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# Editorial: Does Diuretic Therapy Increase the Risk of Renal Cell Carcinoma?

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# Editorial: Does Diuretic Therapy Increase the Risk of Renal Cell Carcinoma?

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Diuretics belong to the most used drugs in the treatment of hypertension. Its efficacy in lowering blood pressure and reduction of morbidity and mortality is proved. However, there is particular concern that diuretics can increase the risk for renal cell carcinoma. Therefore in this review of studies, the connection of diuretic therapy and risk for renal cell cancer was examined.

## Methods

There were eleven studies, in which the relation between diuretic use and renal cell carcinoma was adressed. Nine studies were case control studies [1–9] and two were cohort studies [10, 11]. The nine case control studies included a total of 4183 cases of renal cell carcinoma and 6014 controls, and the two cohort studies included 1,034.096 patients with 309 cases of renal cell carcinoma.

From this data the relative risks and odds ratios with the 95 % confidence intervals were calculated [12] for diuretics and other cofactors.

## Results

The relative risks and odds ratios for renal cell carcinoma for diuretics and different cofactors were as follows:

### Diuretics (Tab. 1, 2)

In the nine *case control studies* [1–9] the relative risk for renal cell carcinoma was between 1.2 and 1.9. In 8 of 9 studies the increased relative risk was significant (lower limit of the 95 % confidence interval > 1.0). The odds ratio was significantly increased between 1.3 and 3.1 in 8 of 9 studies. All studies together showed a relative risk of 1.48 with a 95 % confidence interval between 1.39 and 1.58 and an odds ratio of 1.7 with a 95 % confidence interval of 1.55/1.86.

In the two *cohort studies* [10, 11] the relative risk was significantly increased with 2.1 (95 % confidence interval 1.24/3.48) in one study [10], but not in the other one [11] with a relative risk of 1.2 (95 % confidence interval 0.76/1.89).

Both studies together showed an insignificantly increased relative risk for renal cell carcinoma with 1.23 (95 % confidence interval 0.94/1.63).

### Gender

For the case control studies (Tab. 3) in males [1–7] the relative risk and the odds ratio were significantly increased with 1.8 (95 % confidence interval 1.49/2.18) and 2.1 (1.68/2.62), respectively. In three of six studies in men the risk was increased significantly. For females [1–7] the relative risk and the odds ratio were also significantly increased (1.7 [1.52/1.90] and 2.2 [1.85/2.62]). In women four of seven studies showed a significantly increased risk.

In the cohort study [10, 11] women carried a significantly increased relative risk (1.71, 95 % confidence interval 1.14/2.58), but not men (1.07, 95 % CI 0.69/1.67).

### Obesity

In three case control studies [3–5] only one study [4] showed a significantly increased relative risk and odds ratio (1.20 [1.1/1.3], 2.0 [1.42/2.80]). Taking together the three case control studies there was a significantly increased relative risk

**Table 1.** Relative risk and odds ratio with 95 % confidence interval in the case control studies for renal cell carcinoma in patients with diuretics

| Author (year) | Relative risk (95 % confidence interval) | Odds ratio (95 % confidence interval) | Sign. |
|---|---|---|---|
| Yu et al. (1986) | 1.7 (1.025/2.84) | 1.9 (1.035/3.45) | + |
| McCredie (1992) | 1.2 (1.02/1.46) | 1.3 (1.03/1.74) | + |
| Finkle et al. (1993) | 1.8 (1.45/2.32) | 3.1 (2.08/4.8) | + |
| Kreiger et al. (1993) | 1.9 (1.41/2.45) | 2.0 (1.47/2.75) | + |
| Hiatt et al.(1994) | 1.5 (1.10/2.17) | 2.2 (1.20/3.97) | + |
| Weinmann et al. (1994) | 1.3 (1.09/1.64) | 1.6 (1.11/2.31) | + |
| Mellemgaard et al. (1994) | 1.25 (0.98/1.58) | 1.35 (0.98/1.87) | – |
| McLaughlin et al. (1995) | 1.3 (1.17/1.44) | 1.42 (1.23/1.64) | + |
| Chow et al. (1995) | 1.3 (1.11/1.58) | 1.5 (1.165/1.95) | + |
| **All studies** | **1.48 (1.39/1.58)** | **1.70 (1.55/1.86)** | 1× –<br>8× + |

**Table 2.** Relative risk with 95 % confidence interval in the cohort studies for renal cell carcinoma in patients treated with diuretics

| Author (year) | Relative risk (95 % confidence interval) | Sign. |
|---|---|---|
| Prineas et al. (1977) | 2.1 (1.24/3.48) | + |
| Heath et al. (1997) | 1.2 (0.76/1.89) | – |
| **Both studies** | **1.23 (0.94/1.63)** | **–** |

**Table 3.** Relative risk and odds ratio with 95 % confidence interval in men and women for renal cell carcinoma treated with diuretics (m = male, f = female)

| Author (year) | | Relative risk (95 % confidence interval) | Odds ratio (95 % confidence interval) | Sign. |
|---|---|---|---|---|
| Yu et al. (1986) | m | 1.0 (0.43/2.3) | 1.0 (0.4/2.1) | – |
| | f | 2.4 (1.3/4.5) | 3.6 (1.5/8.7) | + |
| McCredie (1992) | m | 1.6 (1.2/2.2) | 1.7 (1.19/2.72) | + |
| | f | 1.2 (0.99/1.45) | 1.04 (0.69/1.50) | – |
| Finkle et al. (1993) | m | – | – | |
| | f | 1.8 (1.43/2.3) | 3.1 (2.04/4.71) | + |
| Kreiger et al. (1993) | m | 1.9 (1.19/3.03) | 1.98 (1.19/3.27) | + |
| | f | 2.1 (1.5/2.93) | 2.5 (1.67/3.78) | + |
| Hiatt et al. (1994) | m | 1.2 (0.6/2.1) | – | – |
| | f | 4.0 (1.5/10.8) | | + |
| Weinmann et al. (1994) | m | 1.6 (1.08/2.36) | 1.0 (1.14/3.48) | + |
| | f | 1.3 (1.00/1.68) | 1.6 (0.95/2.69) | – |
| Mellemgaard et al. (1994) | m | 1.3 (0.87/1.93) | 1.4 (0.80/2.10) | – |
| | f | 1.3 (0.98/1.72) | 1.5 (0.95/2.40) | – |
| **All studies** | **m** | **1.8 (1.49/2.18)** | **2.1 (1.68/2.62)** | **+** |
| | **f** | **1.7 (1.52/1.90)** | **2.2 (1.85/2.62)** | **–** |

(1,15 [1,08/1,22]), but no increased risk by odds ratio (1.76 [0.96/1.56]).

In two cohort studies [10, 11] the relative risk was significantly increased (1.57 [1.03/2.38]).

**Hypertension**
The relative risk and the odds ratio was significantly increased (1.3 [1.22/1.47] and 1.54 [1.33/1.77]), respectively, in six case control studies [1–3, 5–7].

In two cohort studies [10, 11], the relative risk was significantly increased (2.32 [1.87/2.87]).

**Age**
Age ≥ 50 years seemed to be a significantly decreased risk (0.10 [0.08/0.11]).

**Cigarette Smoking**
Cigarette smoking seemed not to be a risk factor for renal cell carcinoma.

**Drugs**
Significantly increased risk factors were analgetics and alcohol, but not acetaminophen and coffee. Hormone replacement therapy, blood transfusion, and therapy with insulin seemed not to be a risk factor, and with the intake of oral contraceptives, estrogenes, and tea it could not be excluded that the risk will be decreased.

**Various Diseases (Tab. 4)**
Angina, renal stones and renal injuries seemed to increase the risk for renal cell carcinoma, but not diabetes, renal infection, stroke, myocardial infarction, gall stones, heart attack, thyreoid diseases, urologic diseases, and renal diseases in the family.

## Discussion

In nearly all case control and cohort studies [1–6, 8–10] the relative risk and odds ratio were significantly increased by about 50 % by diuretics, where the risk is something higher with odds ratio (1.70) than by calculating the relative risk (1.48).

The risk for renal cell carcinoma is elevated both in men and women by diuretic therapy [1–7, 11] in the same dimensions. Therefore the calculation of other risk factors could be gathered independent from gender. However, the risk for renal cell carcinoma is also increased by obesity [3–5, 10, 11], hypertension [1–3, 5–7, 10, 11], angina [2, 7], renal stones [2, 7], renal injuries [2, 7], alcohol [5], and analgetics [4, 7] (Tab. 4).

It is therefore difficult to discriminate these factors from the influence by diuretics.

If all factors were summarised in the different case control and cohort studies the relative risk varied between 1.1 and 1.4 with a mean of 1.24, and the odds ratio between 1.1 and 2.0 with a mean of 1.3. The relative risk and the odds ratio with all factors is therefore lower than the risk by diuretics (1.48 and 1.7, respectively).

If in case control studies only factors with an increased risk like obesity, hypertension, angina, renal stones and injuries, analgetics, and alcohol will be considered the relative risk and the odds ratio is 1.85 and 2.4, respectively, whereas the risk in patients with renal injuries only (4.0 [RR] and 4.2 [OR]) is distinctly higher compared with diuretics. In patients with obesity, hypertension, angina, renal stones, alcohol, and analgetics there are no significant differences compared with diuretics. However, if all factors were summarised except diuretics, the relative risk and odds ratio is something lower (1.25; 1.36) than with diuretics (1.48; 1.70).

**Table 4.** Relative risk and odds ratio for renal cell carcinoma in patients with various factors in case control studies

| Factors | Relative Risk | Odds ratio | Sign. |
|---|---|---|---|
| Diuretics [1–11] | 1.48 | 1.70 | + |
| Obesity [3–5] | 1.15 | 1.76 | +/– |
| Hypertension [1–3, 5–7] | 1.33 | 1.54 | + |
| Angina [2, 7] | 1.60 | 1.69 | + |
| Renal stones [2, 7] | 1.60 | 1.71 | + |
| Renal injuries [2, 7] | 3.98 | 4.29 | + |
| Alcohol [5] | 1.14 | 3.53 | + |
| Analgetics [4, 7] | 1.47 | 1.65 | + |
| **All factors except diuretics** | **1.25** | **1.36** | **+** |

Therefore it could not be of comparable controls, if they are not randomised and not large enough. In the analysed studies there were only a total of about 6000 controls compared with about 4000 cases. Also a recall bias must be considered, because cases have a better memory for previous expositions than controls. The same is true for cohort studies.

These disadvantages of case control studies are the potential for sample distortion bias and information bias.

Cohort studies have disadvantages if outcomes are rare like renal cell carcinoma and a prolonged follow-up is required.

Therefore results of case control and cohort studies are only references to an association between exponents and diseases but no evidence for the connection. Only in randomised prospective and controlled studies could be proven that the treatment with diuretics is a risk factor for renal cell cancer. But this study will be impossible and further observational studies with great numbers of cases and controls are necessary to firm the suspicion that diuretics increase the risk for renal cell carcinoma. However, increased attention is entitled.

**References:**

1. Yu Mimi C, Mack TM, Hanisch R, Cicioni C, Henderson BE. Cigarette smoking, obesity, diuretic use and coffee consumption as risk factors for renal cell carcinoma. JNCI 1986; 77: 351–6.
2. McCredie M, Stewart JH. Risk factors for kidney cancer in New South Wales, Australia. II. Urologic disease, hypertension, obesity and hormonal factors. Cancer Causes Control 1992; 3: 323–31.
3. Finkle WD, McLaughlin JK, Rasgon SA, Yeoh HH, Low JE. Increased risk of renal cell cancer among women using diuretics in the United States. Cancer Causes Control 1993; 4: 555–8.
4. Kreiger N, Marrett LD, Dodds L, Hilditch S, Darlington GA. Risk factors for renal cell carcinoma results of a population-based case-control study. Cancer Causes Control 1993; 4: 101–10.
5. Hiatt RA, Tolan K, Quesenburry CP Jr. Renal cell carcinoma and thiazide use. A historical case-control study (California, USA). Cancer Causes Control 1994; 5: 319–25.
6. Weinmann SH, Glass AG, Weess NS, Psaty BM, Siscovick DS, White E. Use of diuretics and other antihypertensive medications in relation to the risk of renal cell cancer. Amer J Epidemiol 1994; 140: 792–804.
7. Mellemgaard A, Niwa S, Mehl ES, Engholm G, McLaughlin JK, Olsen JH. Risk factors for renal cell carcinoma in Denmark: role of medication and medical history. Int J Epidemiol 1994; 23: 924–30.
8. McLaughlin JK, Chow WH, Mandel JS, Mellemgaard A, McCredie M, Lindblad P, Schlehofer B, Pommer W, Niwa S, Adami HO. International renal-cell cancer study. VIII. Role of diuretics, other anti-hypertensive medications and hypertension. Int J Cancer 1995; 63: 216–21.

9. Chow WH, McLaughlin JK, Mandel IS, Wacholder S, Niwa S, Fraumeni JF. Risk of renal cell cancer in relation to diuretics, antihypertensive drugs, and hypertension. Cancer Epidemiology, Biomarkers & Prevention 1995; 4: 327–31.
10. Prineas RJ, Folsom AR, Zhang ZM, Sellers TA, Potter J. Nutrition and other risk factors for renal cell carcinoma in postmenopausal women. Epidemiol 1997; 8: 31–6.
11. Heath CW Jr, Lally CA, Calle EE, McLaughlin JK, Thun MJ. Hypertension, diuretics, and antihypertensive medications as possible risk factors for renal cell cancer. Am J Epidemiol 1997; 145: 607–13.
12. Gardner M, Altman DG. Statistics with confidence. BMJ Books, London, 2000.

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