Published in final edited form as:

Cancer Epidemiol Biomarkers Prev. 2014 August ; 23(8): 1539–1545. doi:
10.1158/1055-9965.EPI-14-0251.

Prescription diuretic use and risk of basal cell carcinoma in the nationwide U.S. Radiologic Technologists cohort

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Abstract

Background—Ultraviolet radiation (UVR) exposure is the primary risk factor for basal cell carcinoma (BCC). While prescription diuretics have photosensitizing properties, the relationship between diuretic use and BCC remains unclear.

Methods—Using data from the United States Radiologic Technologists Study, a large, nationwide prospective cohort, we assessed the relationship between diuretic use and first primary BCC while accounting for sun exposure history, constitutional characteristics, lifestyle factors, and anthropometric measurements for geographically-dispersed individuals exposed to a wide range of ambient UVR.

Results—After adjustment for potential confounders, we found a significantly increased risk of BCC associated with diuretic use (hazard ratio (HR) =1.22, 95% CI: 1.07–1.38). This relationship was modified by body mass index (BMI) ($p=0.019$), such that BCC risk was increased with diuretic use in overweight (HR=1.43, 95% CI: 1.16–1.76) and obese individuals (HR=1.43, 95% CI: 1.09–1.88), but not in normal weight individuals (HR=0.99, 95% CI: 0.81–1.21).

Conclusions—Increased risk of BCC associated with diuretic use in overweight and obese participants may be related to higher dosages, longer duration of medication use, reduced drug metabolism, or drug interactions.

Impact—Future cohort studies should obtain more detailed information on medication use, consider factors that affect drug metabolism, and measure intermediate endpoints such as photosensitivity reactions.

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Conflict of Interest: The authors state no conflict of interest

Keywords

Basal cell carcinoma; diuretics; hypertension; United States Radiologic Technologists Cohort; body mass index

Introduction

Approximately 1 million cases of basal cell carcinoma (BCC) are diagnosed each year in the United States and the primary risk factor is exposure to ultraviolet radiation (UVR) (1, 2). Use of photosensitizing medications, such as prescription diuretics, has been shown to lower the minimal UVR dose needed to produce an erythematous or sunburn-like response, increasing the risk of phototoxicity and, potentially, photocarcinogenesis (3–5). Diuretics are the recommended first line of treatment for hypertension (6), and are also less frequently prescribed to treat glaucoma (7), chronic kidney disease and hyperkalemia (8). Hypertension affects an estimated 60 million Americans, among whom 30% to 40% are prescribed diuretics (9, 10).

Despite the potentially broad public health impact, only a handful of epidemiologic studies have examined the relationship between use of photosensitizing medications and BCC. These have reported either null (11) or modestly increased risk (12–14). Registry-based studies have benefitted from large sample sizes and objective ascertainment of prescription records, but do not contain information on sun exposure history, constitutional characteristics (e.g. complexion, hair color, eye color), lifestyle factors (e.g. smoking), or anthropometric measurements (e.g. weight, height) (11, 13). In contrast, observational case-control studies have obtained extensive sun exposure history and personal characteristics, but have been limited by retrospectively collected, self-reported medication use (12, 15), while observational cohort studies have been limited by lack of geographic variability (14). The objective of our study was to assess prospectively the relationship between diuretic use and subsequent risk of first primary BCC using data from the United States Radiologic Technologists (USRT) study, a large nationwide cohort, while accounting for sun exposure history, constitutional characteristics, lifestyle factors, and anthropometric measurements for geographically-dispersed individuals exposed to a wide range of ambient UVR.

Materials and Methods

Study Population

The USRT is an occupational cohort comprised of approximately 146,000 radiologic technologists in the United States who were certified by the American Registry of Radiological Technologists for at least 2 years from 1926 through 1982 (16). Detailed descriptions of the cohort and methods have been previously published (16, 17). Briefly, self-administered questionnaires were mailed to cohort members during three time periods: 1983–1989, 1994–1998 and 2003–2005. The USRT cohort study has been annually approved by the human subjects review boards at the University of Minnesota and the National Cancer Institute.

The current study population was restricted to the subset of participants who are white, completed both the second and third questionnaires, and reported being cancer-free at the time of the second questionnaire ($n=58,213$). Follow-up continued from completion of the second questionnaire until the earlier of first primary cancer diagnosis, including all types of non-melanoma skin cancer (NMSC), or completion of the third questionnaire.

Incident BCC cases ($n=2,255$), defined as a first primary BCC diagnosis after the second questionnaire, were ascertained from the third questionnaire. Medical records to confirm BCC diagnosis were obtained for 666 (28.5%) cases, of whom 638 (95.8%) were confirmed and 28 (4.2%) were denied. Since the confirmation rate for self-reported BCC diagnosis was high, non-validated cases ($n=1,592$) were also included in the study population. During the validation process, an additional 61 cases of BCC were identified during medical validation of reported cancers other than BCC. These are included in the analysis, bringing the total case population for this study to 2,291 subjects.

Data Collection

Prescription diuretic use and duration were ascertained on the second questionnaire (entry into the study population), using the questions: “Have you ever taken prescription diuretics on a regular basis?”, with possible responses being yes or no, and “On average how long have you taken prescription diuretics on a regular basis?”, with possible responses being < 6 months, 6–11 months, 1–2 years, and > 2 years. The second questionnaire also collected information on height, weight, smoking history, physical activity, skin complexion, eye and hair color, Gaelic or Celtic ancestry, work history and diagnosis of selected chronic medical conditions. The third questionnaire ascertained incident BCC, as well as information on highest educational level achieved, location of residence and time spend outdoors at various ages over the lifetime (0–12, 13–19, 20–39, 40–64 and ≥ 65 years). UVR exposures were determined by linking the residential locations reported by respondents with the Total Ozone Mapping Spectrometer (TOMS) database (<http://toms.gsfc.nasa.gov>), as described previously (18). Lifetime solar UVR exposure was estimated by multiplying average hours of summer sun exposure per week by TOMS summer erythema UVR estimates based on residence and weighting by years of life spent at that location.

Statistical Analysis

To evaluate the relationship between prescription diuretic use and first primary BCC, Cox proportional hazards regression analyses was used to compute hazard ratios (HRs) and 95% confidence intervals (CIs) with age as the time-scale, which adjusts for age in all models (19). The following variables were considered potential confounders because they were significantly associated with both diuretic use and BCC incidence, but not believed to be on the causal pathway: birth-cohort (in 5-year intervals), body mass index (BMI), Celtic or Gaelic ancestry, estimated lifetime ambient UVR exposure, total head and neck occupational ionizing radiation dose, smoking history, strenuous exercise, and histories of hypertension, high cholesterol (≥ 240), and cardiovascular disease (angina, myocardial infarction, or coronary bypass surgery). The only potential confounder that changed the risk estimates by at least 10%, and was thus included in the final model, was BMI. Birth cohort, sex, and lifetime ambient UVR exposure were included for *a priori* reasons because they were

considered in previous publications or are strong risk factors for BCC. Potential confounders were tested for interaction with diuretic use. We also conducted a sensitivity analysis to determine if risk estimates differed for early onset BCC (developed age < 50 years *versus* 50 years).

Hazard models were tested for proportionality using a time interaction term and found to satisfy the proportionality assumption. All statistical tests were two-sided and *p* values were considered significant at the 0.05 α level. Analyses were conducted using SAS 9.3 software (SAS Institute, Cary, NC).

Results

The demographic characteristics of the current study population have been previously described (20). Briefly, the study population includes 58,213 white participants who were cancer-free at completion of the second questionnaire, including NMSC. Four percent of the eligible participants reported incident BCC ($n=2,291$) during 509,465 person-years of follow-up from completion of the second to completion of the third questionnaire. BCC cases were roughly 2 years older at study entry and contributed an average of 3 fewer years of follow-up than non-cases (Table 1). Study participants were predominantly women. Fair complexion, light eye and hair color, and high lifetime ambient UVR exposure were related to increased BCC occurrence in this cohort, as previously reported (18, 20). Participants with BCC were more likely to engage in strenuous exercise and be of normal BMI.

Prescription diuretic users were, on average, 4 years older than non-diuretic users (51 years *versus* 47 years). Consistent with the predominance of women in the cohort, diuretic users were more likely to be female (Table 2), but female technologists were also more likely to use diuretics than their male counterparts (13% *versus* 9%; not shown). Diuretic users engaged less in strenuous exercise, had higher BMIs, and were more likely to have been diagnosed with hypertension, high cholesterol, or glaucoma, but did not differ from non-users by complexion, eye color, or hair color.

We observed an increased risk of BCC among prescription diuretic users in the total population (HR=1.22, 95% CI: 1.07–1.38), after adjusting for age, birth cohort, sex, continuous BMI, and average lifetime ambient solar UVR exposure (Table 3). BCC risk increased with duration of diuretic use (*p* for trend <0.001). BMI was the only variable to show statistically significant interaction ($p=0.019$) with diuretic use, thus, the final analyses were stratified by BMI category. BCC risk was not associated with diuretic use in normal weight individuals (HR=0.99, 95% CI: 0.81–1.21), but was significantly increased with diuretic use in overweight (HR = 1.43, 95% CI: 1.16–1.76) and obese (HR = 1.43, 95% CI: 1.09–1.88) participants. BCC risk also increased significantly with increasing duration of diuretic use in both overweight (*p* for trend <0.001) and obese participants (*p* for trend=0.007). A sensitivity analysis to determine if risk estimates differed for early onset BCC (developed before age 50) *versus* late onset (developed age 50 or later) did not find any differences (data not shown).

Discussion

In this large, nationwide, prospective cohort study with information on constitutional characteristics, lifetime residence, lifestyle factors and anthropometric measurements, prescription diuretic use was significantly associated with increased risk of BCC. The relationship between diuretic use and BCC was strongest among overweight and obese participants reporting the longest diuretic use, but null among normal weight individuals.

Our overall findings support previous research demonstrating increased risk of BCC among users of photosensitizing drugs, including diuretics (12, 14, 21). A prospective registry-based study in the Netherlands with complete diagnosis and pharmaceutical information as well as information on lifestyle and personal risk factors reported increased risk of BCC among long term users of high-ceiling diuretics, a class of diuretics which tend to cause extensive diuresis (HR=1.63, 95% CI:1.09–2.42) (14). In a case-control study among residents of European countries with varied ambient UVR exposure, self-reported thiazide diuretic use was associated with actinic keratosis lesions (OR=3.18, 95% CI:1.93–5.26), a representation of severe solar damage in the skin that is highly related to BCC risk (22). Another case-control study also found elevated risk of BCC, though limited to early-onset BCC, among self-reported users of cardiovascular medications, of which diuretic users represent approximately 87% (12). Unlike this case-control study, we found no differences in BCC risk by age at onset. Our findings also differ from one null study based on the Danish National Registry that assessed specific types of diuretic medication use and risk of BCC (11). However, this study was set in a geographic region with relatively low and homogenous ambient UVR and did not adjust for anthropometric measurements such as BMI. Other epidemiological studies of diuretic use and BCC did not report a relationship limited to overweight and obese individuals, however, registry-based studies in Europe did not capture BMI so there was no potential to assess effect modification (11, 13, 14).

There may be several explanations for our findings of increased risk of BCC associated with diuretic use in people of high BMI. Hypertension in overweight and obese individuals is difficult to control (24, 25) so that other anti-hypertensive agents may be more often prescribed in this group (6). These other anti-hypertension medications alone, or in combination with diuretics, may be responsible for the increased risk of BCC in this group. People with high BMI may also receive a higher dose or require longer duration of diuretic medication. Unfortunately, our data did not allow us to examine risk by dosage or long duration (i.e., the highest category is ≥ 2 years). Another possibility is that obesity reduces the rate of diuretic drug metabolism so that the intensity and duration of their photosensitizing properties are increased (26). Finally, individuals with high BMI who are taking diuretics may be under increased medical surveillance and more likely to have a BCC ascertained.

A limitation of our study is that information on type of diuretic used was not collected. However, in the mid-1990s, when diuretic use in the USRT was assessed, thiazide diuretics were among the most commonly prescribed anti-hypertensive medication (10), making up approximately 60%–70% of all diuretics prescribed (23). These findings are consistent with a large New Hampshire-based case-control study of BCC in whites, in which Robinson and

colleagues found that 84% of participants who reported diuretic use for hypertension, used thiazide diuretics (12). Therefore, we assume that the majority of USRT participants who reported using diuretics in 1994–1998 were also using thiazide diuretics.

Although we used self-reported data, 95.8% of cases whose medical records were obtained were confirmed, lending validity to our data. According to Ming and colleagues self-report of BCC has both high positive and negative predictive values (27). Thus, although our study only assessed positive predictive value, there is reason to believe negative self-reports are reliable in this cohort of medical workers as well. Also, sensitivity analysis limited to validated cases did not indicate differences in the proportion of diuretic use and the crude relative risk of diuretic use and BCC in the validated population approximates that in the total study population (1.21 versus 1.24). Furthermore, the study population is comprised of health care workers who likely can report more accurately past diagnoses and medication use than individuals in the general U.S. population. A potential limitation is that we did not collect data on the type or location of BCC, which may follow different etiologic pathways, however it has been noted that 80% of BCCs are located on the head and neck regions (2). Other strengths of our study include prospective assessment of the relationship between diuretic use and first primary BCC while accounting for sun exposure history, constitutional characteristics, lifestyle factors, and anthropometric measurements among residents of a wide geographic area.

In summary, in this large nationwide cohort study, prescription diuretic use was significantly associated with increased risk of BCC in overweight and obese, but not in normal weight individuals. Future cohort studies should obtain more detailed information on prescription diuretic and other medication use, consider factors that affect drug metabolism and examine intermediate endpoints such as sunburns and other photosensitivity reactions associated with diuretic use.

Acknowledgments

Financial support: Intramural Research Program, DCEG, NCI, NIH, DHHS

We thank the study participants and Jerry Reid of the American Registry of Radiologic Technologists for their continued support of this study, Diane Kampa and Allison Iwan of the University of Minnesota for study management and data collection, and Jeremy Miller at Information Management Services, Inc. for biomedical computing support. This research was supported by the Intramural Research Program, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services.

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Table 1

Demographic and personal characteristics of basal cell carcinoma cases and non-cases in the United States Radiologic Technologists cohort

	Without BCC % (n=55,922)	With BCC % (n=2,291)
Age at entry, mean (SD)	47.4 (8.3)	49.6 (9.4)
Person-years at risk, mean (SD)	8.9 (1.6)	5.5 (2.6)
Sex		
Male	19.9	21.2
Female	80.1	78.8
Complexion		
Fair	47.8	57.8
Medium	49.6	40.7
Dark	2.0	0.8
Missing/Other	0.6	0.7
Eye color		
Blue/green/gray	44.6	52.1
Hazel	22.1	22.1
Brown	32.1	24.7
Missing/Other	1.2	1.1
Natural hair color at age 20		
Red/Blonde	20.5	27.5
Brown	75.3	69.3
Black	3.1	2.1
Missing/Other	0.7	0.8
Average lifetime solar UVR, quartile		
Q1 (lowest)	23.6	21.7
Q2	23.6	22.2
Q3	23.6	23.9
Q4 (highest)	23.4	27.0
Missing	5.8	5.2
Smoking status		
Non-smokers	54.6	54.3
Former smoker	32.0	33.9
Current smoker	12.7	11.1
Missing	0.7	0.7
Strenuous exercise (hrs/week)		
None	44.1	42.7
<1 hr	20.8	18.6
1–3 hrs	18.0	18.6
4+ hrs	9.8	12.5
Missing	7.3	7.6
BMI (kg/m ²)		

	Without BCC % (n=55,922)	With BCC % (n=2,291)
Underweight, <18.5	1.4	1.6
Normal, 18.5–24.9	50.4	56.3
Overweight, 25–29.9	30.2	28.1
Obese, 30	16.1	12.2
Missing	1.9	1.9
Ever taken prescription diuretics regularly		
Yes	11.7	14.1
No	87.2	84.3
Missing	1.1	1.6
Duration of diuretic use		
Never	87.2	84.3
<6 months	3.4	2.9
6 months–2 years	3.1	3.7
2 years	5.0	7.2
Missing	1.3	1.9
Ever diagnosed with hypertension		
Yes	12.9	15.2
No	84.8	82.4
Missing	2.3	2.4
Ever diagnosed with high cholesterol (≥ 240)		
Yes	9.8	12.1
No	87.9	85.5
Missing	2.3	2.4
Ever diagnosed with a cardiovascular condition ^a		
Yes	2.7	3.7
No	95.0	94.0
Missing	2.3	2.4
Ever diagnosed with glaucoma		
Yes	1.1	1.4
No	96.6	96.2
Missing	2.3	2.4

Abbreviations: BCC, basal cell carcinoma; SD, standard deviation; BMI, body mass index

^aIncludes angina, myocardial infarction, or coronary bypass surgery

Table 2

Demographic and personal characteristics among diuretic users and non-users in the United States Radiologic Technologists cohort^a

	No diuretics, % (n=50,716)	Diuretics, % (n=6,859)
Age at entry, mean (SD)	47 (8.1)	51.02 (9.0)
Person-years at risk, mean (SD)	8.8 (1.7)	8.6 (1.9)
Sex		
Male	20.6	14.6
Female	79.4	85.5
Complexion		
Fair	48.2	49.2
Medium	49.6	48.3
Dark	1.9	2.1
Unknown	0.3	0.4
Eye color		
Blue/green/gray	45.2	44.3
Hazel	22.2	22.2
Brown	31.8	32.6
Missing/Other	0.8	0.9
Natural hair color at age 20		
Red/Blonde	20.9	20.7
Brown	75.4	75.1
Black	3.0	3.5
Missing/Other	0.7	0.7
Average lifetime solar UV, quartile ^b		
Q1 (lowest)	23.5	24.4
Q2	23.6	23.3
Q3	23.7	22.8
Q4 (highest)	23.7	22.8
Missing	5.6	6.8
Smoking status		
Non-smokers	55.1	51.3
Former smoker	31.5	36.4
Current smoker	12.8	11.6
Unknown	0.7	0.7
Strenuous exercise (hrs/week)		
None	43.4	49.6
<1 hr	21.1	18.6
1–3 hrs	18.5	14.8
4+ hrs	10.2	8.2
Missing	6.9	8.8
BMI (kg/m ²)		

	No diuretics, % (n=50,716)	Diuretics, % (n=6,859)
Underweight, <18.5	1.5	0.6
Normal, 18.5–24.9	52.9	34.3
Overweight, 25–29.9	29.8	33.0
Obese, 30	14.1	29.8
Missing	1.8	2.4
Ever diagnosed with hypertension		
Yes	8.4	46.9
No	89.4	50.8
Missing	2.2	2.3
Ever diagnosed with high cholesterol (≥ 240)		
Yes	8.6	19.3
No	89.2	78.5
Missing	2.2	2.3
Ever diagnosed with a cardiovascular condition ^c		
Yes	2.2	6.9
No	95.6	90.8
Missing	2.2	2.3
Ever diagnosed with glaucoma		
Yes	1.0	1.8
No	96.8	95.9
Missing	2.2	2.3

Abbreviations: SD, standard deviation; hrs, hours; BMI, body mass index

^a missing values for diuretic use (n=638)

^b Solar UV exposure quartile calculated from summer erythema UVR values weighted by time outdoors

^c Includes angina, myocardial infarction, or coronary bypass surgery

Table 3

Hazard ratios of BCC and diuretic use by BMI category in the United States Radiologic Technologists cohort^{a,b,c}

	Cases	Unadjusted HR ^d	95% CI	P for trend	Adjusted HR ^e	95% CI	P for trend
<u>Total population</u>							
<u>Diuretic ever</u>							
No	1932	Ref			Ref		
Yes	323	1.07	0.95 1.20		1.22	1.07 1.38	
<u>Diuretic, length of use</u>							
Never	1932	Ref			Ref		
<6 months	67	0.86	0.67 1.09		0.96	0.75 1.23	
6 months–2 years	85	1.12	0.90 1.39		1.22	0.96 1.53	
>2 years	164	1.16	0.98 1.36	0.089	1.38	1.16 1.64	<0.001
<u>Normal weight^f</u>							
<u>Diuretic ever</u>							
No	1159	Ref			Ref		
Yes	112	0.98	0.80 1.19		0.99	0.81 1.21	
<u>Diuretic, length of use</u>							
Never	1159	Ref			Ref		
<6 months	26	0.71	0.48 1.05		0.74	0.50 1.10	
6 months–2 years	35	1.24	0.89 1.74		1.16	0.81 1.67	
>2 years	50	1.05	0.79 1.39	0.673	1.09	0.81 1.48	0.604
<u>Overweight^g</u>							
<u>Diuretic ever</u>							
No	512	Ref			Ref		
Yes	118	1.293	1.06 1.59		1.43	1.16 1.76	
<u>Diuretic, length of use</u>							
Never	512	Ref			Ref		
<6 months	26	1.22	0.83 1.81		1.37	0.92 2.04	
6 months–2 years	27	1.17	0.79 1.73		1.20	0.80 1.80	
>2 years	63	1.40	1.07 1.83	0.010	1.58	1.20 2.08	<0.001
<u>Obese^h</u>							

	Cases	Unadjusted HR ^d	95% CI	P for trend	Adjusted HR ^e	95% CI	P for trend
Diuretic ever							
No	194	Ref			Ref		
Yes	83	1.30	1.00 1.69		1.43	1.09 1.88	
Diuretic, length of use							
Never	194	Ref			Ref		
<6 months	12	0.88	0.49 1.58		0.98	0.54 1.76	
6 months–2 years	21	1.28	0.82 2.02		1.36	0.85 2.17	
>2 years	46	1.42	1.02 1.99	0.031	1.59	1.12 2.24	0.007

^a Underweight (BMI < 18.5 kg/m²) eliminated in stratified results due to small sample size

^b for trend from treating categorical medication variable as continuous in regression

^c for diuretic BMI interaction = 0.019

^d Adjusted for age

^e Adjusted for age, birth cohort (5 yr categories), sex, continuous BMI and UV quartile

^f Normal is BMI 18.5 kg/m² and < 25 kg/m²

^g Overweight is BMI 25 kg/m² and < 30 kg/m²

^h Obese is BMI 30 kg/m²