CORRESPONDENCE

Commentary on: "The Effects of Sun Exposure and Pigmentation Phenotype on Prognosis in Metastatic Melanoma"

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We read with great interest the study of Svensson et al. (1) based on the BioMEL database in Skåne, Sweden, including patients diagnosed with stage IV melanoma between 2013 and 2023. Sunburns during childhood were recorded retrospectively by questionnaire after diagnosis (n=136). The authors found that severe sunburns during childhood were associated with a decreased risk of all-cause death. They discussed this result in the context of a previous study reporting a positive association between a history of blistering sunburns and tumour mutational burden (TMB) (2), noting that TMB correlates with the number of neoantigens, which in turn correlates with response to treatment with immune checkpoint inhibitors (3, 4).

As stated by the authors (1), it is the first time an association between childhood sunburn (inflammatory response to excessive sun exposure) and all-cause deaths is reported in metastatic melanoma in a modern setting, after the implementation of immunotherapy treatment for advanced melanoma. Inverse associations between sunburns and melanoma-specific death have been reported in epidemiological studies of invasive melanoma (not limited to stage IV). An inverse association between history of sunburns and melanoma death was found in a population-based US study of melanoma patients diagnosed in 1987–1989 (5) and for recent sunburns in a multicentre, international population-based study of melanoma patients diagnosed in 1998–2003 (6). We have just reported a reduced hazard of melanoma-specific and overall death for ever- vs never-sunburn prior to diagnosis and a negative trend for the cumulative number of sunburns (childhood, adolescence plus adulthood prior to diagnosis) in 2,234 female melanoma patients (94% localized melanoma) diagnosed in 1991–2020 in the Norwegian Women and Health cohort study (7).

In our study, we investigated the possibility that selection bias underlies these paradoxical associations (7). Using frailty analysis, we demonstrated that it is possible to observe an inverse association between sunburn and melanoma-specific and overall deaths even if there is no true protective causal effect of sunburn. Sunburn is an established risk factor for melanoma, but when studying sunburn and death after melanoma diagnosis, selection bias may be introduced by the inclusion of only melanoma patients. Potentially, there could be other unobserved factors (e.g. genetic factors) that give an increased risk of melanoma and an increased risk of dying. That is, patients developing melanoma due to such factors could represent an unobserved subgroup of melanoma patients that have a high risk of death regardless of their earlier exposure to sunburns. Comparing melanoma patients with earlier sunburns, where this unobserved subgroup might represent a small fraction of individuals, to a group without earlier sunburns, where the unobserved subgroup potentially represents a larger part, could then result in observing better survival in those exposed to sunburn, even if there is no such causal effect. In fact, we showed that it is possible to observe such a negative association, even if there is actually a harmful causal effect of earlier sunburns.

Svensson et al. (1) concluded that further research is needed to confirm their results, and we would like to add that an observed inverse association between sunburns and melanoma-specific and/or overall deaths could, at least in part, be due to selection bias rather than a causal effect.

"Reply to Commentary on: "The Effects of Sun Exposure and Pigmentation Phenotype on Prognosis in Metastatic Melanoma"

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We thank the authors for their careful reading of our article and for their insightful contribution to the discussion. We are encouraged that their findings, based on a large and well-characterized cohort, are in line with our observations, thereby strengthening the overall empirical evidence for an inverse association between prior sunburn history and survival among patients with melanoma.

We would also like to commend the authors for their rigorous use of frailty analysis to demonstrate that such paradoxical associations may arise from selection bias driven by unobserved heterogeneity. We agree that this represents a plausible explanation and calls for caution in interpreting these findings as indicative of a causal relationship.

At the same time, we would like to emphasize that the potential influence of selection mechanisms does not necessarily diminish the value of prior sun exposure as a prognostic marker in melanoma patients. Rather, such associations may reflect underlying biological or host-related characteristics, whether measured or unmeasured, that are relevant to prognosis. Importantly, as also implied by the authors, a clear distinction must be made between the role of sun exposure in the general population, where it is a well-established risk factor for melanoma, and its prognostic implications among patients already diagnosed with melanoma.

Finally, we also want to underscore the importance of improving our understanding of the mechanisms driving melanoma development and progression. In particular, further research is needed to better characterize the subgroup of patients who develop melanoma in the absence of classical risk factors, as these patients may represent biologically distinct disease pathways associated with less favourable outcomes. A deeper understanding of these pathways may ultimately help refine prognostication and guide more personalized approaches to treatment."

REFERENCES (TO BOTH PAPERS)

1. Svensson T, Sahlberg S, Carneiro A, Isaksson K, Nielsen K, Ekedahl H. The effects of sun exposure and pigmentation phenotype on prognosis in metastatic melanoma. Acta Derm Venereol 2026; 106: 0388. https://doi.org/10.2340/actadv.v106.adv-2026-0388
2. Loo K, Soliman I, Renzetti M, Li T, Wu H, Reddy S, et al. Impact of sun exposure and tanning patterns on next--generation sequencing mutations in melanoma. J Surg Res 2020; 254: 147–153. https://doi.org/10.1016/j.jss.2020.04.021
3. Snyder A, Makarov V, Merghoub T, Yuan J, Zaretsky JM, Desrichard A, et al. Genetic basis for clinical response to CTLA-4 blockade in melanoma. N Engl J Med 2014; 371: 2189–2199. https://doi.org/10.1056/NEJMoa1406498
4. Fortman D, Karunamurthy A, Hartman D, Wang H, Seigh L, Abukhiran I, et al. Automated quantitative CD8+ tumor-infiltrating lymphocytes and tumor mutation burden as independent biomarkers in melanoma patients receiving front-line anti-PD-1 immunotherapy. Oncologist 2024; 29: 619–628. https://doi.org/10.1093/oncolo/oyae054
5. Berwick M, Armstrong BK, Ben-Porat L, Fine J, Kricker A, Eberle C, et al. Sun exposure and mortality from melanoma. J Natl Cancer Inst 2005; 97: 195–199. https://doi.org/10.1093/jnci/dji019
6. Berwick M, Reiner AS, Paine S, Armstrong BK, Kricker A, Goumas C, et al. Sun exposure and melanoma survival: a GEM study. Cancer Epidemiol Biomarkers Prev 2014; 23: 2145–2152. https://doi.org/10.1158/1055-9965.EPI-14-0431
7. Perrier F, Ahimbisibwe A, Valberg M, Green AC, Ghiasvand R, Rueegg CS, et al. Exploring the paradoxical association of sun exposure and melanoma-specific mortality: The Norwegian Women and Health (NOWAC) Study. Eur J Cancer 2026; 241: 116787. https://doi.org/10.1016/j.ejca.2026.116787