The authors reply to: "Antihypertensives and skin cancer" and "Association between thiazide diuretics and skin cancer: still nebulous"

We thank Dr. Dawes[1] and Dr. Parmar[2] for their thoughtful responses to our study.[3] We agree that when interpreting and applying our findings to clinical practice, they must be considered in each individual patient's clinical context. Thiazides are effective, inexpensive antihypertensive medications that lower cardiovascular risk;[4] for most patients the benefits will outweigh the potential risk of skin cancer.

Understanding absolute risk difference would be helpful. However, we cannot estimate the survival function, cumulative incidence function or absolute risk in our study design with cumulative exposure as a time-varying covariate. As Dr. Dawes mentions, hazard ratios (HRs) do not directly translate to and should not be interpreted as relative risks (RRs). The HR is larger in size and in the same direction of effect as the corresponding RR, with the exact relation between the measures changing over the course of study follow-up.[5]

Baseline absolute risk for skin cancer varies across patients and, therefore, the absolute risk difference associated with thiazide exposure is likely variable as well. Our study did not include data on important risk factors for skin cancer such as skin pigmentation, sun exposure or sun damage (e.g., the presence of premalignant lesions [actinic keratosis]). It is likely that any effect of thiazides on photosensitivity and consequent increase in absolute skin cancer risk is accentuated in people with fair skin and propensity to ultraviolet radiation damage. This may explain why studies in European countries, such as Denmark,[6] have found an association whereas studies in other populations, such as Taiwan, have not.[7]

We do not believe the association between thiazides and skin cancer can be explained by confounding by indication. We did not find an association with other antihypertensive classes. In particular, angiotensin-converting-enzyme inhibitors, the most commonly prescribed class, showed no trend toward any association. For angiotensin receptor blockers, we are cautious to avoid overinterpreting the increased HRs given the imprecision of the statistically nonsignificant effect estimates (the adjusted HR for keratinocyte carcinoma associated with angiotensin receptor blockers was 1.09, 95% confidence interval 0.91–1.29).

In summary, the results of our study indicate that increasing cumulative thiazide exposure is associated with increasing rates (and risk) of keratinocyte carcinoma and melanoma, but the size of RR and difference in absolute risk cannot be calculated from our data given the time-varying exposure. For some thiazide users, the absolute increase in the risk of skin cancer may not be clinically important. However, for people with other risk factors for skin cancer, the increased risk for skin cancer associated with thiazides can be included in the discussion of the risks and benefits of treatment with thiazides versus alternative antihypertensive medications.

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References

1. Dawes M. RE: Antihypertensives and skin cancer. *CMAJ* 2021;193:E996. doi: 10.1503/cmaj.78786.
2. Parmar M. RE: Association between thiazide diuretics and skin cancer: still nebulous. *CMAJ* 2021;193:E963. doi: 10.1503/cmaj.78925.
3. Drucker AM, Hollestein L, Na Y, et al. Association between antihypertensive medications and risk of skin cancer in people older than 65 years: a population-based study. *CMAJ* 2021; 193:E508-16.
4. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002;288:2981-97.
5. Sutradhar R, Austin PC. Relative rates not relative risks: addressing a widespread misinterpretation of hazard ratios. *Ann Epidemiol* 2018; 28:54-7.
6. Pedersen SA, Gaist D, Schmidt SAJ, et al. Hydrochlorothiazide use and risk of nonmelanoma skin cancer: a nationwide case–control study from Denmark. *J Am Acad Dermatol* 2018;78:673-81.e9.
7. Pottegård A, Pedersen SA, Schmidt SAJ, et al. Use of hydrochlorothiazide and risk of skin cancer: a nationwide Taiwanese case–control study. *Br J Cancer* 2019;121:973-8.

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