Association between hydrochlorothiazide exposure and skin and lip cancer: a series of population-based nested case-control studies

Study protocol

Data source and study population

The THIN database, which contains longitudinal electronic patient records extracted from over 500 general practices across the UK, will be analysed. For each analysis apart from lip cancer, patients will be required to have no previous skin or other cancer diagnosis before the first diagnosis of each outcome respectively. For the lip cancer analysis, patients will be allowed to have a prior history of non-melanoma skin cancer (basal cell skin cancer or squamous cell skin cancer). Patients will be required to have no record of organ transplantation; HIV diagnosis; or use of azathioprine, cyclosporine, or mycophenolate mofetil, that may predispose to skin cancer risk. Cohort entry will be defined as the date after the latest of the following criteria: start of the study period (01.01.1999); the practices AMR date; the patient's 18th birthday; date of registration with a general practice + one year. Cohort exit will be defined by the earliest of the following criteria: an outcome event; deregistration from the general practice; death; date of last data collection from the general practice; end of the study period (01.05.2016).

Study design, outcomes and control selection

A nested case-control design will be used. Each outcome was defined by Read codes recorded in the patient's electronic medical record. The date of the first event occurring after cohort entry will be the index date for case subjects. Four outcomes will be evaluated:

a) lip cancer

b) basal cell carcinoma skin cancer

c) squamous cell carcinoma skin cancer

d) melanoma

A fifth outcome consisting of oral cancers will also evaluated in an attempt to act as a negative control testing for unmeasured confounding.

Exposures

Ever use of hydrochlorothiazide will be defined as having been issued 1 or more prescriptions for an hydrochlorothiazide -containing drug before the index date and never use as never having been prescribed a hydrochlorothiazide-containing prescription. The dose of hydrochlorothiazide will be identified in all prescriptions to individuals in the study population, and the cumulative dose of hydrochlorothiazide to each individual prior the index date will be calculated. For the lip cancer analysis, high dose use of hydrochlorothiazide will be defined as a cumulative dose equivalent to 25,000 mg or more of HCTZ exposure, corresponding to 1000 or more defined daily doses. For the remaining outcomes, high dose use of hydrochlorothiazide will be defined as a cumulative dose equivalent to 50,000 mg or more of HCTZ, corresponding to 2000 or more defined daily doses. Prescriptions issued within 2 years of the index date (lag time) will be excluded from the calculation of cumulative dose. As a sensitivity analysis, the association will also be analysed using a 5 year exposure lag time.

Confounders

The primary analyses will adjust for age and sex (inherent in the matching criteria), use of selected drugs with suggested photosensitizing properties (retinoids, tetracyclines, macrolides, quinolones, amiodarone), b) use of drugs with suggested antineoplastic effects (aspirin, NSAIDs, and statins), c) history of alcohol abuse, diabetes

and chronic obstructive pulmonary disease (COPD), d) the Charlson Comorbidity Index (CCI) score. Covariate information recorded less than 2 years prior to the index date will be disregarded. In order to assess the impact of previously missing confounders, data on smoking status and body mass index (BMI) will also evaluated in addition to those aforementioned covariates.

Data analysis

Conditional logistic regression will be used to calculate odds ratios (ORs) for the association between each cancer outcome analysed according to predefined categories of cumulative dose use. Analyses will be conducted evaluating all patients irrespective of the duration of patient follow-up first and using patients with at least 10 years follow-up. Adjustment for smoking status and body mass index will then be undertaken. Multiple imputation was used to impute missing data on these two variables. The imputation model included all variables relating to clinical characteristics, outcome events, medication, and comorbidities. Multiple imputation will use fully conditional specification, with five imputations and analysed using Rubin's rules.