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Increased cutaneous squamous cell carcinoma risk with hydrochlorothiazide use: is there a safe alternative?

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Linked Article: Schneider *et al.* *Br J Dermatol* 2021; **185**:343–352.

Multiple studies have shown that hydrochlorothiazide, a photosensitizing drug, increases the risk of skin cancer.[1–6] In this issue of the BJD, Schneider *et al.* confirm the strongly increased risk of cutaneous squamous cell carcinoma (cSCC) in a cohort study using a UK primary care database.[7] Although, weak associations with melanoma and basal cell carcinoma (BCC) have been observed in some studies, these were not observed in the cohort study of Schneider *et al.*[7]

The first studies on hydrochlorothiazide compared users with nonusers of antihypertensive drugs.[5,6] In order to address the clinically important question of how skin cancer risk compares with alternative first-line antihypertensives, Schneider *et al.*[7] compared the skin cancer incidence of users of hydrochlorothiazide, bendroflumethiazide (another thiazide) and indapamide (a thiazide-like diuretic) with users of calcium channel blockers (another type of first-line antihypertensive drug). Recently, Rouette *et al.*[8] compared hydrochlorothiazide with all other thiazides. They obtained comparable results to Schneider *et al.*: an increased risk of cSCC was observed, but no associations for BCC and melanoma were observed.[8]

While most studies report relative risk (e.g. odds ratios or hazard ratios), Schneider *et al.*[7] calculated absolute risk increases, which is of importance for health policymakers to determine the absolute amount of extra skin cancers that can be expected among hydrochlorothiazide users. Despite the fact that these estimates were not yet available back in 2018, the European Medicines Agency, had already evaluated the two Danish studies carefully in 2018, and concluded that the association found between hydrochlorothiazide and risk of SCC was strong enough to incorporate an alert to the summary of product characteristics, recommending to reconsider the use of hydrochlorothiazide carefully, in patients with a history of skin cancer.[9]

In the two Danish case–control studies performed,[1,2] other drugs with comparable indications to hydrochlorothiazide, including bendroflumethiazide, had no association to skin cancer. The findings of Schneider *et al.* confirmed that bendroflumethiazide may be a safe alternative to hydrochlorothiazide, as there was no association with SCC and BCC. However, short-term use was associated with a 36% increase in melanoma incidence rate. Due to the absence of a clear dose–response relationship (i.e. long-term use was not associated with melanoma risk) causality seems unlikely and this may have been a chance finding. On the other hand, most melanomas occurred 3.6 years after initiation of bendroflumethiazide therapy, which may be a sufficiently long duration for a carcinogenic effect.

The association between BCC and hydrochlorothiazide showed the same pattern: short-term use seemed to increase the risk of BCC, but there was no association with long-term use. Therefore, external validation of their results is of vital importance. While the association with hydrochlorothiazide and cSCC is now externally validated in multiple studies,[7,8] Schneider *et al.* confirmed that bendroflumethiazide is an example of a safe alternative for prescribing physicians, in terms of choice of thiazide for patients at increased risk of nonmelanoma skin cancer.

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Is consumption of citrus associated with a higher risk of melanoma?

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Cutaneous melanoma is the most lethal form of skin cancer and the worldwide incidence has risen considerably over recent decades. Established risk factors for this cancer include sun exposure,[1] presence and number of naevi, a fair pigmentary phenotype and family history of melanoma.[2] Although some dietary factors, such as anti-inflammatory nutrients,[3] have been proposed to prevent melanoma development, recent studies have reported that the intake of citrus products appears to be associated with an increased melanoma risk.[4,5]

In this issue of the *BJD*, Marley *et al.* prospectively examined the relationships between citrus consumption and the risk of melanoma among 1592 cases and 197 372 controls from the UK Biobank cohort.[6] The strengths of this study include the large sample size, detailed subgroup analyses and adjustment for several confounding factors such as sun exposure and pigmentary traits. This study reports that high total citrus intake was associated with a 65% higher risk of melanoma compared with no consumption. Specifically, intake of oranges and orange juice were strongly associated with melanoma risk, whereas grapefruit and grapefruit juice/satsuma (mandarin or tangerine) intakes were not associated with melanoma risk. Interestingly, the positive and linear association between total citrus intake and melanoma risk was restricted to fair-skinned participants compared with dark-skinned participants, which may suggest potential interactions either with genetic factors or with sun exposure. These associations are highly plausible biologically, as citrus products are rich in furocoumarins such as psoralens, which exhibit carcinogenic and phototoxic properties. In support of this hypothesis, higher intakes of furocoumarins have recently been reported to be associated with an increased risk of melanoma.[7]

Findings by Marley *et al.* lend support to previous results on this topic. Two large prospective cohort studies in the USA reported positive and linear associations between citrus consumption and the risk of melanoma in both women and men.[4] Consistently, findings from a European cohort found that high intakes of citrus fruit were associated with a higher melanoma risk.[5] A prospective cohort study of postmenopausal women additionally suggested a positive association between citrus juice intake and melanoma risk, whereas citrus fruit was not associated with risk.[8] In contrast, these results contradict those of Fortes *et al.* who found that citrus fruit consumption was associated with a lower risk of melanoma.[9] Citrus products are a significant source of vitamin C, and foods rich in vitamin C have been suggested to reduce cardiovascular disease and cancer risk.[10]

In conclusion, although further studies are required in order to examine the phototoxicity mechanisms of furocoumarin-rich foods, the findings from this research are consistent with previous cohort studies. No specific public health recommendations can be made regarding citrus intake at this stage. However, if replicated and confirmed, these findings may ultimately have important implications in skin cancer prevention. In order to enhance our understanding of these associations going forward, future research should focus on blood/urine markers of furocoumarins and dietary furocoumarins, and evaluate their association with the risk of melanoma and also with the risk of keratinocyte cancers. As psoralens are found in particularly high concentrations in the peel of citrus products, additional epidemiological studies with detailed information on type of citrus fruit and juice, origin of citrus juice (commercial vs. homemade), and ultraviolet exposure would be worthwhile.