CORRESPONDENCE

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Comment on "Hydrochlorothiazide use and the risk of skin cancer in patients with hypertensive disorder: a nationwide retrospective cohort study from Korea"

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We read with interest the paper by Park et al. [1] investigating the association between hydrochlorothiazide and non-melanoma and melanoma skin cancer in South Korean patients. We were, however, surprised to read that hydrochlorothiazide use was inversely associated with skin cancer risk. This contradicts previous studies [2,3], the underlying biological rationale based on hydrochlorothiazide's known photosensitizing properties, as well as conclusions reached by medicines regulators [4]. We believe, however, that these contrasting findings arise due to bias in the study design.

In the study, Park et al. [1] follow patients from their first antihypertensive prescription which, as described, may not be a prescription for hydrochlorothiazide in the hydrochlorothiazide exposed group. Hydrochlorothiazide is often prescribed in combination with other antihypertensives and may therefore be less likely to be prescribed first-line. In the absence of a time-varying analysis, this will induce immortal time bias in the hydrochlorothiazide user group.

Patients were followed until the last day of data capture or the day of the first diagnosis of skin cancer. Exposure to hydrochlorothiazide was analyzed as having at least three hydrochlorothiazide prescriptions filled throughout that patient's total follow-up. However, the duration of follow-up is shorter for patients receiving a skin cancer diagnosis (as this censor follow-up). Having filled ≥ 50,000 mg of hydrochlorothiazide (the highest strata in the dose-response analyses) will, with a high dose of 25 mg/day, take > 5 years, or with 12.5 mg/day > 10 years. This has to be achieved within the maximum study period of 7.5 years (January 2009 to June 2017). As such, achieving such cumulative hydrochlorothiazide exposure levels is equivalent to requiring the near-total absence of a censoring event. Such bias will be much more pronounced in the dose-response analyses and corresponds quite well to the finding that exposure yields a very strong 'protective' effect against skin cancer.

Whether these issues have been correctly identified, and whether they explain the findings or not, can easily be tested by the authors. First, any antihypertensive drug should display similar properties, that is, if the authors performs similar cumulative analyses using their design for e.g., angiotensin-converting enzyme inhibitors or calcium channel blockers, we would

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expect them to identify similar protective associations. Second, hydrochlorothiazide use should be handled as a time-varying exposure. As such, each individual should contribute to the non-hydrochlorothiazide cohort from the time of the first antihypertensive prescription until the time of the first hydrochlorothiazide prescription. From the time of the first hydrochlorothiazide prescription, that person should contribute person-time to the hydrochlorothiazide user group only. If person-time is handled in this way, we would expect the protective associations obtained for 'ever use of hydrochlorothiazide' to vanish.

Nevertheless, we may not expect to see similar risks observed in a European population [2,3] replicated in an Asian population. In fact, in a recent Taiwanese study, hydrochlorothiazide showed no significant association to skin cancer [5]. This may be explained by several factors, including differences in skin phenotype, use of lower hydrochlorothiazide doses, and cultural differences in sun behavior. However, additional studies in Asian populations are necessary to confirm these findings.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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