Hydrochlorothiazide and squamous cell carcinoma

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Clinical question

Does hydrochlorothiazide (HCTZ) increase the risk of squamous cell carcinoma (SCC)?

Bottom line

Observational data suggest an association between HCTZ and the risk of SCC. Risk appears to consistently increase with dose and duration of use (eg, 5 years increases risk 3 to 4 times). Baseline incidence of SCC is less than 0.1% annually. The same risk has not been established with thiazidelike diuretics. The benefit of switching from HCTZ to another agent should be weighed against the risk of changing medications.

Evidence

Evidence is statistically significant unless otherwise stated.

- In a systematic review[1] of 2 cohort and 7 case-control studies (N=395789), SCC was associated with taking thiazide diuretics (odds ratio [OR] of 1.9).
  -Subgroup analysis found HCTZ and HCTZ combinations increased SCC risk (OR=2.0), and long-term HCTZ use (≥4.5 years) was associated with higher risk (OR=3.3).
  -Limitations: potential unmeasured confounders; recall and detection bias; and multiple comparisons.
- In a large case-control study,[2] 80162 SCC cases in Denmark were matched with 1603345 controls.
  -A cumulative HCTZ dose of 50000 mg or greater (about 6 years' use) was associated with SCC risk (OR=4.0).
  -A consistent dose-response relationship was observed for SCC (OR=7.4) with a cumulative HCTZ dose of 200000 mg or greater (about 20 years' use).
- Use of HCTZ is associated with risk of SCC of the lip[3]:
  -A dose-response effect was observed (OR=7.7) with a cumulative dose of 100000 mg or greater.
- Another systematic review[4] reported no effect with thiazides but did not include studies of HCTZ alone.
- Increased risk of basal cell carcinoma is very small (OR=1.2 to 1.3), if real.[1,2]

Context

- Baseline SCC risk varies with ethnicity, age, sex, and location. A recent UK cohort study reported an incidence of 77 cases per 100000 (<0.1%) per year.[5] Metastatic SCC developed in 1.1% to 2.4% of SCC patients.[6]
- Non-randomized studies might overestimate beneficial and harmful effects and cannot prove causation.
- Thiazide and thiazidelike agents reduce morbidity and mortality in RCTs and are recommended as first-line therapy in hypertension.[7]
- One hypertension society recommends thiazidelike diuretics as the preferred initial option for hypertension, although it suggests continuing HCTZ in stable patients.[8]

Implementation

Physicians might counsel patients about the potentially small increased risk of SCC from baseline with HCTZ. Patients already at increased risk might want to avoid HCTZ. Patients taking HCTZ should be counseled about surveillance for new or changing moles and sun safety. Thiazidelike diuretics are an option and appear at least as good or better than HCTZ for blood pressure and clinical outcomes.[9] Side effects such as electrolyte abnormalities should be considered. Online cardiovascular risk calculators might assist in reviewing the benefits of hypertension treatment and aid in shared informed decision making.[10]

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Competing interests
None declared

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