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High-ceiling diuretics are associated with an increased risk of basal cell carcinoma in a population-based follow-up study

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ABSTRACT

Introduction: In Caucasians, basal cell carcinoma (BCC) is among the most frequently diagnosed cancers and its incidence is increasing. Known risk factors for the development of BCC are age, sun exposure, and certain skin characteristics. Despite photosensitizing abilities of diuretic agents, little is known about a possible association with BCC.

Methods: Data were obtained from the Rotterdam Study; a large prospective population-based follow-up study with coverage of prescription-only drugs from pharmacies. The diagnoses of BCC were obtained through general practitioners, and by linkage with a registry of histo- and cytopathology. Cumulative use of diuretics at the date of diagnosis was categorized into quartiles for users of high-ceiling diuretics, potassium sparing agents and thiazides. The association between these drugs and BCC was assessed by Cox proportional hazard modeling with adjustment for age, gender and potential confounders. Effect modification was tested with interaction terms.

Results: Use of high-ceiling diuretics in the highest quartile (>3.7 years cumulative exposure) was associated with an increased hazard of BCC of 62% compared to no use (HR 1.6; 95% CI 1.1–2.4). Patients who used high-ceiling diuretics and had a high tendency of getting sunburned had a higher risk of diagnosis than non-users who do not easily get sunburned. Neither the use of potassium sparing agents, nor the use of thiazides was associated with BCC.

Conclusion: In our study, cumulative use of high-ceiling diuretics was associated with an increased risk of diagnosis of BCC. This effect is stronger in patients who easily get sunburned.

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1. Introduction

In Caucasians, basal cell carcinoma (BCC) is among the most frequently diagnosed cancers[1] and its incidence is increasing.[2–4] In a large region of The Netherlands, the age-adjusted incidence for males rose from 40 per 100,000 person years in 1973 to 92 per 100,000 person years in 2000. For females, the incidence rate rose from 34 to 79 per 100,000 person years during the same period.[2] However, mortality rates are low since BCC metastasizes rarely.[5,6] Nonetheless, morbidity can be high due to local tissue destruction, and residual scarring after surgery. Cosmetic considerations and the high incidence make BCC among the five most costly cancers to treat.[7]

Known risk factors for the development of BCC are age and phenotypic characteristics such as hair color, eye color and skin phototype. In addition to genodermatoses (specific inherited genetic skin conditions), genetic risk factors have been elucidated.[8–10] The major environmental risk factor for the development of BCC is excessive exposure to ultraviolet radiation (UV), both chronic and intermittent.[11] UV-B causes specific DNA mutations and UV-A indirectly damages the DNA via reactive oxygen molecules.[12–14] UV induced DNA damage, and therefore the risk of BCC, may be enhanced in patients with increased photosensitivity because they are more likely to get (severe) sunburns due to a lower Minimal Erythema Dose. A wide range of drugs have photosensitizing abilities including sulfonylurea derivatives used in diabetes mellitus, non-steroidal anti-inflammatory drugs, antipsychotic drugs, antimicrobials, antimalarials, amiodarone, diuretics and cardiovascular drugs.[15–17] Of these drugs, amiodarone has been associated with the development of BCC[18] and self-reported use of photosensitizing drugs in general was associated with an increased risk of BCC and squamous cell carcinoma (SCC).[19] Furthermore, an association between the total dispensed amount of photosensitizing diuretics in mg (i.e. thiazides, potassium sparing agents and furosemide) and risk of SCC and malignant melanoma has been described.[20] However, no clear associations were found between diuretics and BCC.

Despite the photosensitizing abilities of diuretic agents, little is known about a possible association between use of these frequently used drugs and the risk of BCC.[19,20] The objective of this study was to test the hypothesis that long-term use of diuretics is associated with an increased risk of BCC.

2. Methods

2.1. Setting

Data were obtained from the Rotterdam Study, a large population-based follow-up study. The objectives and design were extensively described earlier.[21–23] In the Rotterdam Study I, 7983 of 10,275 eligible persons aged 55 years and over, participated and are followed since inclusion. They are mainly Caucasians. In 1999, 3011 participants (of 4472 invitees) who had became 55 years of age or older, or moved into the study district since the start of the study were added to the cohort (Rotterdam Study II).

The study was approved by the Medical Ethics Committee of the Erasmus MC and all participants gave written informed consent. All participants were examined in detail at baseline. Participants were interviewed at home by trained interviewers and investigations took place during two subsequent visits at the research center. During follow-up, they underwent additional interviewing, laboratory assessments, clinical examinations and imaging procedures every 3–4 years. The vital status of the participants was obtained regularly from the municipal population registry. Morbidity and mortality were assessed by information from the general practitioner or, in case of hospitalization, by discharge reports from medical specialists.

Data concerning filled prescription-only drugs are provided by the seven computerized pharmacies that dispense out-patient prescriptions for all participants. Information on prescriptions was available as of 1st January 1991 and included product name, Anatomical Therapeutical Chemical (ATC) code,[24] dispensing date, total amount of drug units per prescription, prescribed daily number of units, dosage and regimen.

2.2. Study population and outcome

To ensure that only incident users of diuretics were included, the study cohort consisted of all patients in the Rotterdam Study who did not receive a prescription of diuretics before 1st April 1991. Complete coverage of pharmacy data started namely only in 1st January 1991 and prescriptions in the Netherlands have a maximum of 90 days. The diagnoses of BCC were obtained through the general practitioners and by linkage with a nationwide registry of histo- and cytopathology in the Netherlands (PALGA) from 1st January 1986 to 31st December 2007. Two research physicians independently assessed the first date and diagnosis of BCC. All events were classified according to the International Classification of Disease (ICD) tenth edition.[25] In case of discrepancy, consensus was sought or a cancer epidemiologist decided. The index date was defined as the date of the first diagnosis of BCC in the pathology data. Patients were followed since inclusion in the Rotterdam Study until the diagnosis of BCC, death, or end of the study period (31st December 2007), whichever came first.

2.3. Exposure

Cumulative time of use and average defined daily dose of diuretic dispensions were calculated over the period 1st April 1991 through 31st December 2007. Each participant could contribute cumulative exposure time to one or more of three categories, i.e. high-ceiling diuretics (ATC-code C03C), potassium sparing agents (ATC-code C03D), thiazides including chlortalidon (ATC-code C03A) and thiazides in combination with other drugs (C03EA). The potential association was assessed continuously per additional year of cumulative use and categorically by dividing cumulative use at the index date into four quartiles for each drug group. Quartiles were preferred

over other cut-off points to establish equal power in all groups, and because it guarantees unbiased cut-off points and facilitates trend analyses. To analyze the effect of dosage on the risk of BCC we categorized the average defined daily dosage (DDD, calculated over available prescriptions)[24] of diuretic users into four quartiles for each drug group.

2.4. Covariates

The following baseline patient characteristics, all determined by baseline interview or during the visit to the examination center, were individually assessed as potential confounders and/or effect modifier: gender, age, smoking status (current smoker, former smoker or never smoked), self-reported tendency to sunburn (high or low), outdoor work (>4 h daily for >25 years), history of living in a country with a high sun exposure (>1 year), ethnicity, natural hair color during childhood (blond, brown, red or black), natural hair color when adult (black or brown; blond or red), eye color (blue, intermediate or brown) and cohort (Rotterdam Study I or Rotterdam Study II).

Furthermore, concomitant use of other diuretics and/or other photosensitizing drugs was considered as potential confounder and/or effect modifier. The following drugs, known for their photosensitizing abilities were included: amiodarone, quinidine, calcium antagonists, sulfonylurea derivatives used in diabetes mellitus (tolbutamide, glibenclamide, gliclazide, glimepiride), non-steroidal anti-inflammatory drugs (piroxicam, flurbiprofen, ibuprofen, ketoprofen, naproxen, celecoxib and diclofenac), antipsychotics (chlorpromazine, haloperidol, phenothiazines), antibiotics (tetracyclines, fluoroquinolones, sulfonamides) and antimalarial drugs (aminoquinoline and methanolquinolines). Use was assessed in days of cumulative exposure at the index date.

2.5. Statistical analysis

The association between diuretics and BCC was analyzed using Cox proportional hazard models with cumulative drug use as a time-varying determinant, while adjusting for age at baseline and gender.[26] At the date of diagnosis cumulative exposure in participants with a BCC was compared to cumulative exposure in all individuals without a BCC with the same follow-up time in days. To encounter the exponential age-related risk of cancer, a sub-analysis was done in which the comparison was further restricted to participants who also had the same age as the persons with BCCs (±180 days). Covariates that changed the hazard ratio of BCC risk by more than 10% were considered as confounders.[27] To test for effect modification by covariates mentioned above, interaction terms were introduced in the statistical model and separate analyses were performed in different categories. In addition, proportionality of the model was tested by adding an interaction term of the determinant and the follow-up time. Analyses were performed using SPSS software (version 15.0, Chicago, US) and SAS software (version 9.1.3, Cary, US). All p-values are two-sided and were considered significant if $p < 0.05$.

Table 1 – Baseline characteristics of the study population (n = 10,692).

Characteristic[a]		Number (SD or %)
Gender	Males (%)	4288 (40%)
	Females (%)	6404 (60%)
Age at entry (years)		69 (9.7)
Cohort of entry	Rotterdam Study I	7770 (73%)
	Rotterdam Study II	2922 (27%)
High tendency to sunburn	Yes	3216 (30%)
	No	6607 (62%)
Outdoor work (>4 h daily for >25 years)	Yes	1187 (11%)
	No	6047 (57%)
Living in a sunny country (>1 year)	Yes	1017 (9%)
	No	8929 (84%)
Hair color when young	Blond	2245 (21%)
	Brown	6402 (60%)
	Red	295 (3%)
	Black	1000 (9%)
Hair color at present time	Blond or red	2540 (24%)
	Black or brown	7402 (69%)
Eye color	Blue	6239 (58%)
	Intermediate	769 (7%)
	Brown	2231 (21%)
Smoking status	Current smoker	2286 (21%)
	Former smoker	4644 (42%)
	Never smoked	3707 (34%)
Ethnicity	Caucasian	9645 (90%)
	Other	212 (2%)

SD: standard deviation.

[a] If numbers do not add up to 10,692 or 100% this is due to missing values.

3. Results

We excluded 14 participants from the study population (10,994) who had a diagnosis of BCC and another 288 because they had a prescription for a diuretic before 1st April 1991. The baseline characteristics for the remaining study cohort (10,692) are presented in Table 1. During the period of 1st April 1991 through 31st December 2007, 522 first diagnoses basal cell cancer were made. Of these, 193 patients had drug dispensing data for a diuretic of whom 137 had one or more prescriptions for thiazides (ATC-codes C03A and C03EA), 110 for high-ceiling diuretics (C03C) and 26 participants with a BCC had one or more prescriptions for potassium sparing agents (C03D).

After adjusting for age and gender, cumulative use of high-ceiling diuretics was significantly associated with an increased hazard ratio of BCC of 1.07 per year (95% CI 1.01–1.13). Use of high-ceiling diuretics in the highest quartile (>3.7 years of cumulative use) was associated with a 62% increased risk of BCC compared to no use (HR 1.62, 95% CI 1.09–2.42). Neither the use of potassium sparing agents nor the use of thiazides was associated with a statistically significantly increased hazard ratio of BCC (Table 2). Use of high-ceiling diuretics in the highest dosage quartile (>1.16 average DDD) during the whole period of use was associated with a slightly higher risk of BCC (HR 1.48, 95% CI 0.99–2.21, *p*-value for trend 0.03) but these results were not significantly different from those using a dosage in other quartiles (lowest quartile (<0.72 average DDD) HR 1.15, 95% CI 0.77–1.72, second quartile (average DDD 0.72–1.00) HR 1.33, 95% CI 0.82–2.16 and third quartile (average DDD 1.00–1.16) HR 1.43, 95% CI 0.86–2.40).

None of the potential covariates was a confounder. With regard to concomitant drug use, this was tested as well in a cumulative manner (any use) as on drug specific level. Tendency to sunburn was an effect modifier (*p*-value for interaction 0.03). Patients who used high-ceiling diuretics and who tended to get sunburned easily had a higher risk of BCC than non-users who did not easily get sunburned (HR per year use 1.13, 95% CI 1.05–1.22, *p*-value 0.001). Compared to persons who do not sunburn easily and who do not use high-ceiling diuretics, users of high-ceiling diuretics for more than 1360 d and who easily get sunburned had a higher hazard of BCC of 2.6 (*p*-value 0.001, 95% CI 1.49–4.84).

To further encounter the age-specific risk of cancer, a subanalysis was done. The comparison was further restricted to participants who had the same age (±180 days) at the time of diagnosis. Although slightly lower, the gender-adjusted, hazard ratio for developing a BCC was 1.04 per year (95% CI 1.01–1.07) when compared to participants with the same age. Proportionality, of the models used, was tested and yielded no statistically significant deviations from the null.

Table 2 – Age and gender adjusted risk of basal cell carcinoma during use of diuretics.

	N (cases)	Hazard ratio	95% confidence interval
Thiazides	137	1.00	0.95–1.05
No use	385	Reference	
<94 d	34	1.02	0.72–1.45
94–524 d	35	0.98	0.69–1.39
524–1646 d	34	0.86	0.60–1.22
>1646 d	34	1.10	0.77–1.58
K^+ sparing agents	26	1.04	0.93–1.17
No use	496	Reference	
<152 d	6	0.73	0.32–1.63
152–475 d	7	1.23	0.58–2.61
475–923 d	7	1.90	0.90–4.02
>923 d	6	0.92	0.41–2.08
High-ceiling diuretics*	110	1.07	1.02–1.13
No use	412	Reference	
<82 d	27	0.97	0.65–1.44
82–400 d	28	1.11	0.75–1.65
400–1360 d	28	1.23	0.83–1.81
>1360 d	27	1.62	1.09–2.42

* *p*-Value for trend: 0.01.

4. Discussion

Although UV exposure is a well-established risk factor for BCC, little is known about the contribution of photosensitizing drugs to BCC development.[18–20,28] In this study, cumulative exposure time of high-ceiling diuretics was associated with an increased risk of BCC but a significant dose-dependency was not demonstrated. A significantly higher risk of BCC was observed in users of high-ceiling diuretics who tend to get sunburned easily. An explanation could be that the use of high-ceiling diuretics might lower the Minimal Erythema Dose.

BCC characteristically appear on body areas exposed to the sun, with 80% appearing on the head and neck.[29] After all, sunlight remains one of the major risk factors for non-melanoma skin cancer.[12–14] In addition, it has been postulated that photosensitizing reactions followed by sun exposure may enhance the risk of sunburns and photo damage and subsequently the risk of skin cancer.[30] Our findings are in line with these hypotheses.

In our analysis, we did not find an increased risk of BCC to thiazides despite earlier publications.[31] Furthermore, we did not verify whether the increased risk of BCC diminishes after discontinuation of diuretic therapy. However, use of diuretic agents is mainly a long-term treatment. In addition, in the well-known association between oral psoralen and ultraviolet-A light (PUVA) therapy for psoriasis and squamous cell carcinoma, a persistent risk of non-melanoma skin cancer was seen after discontinuation of therapy.[32]

The association between high-ceiling diuretics and BCC is possibly explained through the fact that the two mainly prescribed high-ceiling diuretics, furosemide and bumetanide, both contain a sulfa-group. Sulfonamides are known for their photosensitizing abilities through phototoxic oxygen dependent reactions, but also act through photoallergic reactions.[16,33,34] A phototoxic reaction is the more common of the two and resembles sunburn. Photoallergy is an acquired immune response through antigen–antibody or cell-mediated mechanisms. Photosensitivity is a broader term for the entities phototoxicity and photoallergy.[16,33] A possibility for the

explanation of our finding could be that furosemide acts as a photosensitizer through UV-A and chlorothiazide acts through UV-B.[35]

4.1. *Methodological considerations*

Population-based studies may be affected by selection bias, information bias and confounding. In this study, selection bias probably did not occur because all BCC patients were ascertained independently of their diuretic exposure status within a large population-based cohort study. Information bias is also unlikely as all information was gathered prospectively and without knowledge of the research hypothesis. Although there will probably be an underestimation of the number of pathologically proven BCCs, this most likely resulted in non-differential misclassification.

Acute and intermittent ultraviolet exposure at young age is one of the risk factors for which we could not adjust. However, in our opinion this variable will not be a true confounder since it is probably not associated with the exposure. Hence, as was described earlier, adjustment of the association with ultraviolet exposure for high-ceiling diuretics does not change the risk.[36]

The long follow-up of almost 20 years is one of the strengths of this study. When analyzing drug exposure and a risk of cancer, this is of pivotal importance since cancer usually has a long induction and latent time. In addition, the complete prospectively collected information on drug dispension excludes the possibility that our findings can be explained by recall bias or other types of information bias. The latter may explain why our study found this association and others did not.[20] In addition, information on co-factors was extensive in our study.

In conclusion, in our study, cumulative exposure time to high-ceiling diuretics was associated with an increased risk of BCC. This effect is more pronounced in patients who easily get sunburned. Patients on high-ceiling diuretics should be more carefully advised to undertake measures to protect themselves against sun exposure.

Conflict of interest statement

None of the authors has declared any conflict of interest.

REFERENCES

1. Boring CC, Squires TS, Tong T, Montgomery S. Cancer statistics. *CA Cancer J Clin* 1994;**44**(1):7–26.
2. de Vries E, Louwman M, Bastiaens M, de Gruijl F, Coebergh JW. Rapid and continuous increases in incidence rates of basal cell carcinoma in the southeast Netherlands since 1973. *J Invest Dermatol* 2004;**123**(4):634–8.
3. Ko CB, Walton S, Keczkes K, Bury HP, Nicholson C. The emerging epidemic of skin cancer. *Br J Dermatol* 1994;**130**(3):269–72.
4. Roewert-Huber J, Lange-Asschenfeldt B, Stockfleth E, Kerl H. Epidemiology and aetiology of basal cell carcinoma. *Br J Dermatol* 2007;**157**(Suppl. 2):47–51.
5. Lo JS, Snow SN, Reizner GT, et al. Metastatic basal cell carcinoma: report of twelve cases with a review of the literature. *J Am Acad Dermatol* 1991;**24**(5 Pt. 1):715–9.
6. Ting PT, Kasper R, Arlette JP. Metastatic basal cell carcinoma: report of two cases and literature review. *J Cutan Med Surg* 2005;**9**(1):10–5.
7. Housman TS, Feldman SR, Williford PM, et al. Skin cancer is among the most costly of all cancers to treat for the Medicare population. *J Am Acad Dermatol* 2003;**48**(3):425–9.
8. Gudbjartsson DF, Sulem P, Stacey SN, et al. ASIP and TYR pigmentation variants associate with cutaneous melanoma and basal cell carcinoma. *Nat Genet* 2008;**40**(7):886–91.
9. Stacey SN, Gudbjartsson DF, Sulem P, et al. Common variants on 1p36 and 1q42 are associated with cutaneous basal cell carcinoma but not with melanoma or pigmentation traits. *Nat Genet* 2008;**40**(11):1313–8.
10. Stacey SN, Sulem P, Masson G, et al. New common variants affecting susceptibility to basal cell carcinoma. *Nat Genet* 2009;**41**(8):909–14.
11. Armstrong BK, Kricker A. The epidemiology of UV induced skin cancer. *J Photochem Photobiol* 2001;**63**(1–3):8–18.
12. Gallagher RP, Hill GB, Bajdik CD, et al. Sunlight exposure, pigmentary factors, and risk of nonmelanocytic skin cancer. I. Basal cell carcinoma. *Arch Dermatol* 1995;**131**(2):157–63.
13. Rosso S, Zanetti R, Martinez C, et al. The multicentre south European study 'Helios'. II: Different sun exposure patterns in the aetiology of basal cell and squamous cell carcinomas of the skin. *Br J Cancer* 1996;**73**(11):1447–54.
14. Zanetti R, Rosso S, Martinez C, et al. The multicentre south European study 'Helios'. I: Skin characteristics and sunburns in basal cell and squamous cell carcinomas of the skin. *Br J Cancer* 1996;**73**(11):1440–6.
15. Lankerani L, Baron ED. Photosensitivity to exogenous agents. *J Cutan Med Surg* 2004;**8**(6):424–31.
16. Moore DE. Drug-induced cutaneous photosensitivity: incidence, mechanism, prevention and management. *Drug Safety* 2002;**25**(5):345–72.
17. Stein KR, Scheinfeld NS. Drug-induced photoallergic and phototoxic reactions. *Expert Opin Drug Safety* 2007;**6**(4):431–43.
18. Monk BE. Basal cell carcinoma following amiodarone therapy. *Br J Dermatol* 1995;**133**(1):148–9.
19. Karagas MR, Stukel TA, Umland V, et al. Reported use of photosensitizing medications and basal cell and squamous cell carcinoma of the skin: results of a population-based case-control study. *J Invest Dermatol* 2007;**127**(12):2901–3.
20. Jensen AO, Thomsen HF, Engebjerg MC, et al. Use of photosensitising diuretics and risk of skin cancer: a population-based case–control study. *Br J Cancer* 2008;**99**(9):1522–8.
21. Hofman A, Breteler MM, van Duijn CM, et al. The Rotterdam study: objectives and design update. *Eur J Epidemiol* 2007;**22**(11):819–29.
22. Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA. Determinants of disease and disability in the elderly: the Rotterdam elderly study. *Eur J Epidemiol* 1991;**7**(4):403–22.
23. Hofman A, Breteler MM, van Duijn CM, et al. The Rotterdam study: 2010 objectives and design update. *Eur J Epidemiol* 2009;**24**(9):553–72.
24. WHO Collaborating Centre for Drug Statistics Methodology (accessed at: http://www.whocc.no/atc_ddd_index).
25. WHO (World Health Organization). International statistical classification of diseases and related health problems, 10th revision; 1992 (accessed at: http://www.who.int/classifications/icd/en).
26. Stricker BHC, Stijnen T. Analysis of individual drug use as a time-varying determinant of exposure in prospective

population-based cohort studies. *Eur J Epidemiol* 2010;**25**(4):245–51.
27. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. *Ann Intern Med* 2007;**147**(8):W163–94.
28. Karagas MR, Cushing Jr GL, Greenberg ER, et al. Non-melanoma skin cancers and glucocorticoid therapy. *Br J Cancer* 2001;**85**(5):683–6.
29. Rubin AI, Chen EH, Ratner D. Basal-cell carcinoma. *N Engl J Med* 2005;**353**(21):2262–9.
30. Stern RS, Liebman EJ, Vakeva L. Oral psoralen and ultraviolet-A light (PUVA) treatment of psoriasis and persistent risk of nonmelanoma skin cancer. PUVA follow-up study. *J Natl Cancer Inst* 1998;**90**(17):1278–84.
31. Robinson HN, Morison WL, Hood AF. Thiazide diuretic therapy and chronic photosensitivity. *Arch Dermatol* 1985;**121**(4):522–4.
32. Nijsten TE, Stern RS. The increased risk of skin cancer is persistent after discontinuation of psoralen + ultraviolet A: a cohort study. *J Invest Dermatol* 2003;**121**(2):252–8.
33. Epstein JH. Phototoxicity and photoallergy. *Semin Cutan Med Surg* 1999;**18**(4):274–84.
34. Epstein S. Photoallergy and primary photosensitivity to sulfanilamide. *J Invest Dermatol* 1939;**2**:43–51.
35. Onoue S, Yamauchi Y, Kojima T, Igarashi N, Tsuda Y. Analytical studies on photochemical behavior of phototoxic substances; effect of detergent additives on singlet oxygen generation. *Pharm Res* 2008;**25**(4):861–8.
36. Dore DD, Lapane KL, Trivedi AN, Mor V, Weinstock MA. Association between statin use and risk for keratinocyte carcinoma in the veterans affairs topical tretinoin chemoprevention trial. *Ann Intern Med* 2009;**150**(1):9–18.