects against MM or not (20). There is a general agreement that overexposure to UVR should be avoided.

In relation to the National Cancer Institute's call, it might be effective to address the above highest-risk group who used sunscreen to enable long time exposure to the sun and recommend not to overexpose (1). The prior one size-fits-all approach only focusing on sunscreen use, might give a false sensation of security, explaining part of the rise in MM incidence. Daily short sun exposure, at mid-day, without the use of sunscreens, might be optimal for health. Fair individuals need less sun exposure than those with more pigmented skin (15). A too restrictive sun exposure advice might do more harm than good by increasing the risk of death due to other diseases such as myocardial infarction and stroke (4). Sweden is a country with scarcity of sun; advice will presumably differ in countries with higher UV intensity.

Type 2 Diabetes Mellitus (T2DM)

In 2010, we reported observational evidence of an inverse dose-dependent association to T2DM frequency with increasing sun exposure (21). We showed that the decrease in risk for T2DM was still significant after adjusting for exercise and smoking habits. The risk reduction was inversely associated to BMI, with 40% to 60% reduction of T2DM among lean, 20% to 40% among overweight, and no risk reduction in the obese subgroup (21). A similar relationship with BMI is seen in the risk of endometrial cancer (22). Experimental research on mice given a diabetogenic diet together with long-term sub-erythemal UVR indicated not only an increase in glucose tolerance and decrease in insulin resistance but also suppression of weight gain and cholesterol levels (23). In addition, UVR exposure of obese mice reduced risk factors for cardio-metabolic dysfunction and weight (24, 25).

The relationship between vitamin D and T2DM have attained much interest. Low levels of vitamin D in the plasma in women are associated with high incidence of both T2DM and gestational diabetes (26-28). However, supplementation with 4000 U vitamin D did not lower the incidence of T2DM significantly (29). In Sweden, half of pregnant women are low in vitamin D and an even greater proportion during the winter season (30). Women with active sun exposure habits are reported to have normal vitamin D levels the whole year (31). In response to UV exposure, the increase in vitamin D in the plasma is lower among obese as compared to lean individuals, and there is an inverse relationship between BMI and vitamin D levels (28, 32). A large study using bidirectional Mendelian randomization analysis showed that higher BMI leads to lower vitamin D in the plasma, while the likelihood of low vitamin D levels to increase BMI is small (33). Thus, BMI seems to be in the causal pathway between sun exposure/ vitamin D and health effects (33). The association between the adipose tissue and vitamin D levels in the plasma need to be further elucidated.

The low vitamin D values, constantly seen in T2DM cohorts, might be a marker of low sun exposure or an effect of increased BMI/adipose tissue. Sun exposure has additional effects apart from vitamin D production such as an effect on systemic inflammation, immunomodulation, melatonin system, nitric oxide, and calcium transport. In addition, low levels of sun exposure/vitamin D might also be a marker for an unhealthy lifestyle that precedes the diagnosis of T2DM. The combination of similar hypothesis generating and experimental results increase the likelihood of a causal inverse relationship between sun exposure and T2DM.

Cardiovascular Disease (CVD) and CVD Mortality

Venous thromboembolism. We have assessed the risk of venous thromboembolic events (VTE) during 11 years in the MISS cohort (2). For every "yes" of the four questions of sun exposure, the risk of VTE decreased by approximately 30%. The risk of VTE was approximately 50% higher in winter compared to summer. Women with a presence of VTE were at a 4-fold higher risk of being diagnosed with a cancer during the study period. Women with a prior use of combined oral contraceptives were at a significantly 30% lower risk of VTE (2).

Several studies have showed an inverse relationship between vitamin D levels and VTEs (34). Low vitamin D levels have been shown to be associated with increased interleukin 6 (IL-6), homocysteine, plasminogen activator inhibitor-1 (PAI-1), and tissue factor pathway inhibitor (TFPI) levels (35). There is need of experimental studies exploring the relationship between UV exposure, plasma levels of

vitamin D, coagulation system and thromboembolism. During the last 10 years, lifestyle advice in the Swedish guidelines for pregnant women at increased risk of thromboembolism has included active sun exposure habits (36).

Hypertension and cardiovascular (CVD) mortality. Hypertension is the major modifiable driver for morbidity and mortality (37) and a procedure that would lower blood pressure on a population level would produce a major difference to the burden of diseases. There are several experimental studies showing a transient effect of UVR on blood pressure, but studies to date have been small and have given divergent results (38-42). Two population based studies report an inverse relationship between ambient UVR and systolic blood pressure (43, 44), with a 59% increased risk of stroke in areas below the median of ambient UVR, as compared to above (43). The effect on blood pressure was reported to be independent of plasma vitamin D (43, 45). A Chinese study reported that women who sunbathed 30 minutes per day had a 40% lower risk of hypertension (46). In a Saudi Arabian study of overweight patients, the prevalence of hypertension decreased from 28.1% to 11.1%, blood pressure decreased from a mean of 118.3/76.0 to 112.6/73.9 and the mean BMI dropped, after recommendation of increased dietary vitamins and 5 to 30 minutes of sun exposure twice a week during one year (47). A recent study comprising dialysis patients in the US shows that higher incident UVR was associated with lower blood pressure (48).

A major breakthrough of our understanding of a possible effect of sun exposure was when Liu and coworkers presented an alternative explanation for the known inverse association between vitamin D levels in the plasma and CVD risk (39, 49). They showed skin mobilization of nitric oxide (NO) in response to UVA radiation, not depending of circulatory nitric oxide synthases (NOS), which caused transient blood pressure reduction through photolysis of cutaneous nitrite or nitrate (39). They suggested vitamin D levels to be a biomarker for sunlight exposure (39). Recently, we assessed whether the level of sun exposure was associated with being treated for hypertension within the MISS cohort (50). In Sweden, all prescription drugs are recorded into a central registry since 2005. The reported sun exposure habits from the questionnaire year 2000 and all antihypertensives prescribed on an individual basis that were registered between 2005 and 2007 were accessed, and all women who had had at least one prescription were considered to have hypertension (n=23,593). Thus, we used prescription of antihypertensive medication as a proxy for hypertension. As compared to the group with greatest sun exposure, those with lowest and moderate sun exposure were at 41% and 15% greater odds of being on hypertensive medication five to seven years later (OR=1.41, 95%CI=1.3-1.6 and OR=1.15, 95%CI=1.1-1.2). There was an age-related ~two-fold increased risk per 10-year increase in age. Other risk factors were lack of exercise 36% increased (OR=1.36, 95%CI=1.2-1.5), non-fair phenotype 8% increased (OR=1.08, 95%CI=1.01-1.15), high chronic stress-related comorbidity 80% increased (OR=1.8, 95%CI=1.4-2.3), lack of university schooling 30% increased (OR=1.3, 95%CI=1.3-1.4) odds of being on antihypertensive medication (50). A Swiss population-based study showed decreasing CVD mortality with increasing altitude, 20% per 1,000 m for coronary heart disease and 12% per 1,000 m for stroke (51). The authors concluded that this was not due to established risk factors and suggested it might be due to the weather (higher UV exposure). In our competing risk analysis, we showed that the risk of CVD mortality was highest among those with low sun exposure habits [60% increased (sHR=1.6, 95%CI=1.3-2.0)](4). As compared to those with the highest sun exposure habits, those with moderate and low were at 50% and 130% increased risk of death within the study interval of 20 years (sHR=1.5, 95%CI=1.2-2.8, and sHR=2.3, 95%CI=1.8-3.1, respectively) (4).

The combination of experimental transient decrease in blood pressure by UVR and a dose-dependent decreased risk antihypertensive medication and CVD mortality with increasing sun exposure increase the likelihood of a causal relationship between sun exposure and CVD. However, effect from confounding factors cannot be excluded.

Non-cancer/non-CVD. In our competing risk analysis, we showed the risk of non-cancer/non-CVD mortality was highest among those with low or moderate sun exposure habits. These women were at 70% increased risk of death (sHR=1.7, 95%CI=1.4-2.1) (4), as compared to those with the highest sun exposure habits. Those with moderate and low sun exposure habits were at 60% and 110% increased risk of death within the study interval of 20 years (sHR=1.6, 95%CI=1.3-1.9, and sHR=2.1, 95%CI=1.7-2.8, respectively) (4).

All-cause Mortality and Sun Exposure

Yang and coworkers showed in 2011 that those having > 1 week of sun bathing holiday for 20-30 years were at 30% lower all-cause mortality compared to their background population (52). We showed a dose-dependent inverse relationship between sun exposure and all-cause mortality, with doubled risk among those with low, compared to greatest sun exposure (HR=2.0, 95%CI=1.6-2.5) (5). In our competing risk analysis, smokers had a higher death ratio within the study interval. When also stratifying for sun exposure habits, non-smokers with low sun exposure had a similar death rate as smokers with greatest sun exposure, in each age-interval. We draw the conclusion that low sun exposure is a risk factor for death in the same magnitude as smoking (4). In addition, as compared to those with the greatest sun exposure, woman with age > 55 and low sun

exposure had 1 month shorter life expectancy, per year (15). Since we all will die from some cause and the greatest reductions in risk of death were in the CVD and non-cancer/non-CVD groups, death due to cancer will increase. If we live 2-3 years longer, we will increase the risk of attaining a cancer and die from it. However, the age-standardized risk of death due to cancer will not increase.

Conclusion

There is an established relationship between sun exposure and an increased risk of skin cancer. This risk is further increased among fair women, but these women seem to have a survival advantage. There seem to be an inverse association between sun exposure and hypertension, T2DM, venous thromboembolism, CVD, and cancer prognosis. All of these effects might explain the inverse association between sun exposure and all-cause mortality. Both vitamin D and NO seem to be major contributors to the above effects. Although, our results are not in opposition to the results of others, confounding factors cannot be excluded.

Conflicts of Interest

The Authors have no competing interests in relation to this study.

Authors' Contributions

Conception and design of the study: PLT, EE and MLO. Analysis and interpretation of data: PLT. Collection and assembly of data: PLT, EE and MLO, Drafting of the article: PLT, Critical revision and final approval of the article: PLT, EE and MLO.

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Received January 13, 2022
Revised February 24, 2022
Accepted February 25, 2022