Renal cell carcinoma and thiazide use: a historical, case-control study (California, USA)

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Renal cell carcinoma has been linked to hypertension and antihypertensive medications. We investigated the association between renal cell carcinoma and the use of thiazide in a case-control study of 167 men and 90 women. Subjects were members of the Kaiser Permanente Medical Care Program in northern California (United States) who had taken a multiphasic health check-up from 1964 through 1988 and who were evaluated for cancer until the end of 1989. Control subjects received the same check-up, were matched by gender, year of check-up, and age at check-up, and had to be in the health plan until the date on which renal cell carcinoma was diagnosed. Data on known and potential risk factors, including hypertension, body mass index (BMI), and smoking status, were collected from the record of the check-up. Thiazide use was abstracted from the medical chart, which was reviewed from the date of the first entry until the date on which the cancer was diagnosed or the equivalent date for control subjects. The mean follow-back to check-up was 11.3 years. Among women, we found a significantly elevated risk of 4.0 (95 percent confidence interval [CI] 1.5-10.8) associated with ever having used thiazide after we adjusted for smoking, BMI, hypertension, and history of kidney infection at check-up. We did not find a statistically significantly elevated risk in men. Smoking was related to renal cell carcinoma in men (odds ratio [OR] 2.5, CI = 1.1-5.4) for those who smoked at least one pack per day compared with those who had never smoked, but was not related in women. We found a statistically nonsignificant relation between BMI and renal cell carcinoma. After we adjusted for thiazide use, we did not find that hypertension was a statistically significant risk factor for renal cell carcinoma. Analysis of the dosage of thiazide measured by time since first use, duration of use, number of mentions of use in the chart, and an estimate of total grams of exposure did not result in any convincing dose-response relation. These findings are consistent with a growing body of data linking antihypertensive medication with renal cell carcinoma. We are unable to conclude whether thiazide use or some other characteristic of hypertensive persons taking these medications is responsible for the association. Cancer Causes and Control 1994, 5, 319-325

Key words: Antihypertensive agents, diuretics, gender, hypertension, kidney neoplasms, renal cell carcinoma, smoking, USA

Introduction

Within the last few years, at least five case-control studies and four cohort studies have found a link between renal cell carcinoma and hypertension or the use of prescription antihypertensive or diuretic agents. The relation is almost always confined to women. Epidemiologists should find this link of particular interest.
for a cancer which has few recognized risk factors beyond male gender, smoking, and body mass index (BMI). The general finding for antihypertensive agents has, thus far, been remarkably consistent. However, difficulty has arisen in isolating the possible effect of antihypertensive medication from the effect of hypertension itself or another factor associated with being hypertensive. In addition, the type of antihypertensive agent may be important, and information on the dose-response characteristics of various suspected medications is lacking. Four of the five case-control studies have been interview-questionnaire studies and thus are subject to recall bias, and the fifth was based on medical record review. The cohort studies have either examined few cases or have included limited information on exposure to diuretics and antihypertensives as well as on other risk factors, such as smoking or hypertension. However, no studies which have looked at the association between renal cell carcinoma and antihypertensive medication have found a complete absence of such an association. We previously observed an association between renal cell carcinoma and thiazide but not other antihypertensive agents as part of our ongoing surveillance of cancer outcomes among prescription drug users in Oakland, California (United States) (Van Den Eeden S, unpublished data). Our study thus looked specifically at thiazide, which until recently was the most commonly prescribed diuretic and antihypertensive medication. In the US in 1984 and 1985, hydrochlorothiazide/triamterene combinations were the most commonly prescribed medication type, and hydrochlorothiazide was the sixth most frequently prescribed generic drug in 1987 and 1988.

Materials and methods

The study population was drawn from the Kaiser Permanente Medical Care Program in northern California, which currently has over 2.4 million members. Surveys and census-block group data have shown that the membership is similar to the general population enumerated by the census except for a slight underrepresentation of extremes of income. About 30 percent of the population of the greater San Francisco Bay Area currently belong to this health plan.

Cases were selected from a cancer incidence file of all cancers diagnosed within the health plan membership since 1960. These cases were linked through a unique medical record number to persons who took a multiphasic health check-up (MHC) from 1964 through 1988 at the Oakland and San Francisco Kaiser Permanente Medical Centers. Members took the MHC as a baseline or periodic health appraisal and were usually not acutely ill. Persons taking an MHC tended to be more highly educated than the general health-plan population. In the period from 1964 through 1989, 1,644 renal cell carcinomas with the ICD-9 codes 189, 189.0, 189.9 were diagnosed; 360 of the patients who had these cancers had received an MHC. After medical chart review, 257 of the 360 were documented to have renal cell carcinoma and had received an MHC before their diagnosis. Control subjects were selected from persons who did not have renal cancer who had also taken the MHC and were matched by gender, year of MHC, and age at MHC ± 1 year. Control subjects must also have been in the Kaiser Permanente Medical Care Program when their case was diagnosed.

The MHC file provided data on potential risk factors, including race, education, hypertension, height and weight, smoking status, coffee and alcohol consumption, chronic medical conditions, including kidney infection and kidney stones, and medication. Hypertension was defined as the subject reporting a physician’s diagnosis of hypertension or treatment for hypertension at MHC. Finally, we used a standard, precoded form to review the medical chart to supplement any data missing from the MHC and to obtain information on thiazide use from patient entry into the health plan to a point six months before diagnosis and an equivalent date for matched control subjects. The study focused entirely on the presence and frequency of thiazide use because thiazide was the most frequently used prescription diuretic and antihypertensive agent during the study period. To blind the medical chart analyst to the case or control status of the subject, charts were masked six months before the date of diagnosis by one medical chart analyst, and another analyst unaware of the case or control status of the subject reviewed the part of the medical chart which covered the period before that six-month period.

Standard analytic approaches for matched case-control studies were used. Continuous variables were divided into quartiles based on the distribution of all subjects for analysis. The odds ratio (OR) and 95 percent confidence interval (CI) for matched pairs were determined by conditional logistic regression. Variables which may have confounded the relation between renal cell carcinoma and thiazide use were included in models which evaluated the risk from ever having used thiazide as well as several quantitative measures of thiazide use, that is, duration (in years) from date of first use to renal cell carcinoma diagnosis; duration (in months) from first to last recorded use; number of mentions in the medical chart of a thiazide prescription; and estimate of total grams of exposure to hydrochlorothiazide equivalents. Total grams of exposure was calculated as the product of daily mil-