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Antihypertensive Medication as a Risk Factor For Basal Cell Carcinoma: A Nationwide Registry-based Case-control Study

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Hydrochlorothiazide has been associated with increased cutaneous squamous cell carcinoma risk. Meanwhile, its association with basal cell carcinoma (BCC) risk is controversial. The association between commonly prescribed antihypertensive medications and BCC risk in the Swedish population was investigated. All cases with a histopathologically verified BCC in Sweden during 2007–2017 and 2 matched controls per case were included in this nationwide, registry-based, case-control study. Information on prescribed antihypertensive drugs, comorbidities, co-medications, and socioeconomic factors was retrieved from nationwide registries. The odds of being treated with any of the chosen treatments in relation to BCC diagnosis were estimated. In total, 133,539 cases and 257,849 controls were studied. Thiazide-containing combination treatments (OR 1.09), angiotensin II receptor blockers (OR 1.09), calcium channel blockers (OR 1.09), and beta-blockers (OR 1.07) were associated with an increased BCC risk. Use of single-agent thiazide treatment did not affect BCC risk. In conclusion, statistically significant associations were found between several commonly prescribed antihypertensives and an increased BCC risk. Thiazide treatment affected BCC risk only when given as combination treatment, indicating that relevant adjunctive substances should be studied further in relation to BCC risk. Presently, it is suggested that prevention efforts focus on UV protection rather than altering antihypertensive treatments.

Key words: basal cell carcinoma; epidemiology; hypertension; pharmacology; skin cancer.

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SIGNIFICANCE

Basal cell carcinoma is the most common skin cancer with a substantial effect on quality of life and health economy. Meanwhile, hypertension, a very common disease, is known to increase risk of myocardial infarction and stroke. We investigated hydrochlorothiazide and other commonly prescribed antihypertensive medications and their association with basal cell carcinoma risk in Sweden. Several of the studied medications were associated with an increased risk of basal cell carcinoma, especially hydrochlorothiazide when given as combination treatment. However, the risk increase was slight, and focus should lie on communicating UV protection strategies instead of cessation of antihypertensive treatment.

Basal cell carcinoma (BCC) is the most common skin cancer in fair-skinned individuals (1). In Sweden, an increasing person-based incidence, reaching 387/100,000 person-years among women and 423/100,000 among men in 2017, has been reported (European age-standardized rate) (2).

Hypertension and cardiac disease are common illnesses worldwide. In Sweden, 22% of the population were prescribed an antihypertensive medication in 2023, and its use is increasing (3, 4). Commonly prescribed antihypertensive medications in Sweden include angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARB), thiazide diuretics, ß-blockers, and calcium channel blockers (CCB) (3).

In past years, several studies have implicated hydrochlorothiazide (HCTZ) as a potential risk factor for skin cancer, mainly related to cutaneous squamous cell carcinoma (cSCC) (5, 6). Meanwhile, studies on the relation between HCTZ and BCC have been more ambiguous (7–14), and whether other antihypertensive drugs increase BCC risk is still unclear (15–17). To enable valid recommendations regarding skin cancer prevention in individuals treated with antihypertensive medications, further knowledge of its association with skin cancer risk is essential.

In Sweden, we have a long-standing tradition of well-established registries. All histopathologically verified BCC and all prescribed drugs have been registered nationally since 2004 (18) and 2005, respectively. Using this information, we aimed to investigate, in the whole Swedish population, any association between the risk of BCC and the use of commonly prescribed antihypertensive treatments.

MATERIALS AND METHODS

We conducted a registry-based case-control study during the period 2007–2017. The Swedish unique personal identification number enabled us to link data from several national registries.

The study was approved by the Regional Ethics Committee, Lund University, and the Swedish Ethical Review Authority (#2017-378, #2017-993, #2021-01784, #2022-02239-02).

Selection of cases and controls

Since 2004, all histopathologically verified primary BCC tumours in Sweden have been registered through the National Board of Health and Welfare (NBHW) (18). In the present study, cases constituted all individuals with a first registered BCC tumour in the Swedish BCC Registry 1 January 2007–31 December 2017. To avoid confounding, cases and controls with potential immunosuppression secondary to solid organ transplantation; or with a diagnosis of psoriasis, HIV, xeroderma pigmentosum, or Gorlin syndrome at any time before first BCC diagnosis (index date); or with melanoma, cSCC, lymphoma, or leukaemia within 10 years before the index date were excluded. Cases and controls on immunosuppressive medication for at least 100 days before index date, including selective immunosuppressives, TNF alpha inhibitors, interleukin inhibitors, calcineurin inhibitors, and other immunosuppressives such as azathioprine and methotrexate, were also excluded from the study.

Two controls per case were extracted from the Swedish Total Population Registry (Statistics Sweden) and were assigned the index date of their respective case. Controls were matched by sex, age, and region of residence according to the 6 major healthcare regions in Sweden (Fig. S1). Controls were chosen with replacement. Cases were restricted from being chosen as controls.

Data collection

Exposure data were collected for cases and controls regarding use of antihypertensive medication and co-medications (National Prescribed Drug Registry, NBHW), comorbidities (National Patient Registry and National Cancer Registry, NBHW), and socioeconomic factors (Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA), Statistics Sweden). All extracted diagnoses and medications are listed in Appendix S1.

Definition of antihypertensive drug exposure in cases and controls

Exposure to the most common antihypertensive medications in Sweden was studied, including ACEi, ARB, CCB, and ß-blockers, given as either single agents or combination treatments (3). Single-agent treatment regarding 2 variants of ACEi (enalapril and ramipril) and 2 variants of CCB (amlodipine and felodipine) were investigated. Single-agent treatment with thiazides (HCTZ and bendroflumethiazide, BFTZ), and treatment with thiazide-containing combinations, including HCTZ + amiloride, were studied separately. Thiazide-containing combination treatments were included only under this category and were thus excluded from all other antihypertensive drug groups.

Exposure (ever use) was defined as 1 or more registrations (prescription and retrieval) of an antihypertensive medication before the first diagnosis of BCC. However, adhering to methodologies of previous studies, to minimize potential surveillance bias and allow for biological impact of the medication to take effect, prescriptions registered within a lag-time of 2 years before first diagnosis of BCC were not included in the analysis (7, 8, 19). Cases included during the period 1 January–30 June 2007 were assigned a lag-time of 1.5–2 years because no information regarding medication was available from the National Prescribed Drug Registry before 1 July 2005.

Data regarding cumulative dose were collected, using the variable pDDD (prescribed Defined Daily Dose) in the National Prescribed Drug Register, i.e., the number of prescribed Defined Daily Doses (DDD). DDD is defined by the World Health Organization as the assumed average daily dose in an adult for the main indication of the selected pharmaceutical (20). Our study defined high use as being prescribed $\geq$ 2000 pDDD, corresponding to approximately 5.5 years of treatment. The same definition has been used in previous studies (7, 10). To further study BCC risk in relation to cumulative dose, a separate analysis, using more finely tuned dose categories, was adapted and presented separately.

Confounders

Adhering to published literature, analyses were adjusted for the use of medications that independently might influence risk of skin cancer, such as loop-diuretics (i.e., high-ceiling diuretics), amiodarone, acetylsalicylic acid, statins, and metformin when registered within 10 years before first BCC diagnosis (7, 15, 16, 19, 21–23). Similarly, analyses were adjusted for presence of ischaemic heart disease, heart failure, diabetes, and chronic renal failure (7, 24–26). Furthermore, as socioeconomic factors have been shown to influence skin cancer incidence and outcome (27, 28), the results were adjusted for gross salary and highest level of education.

Statistics

Descriptive statistics were compiled for exposure variables and confounding variables. Odds ratios (OR) with 95% confidence intervals (CI) were estimated, using conditional logistic regression analyses for drug exposure, comparing "never users" with "ever users", in relation to occurrence of BCC. The association between cumulative dose and BCC risk was evaluated with conditional logistic regression analysis using the lowest cumulative dose as reference category. *P*-values < 0.05 were considered statistically significant. Sensitivity analyses regarding BCC risk for "never users" vs "ever users" were performed by stratifying risk assessments by sex, age and time period. All analyses were performed in R v. 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) (29).

RESULTS

In total, 133,539 individuals (47.3% male and 52.7% female) with a first diagnosis of primary BCC ("cases") and 257,849 controls (47.1% male and 52.9% female) without a BCC diagnosis were included in the study (**Table I**). During the period 1 January 2007–30 June 2007, 16,715 cases were diagnosed and assigned a lag-time of 1.5–2 years. From 1 July 2007–31 December 2017, 116,824 cases were diagnosed and assigned a lag-time of 2 years. Mean age was 67 years. Exclusions are presented in **Fig. 1**. Descriptive statistics regarding exposure to the selected drugs and confounding variables are summarized in **Tables I** and **II**, respectively. The proportion of people with diabetes, heart failure, and ischaemic heart disease was lower among cases than among controls. Regarding socioeconomic status, cases had a higher educational level and gross salary level than controls.

Thiazide diuretics

Concerning single-agent thiazide diuretic use, 9,226 BCC cases (6.9%) and 17,732 controls (6.9%) were exposed. There was no difference regarding the overall use of thiazide diuretics between BCC cases and controls

Table I. Ever users of antihypertensive medication among cases and controls, presented as numbers and percentages, and cumulative dose, categorized as low use (< 2,000 daily doses) and high use (≥ 2,000 daily doses)

Drug	Cumulative dose (pDDD)[‡]	BCC case (%)	Control (%)	Total (%)
Thiazide diuretics		9,226 (6.9)	17,732 (6.9)	26,958 (6.9)
(single-agent)	< 2,000	7,217 (78.2)	13,800 (77.8)	21,017 (78.0)
	≥ 2,000	2,009 (21.8)	3,932 (22.2)	5,941 (22.0)
HCTZ		2,768 (2.1)	5,382 (2.1)	8,150 (2.1)
	< 2,000	2,495 (90.1)	4,882 (90.7)	7,377 (90.5)
	≥ 2,000	273 (9.9)	500 (9.3)	773 (9.5)
BFTZ		6,706 (5.0)	12,788 (5.0)	19,494 (5.0)
	< 2,000	4,994 (74.5)	9,377 (73.3)	14,371 (73.7)
	≥ 2,000	1,712 (25.5)	3,411 (26.7)	5,123 (26.3)
Thiazide-containing		14,250 (10.7)	26,088 (10.1)	40,338 (10.3)
combinations	< 2,000	10,768 (75.6)	20,358 (78.0)	31,126 (77.2)
	≥ 2,000	3,482 (24.4)	5,730 (22.0)	9,212 (22.8)
HCTZ + amiloride		6,470 (4.8)	11,670 (4.5)	18,140 (4.6)
	< 2,000	5,137 (79)	9,473 (81)	14,610 (81)
	≥ 2,000	1,333 (21)	2,197 (19)	3,530 (19)
ACEi		21,369 (16.0)	44,020 (17.1)	65,389 (16.7)
	< 2,000	15,870 (74.3)	32,655 (74.2)	48,525 (74.2)
	≥ 2,000	5,499 (25.7)	11,365 (25.8)	16,864 (25.8)
Enalapril		16,764 (12.6)	34,345 (13.3)	51,109 (13.1)
	< 2,000	13,462 (80.3)	27,678 (80.6)	41,140 (80.5)
	≥ 2,000	3,302 (19.7)	6,667 (19.4)	9,969 (19.5)
Ramipril		4,141 (3.1)	8,849 (3.4)	12,990 (3.3)
	< 2,000	2,280 (55.1)	4,854 (54.9)	7,134 (54.9)
	≥ 2,000	1,861 (44.9)	3,995 (45.1)	5,856 (45.1)
ARB		13,460 (10.0)	24,845 (9.6)	38,305 (9.8)
	< 2,000	10,030 (74.5)	18,462 (74.3)	28,492 (74.4)
	≥ 2,000	3,430 (25.5)	6,383 (25.7)	9,813 (25.6)
CCB		21,782 (16.3)	40,832 (15.8)	62,614 (16.0)
	< 2,000	16,258 (74.6)	30,623 (75.0)	46,881 (74.9)
	≥ 2,000	5,524 (25.4)	10,209 (25.0)	15,733 (25.1)
Amlodipine		10,555 (7.9)	19,987 (7.8)	30,542 (7.8)
	< 2,000	8,229 (78.0)	15,670 (78.4)	23,899 (78.2)
	≥ 2,000	2,326 (22.0)	4,317 (21.6)	6,643 (21.8)
Felodipine		10,421 (7.8)	19,375 (7.5)	29,796 (7.6)
	< 2000	7,906 (75.9)	14,717 (76.0)	22,623 (75.9)
	≥ 2,000	2,515 (24.1)	4,658 (24.0)	7,173 (24.1)
ß-blockers		33,833 (25.3)	64,859 (25.2)	98,692 (25.2)
	< 2,000	30,670 (90.7)	58,659 (90.4)	89,329 (90.5)
	≥ 2,000	3,163 (9.3)	6,200 (9.6)	9,363 (9.5)
Total		133,539	257,849	391,388
Male		63,116,(47.3)	121,361 (47.1)	184,477 (47.1)
Female		70,423,(52.7)	136,488 (52.9)	206,911 (52.9)
Age, years (SD)[*]		67 (14)	67 (14)	67 (14)

[‡]Cumulative dose, depicted as number of prescribed defined daily doses (pDDD). Presented in numbers and percentages of treated individuals. [*]Mean age of cases and controls, presented together with standard deviation (SD).
pDDD: prescribed Defined Daily Doses; BCC: basal cell carcinoma; HCTZ: hydrochlorothiazide; BFTZ: bendroflumethiazide; ACEi: angiotensin converting enzyme-inhibitors; ARB: angiotensin II receptor blockers; CCB: calcium channel blockers; SD: standard deviation.

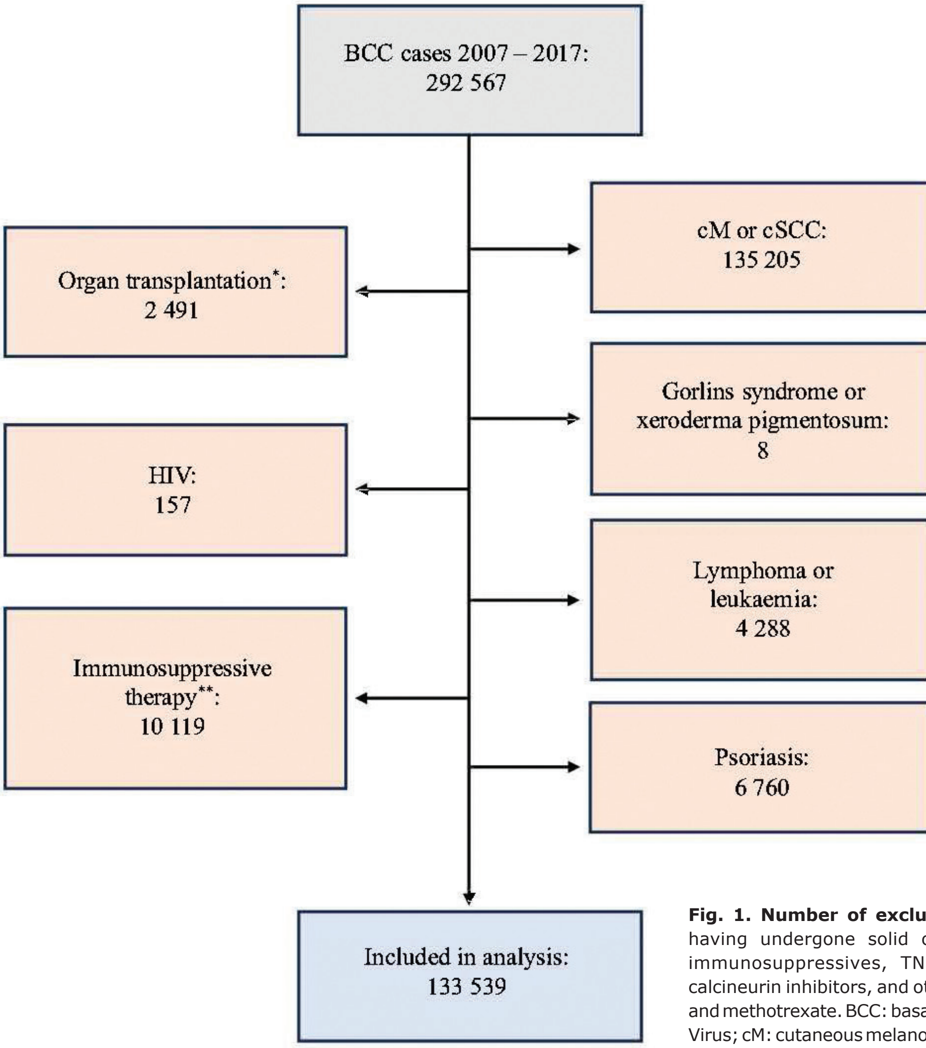

Fig. 1. Number of exclusions per category among cases. *Cases having undergone solid organ transplantation. **Including selective immunosuppressives, TNF-alfpha inhibitors, interleukin inhibitors, calcineurin inhibitors, and other immunosuppressives such as azathioprine and methotrexate. BCC: basal cell carcinoma; HIV: Human Immunodeficiency Virus; cM: cutaneous melanoma; cSCC: cutaneous squamous cell carcinoma.

Table II. Descriptive statistics for independent variables, presented as numbers and percentages

	BCC (%)	Control (%)	Total (%)
Drug			
Loop diuretics	17,793 (13.3)	37,866 (14.7)	55,659 (14.2)
Amiodarone	488 (0.4)	922 (0.4)	1,410 (0.4)
Acetylsalicylic acid	32,193 (24.1)	64,506 (25.0)	96,699 (24.7)
Statins	35,323 (26.5)	68,137 (26.4)	103,460 (26.4)
Metformin	7,598 (5.7)	19,400 (7.5)	26,998 (6.9)
Disease			
Ischaemic heart disease	13,320 (10.0)	28,321 (11.0)	41,641 (10.6)
Heart failure	5,782 (4.3)	13,509 (5.2)	19,291 (4.9)
Diabetes	8,684 (6.5)	21,682 (8.4)	30,366 (7.8)
Chronic kidney failure	1,470 (1.1)	3,395 (1.3)	4,865 (1.2)
Gross salary (per year, 100 SEK)			
< 2,000	92,714 (71.7)	185,702 (74.9)	278,416 (73.8)
2,000–2,999	11,482 (8.9)	23,202 (9.4)	34,684 (9.2)
3,000–3,999	11,670 (9.0)	21,321 (8.6)	32,991 (8.7)
4,000–4,999	5,771 (4.5)	8,821 (3.6)	14,592 (3.9)
5,000–5,999	3,054 (2.4)	4,004 (1.6)	7,058 (1.9)
6,000–6,999	1,614 (1.2)	1,920 (0.8)	3,534 (0.9)
≥ 7,000	2,974 (2.3)	2,897 (1.2)	5,871 (1.6)
Highest level of education			
Pre-high school	35,899 (27.8)	84,945 (34.3)	120,844 (32.0)
High school	51,080 (39.5)	100,649 (40.6)	151,729 (40.2)
Post-secondary	40,458 (31.3)	59,796 (24.1)	100,254 (26.6)
Postgraduate education	1,842 (1.4)	2,477 (1.0)	4,319 (1.1)

BCC: basal cell carcinoma, SEK: Swedish Krona.

(OR 1.02; CI 95% 1.00–1.05). Similarly, there was no significant association between BCC risk and the use of the 2 most prescribed variants of thiazides, HCTZ and BFTZ (**Fig. 2**).

Thiazide-containing *combination* treatments, analysed as a group, were prescribed to 14,250 BCC cases (10.7%) and 26,088 controls (10.1%). There was a significantly higher BCC risk associated with use of these medications, which was maintained in the adjusted model (OR 1.09, CI 95% 1.07–1.12) (see Fig. 2). The risk was significantly increased among individuals with a higher accumulated dose (≥2,000 compared with <2,000 pDDD) (OR 1.32, CI 95% 1.18–1.48) (**Table III**). The risk was further increased after >4,000 pDDD (OR 2.15, CI 95% 1.28–3.63) (Table SI). Additionally, we studied separately one of the most commonly prescribed thiazide-containing combinations, HCTZ + amiloride. This medication constituted about half of all prescriptions in the thiazide combination treatment group (see Table I) and increased BCC risk significantly in the adjusted model (OR 1.09, CI 95% 1.05–1.12) (see Fig. 2).

Table III. Association between antihypertensive medication and the development of basal cell carcinoma, comparing low use (< 2,000 daily doses) with high use (≥ 2,000 daily doses), calculated with conditional logistic regression with low use as reference

Drug	Cumulative dose (pDDD)§	OR (95% CI)‡	*p*-value	Adjusted OR (95% CI)†	*p*-value
Thiazide diuretics (single-agent)	< 2,000	–	–	–	–
	≥ 2,000	1.00 (0.87–1.16)	0.990	1.01 (0.87–1.17)	0.940
HCTZ	< 2,000	–	–	–	–
	≥ 2,000	0.78 (0.43–1.42)	0.421	0.76 (0.39–1.48)	0.415
BFTZ	< 2,000	–	–	–	–
	≥ 2,000	0.91 (0.76–1.10)	0.327	0.93 (0.77–1.12)	0.427
Thiazide-containing combinations	< 2,000	–	–	–	–
	≥ 2,000	1.31 (1.18–1.47)	< 0.001*	1.32 (1.18–1.48)	< 0.001*
HCTZ + amiloride	< 2,000	–	–	–	–
	≥ 2,000	1.13 (0.89–1.44)	0.302	1.13 (0.88–1.46)	0.326
ACEi	< 2,000	–	–	–	–
	≥ 2,000	0.98 (0.92–1.04)	0.549	1.01 (0.95–1.08)	0.713
Enalapril	< 2,000	–	–	–	–
	≥ 2,000	0.98 (0.90–1.07)	0.677	1.01 (0.92–1.10)	0.855
Ramipril	< 2,000	–	–	–	–
	≥ 2,000	0.86 (0.67–1.11)	0.258	0.85 (0.65–1.11)	0.243
ARB	< 2,000	–	–	–	–
	≥ 2,000	1.04 (0.94–1.15)	0.474	1.07 (0.96–1.19)	0.209
CCB	< 2,000	–	–	–	–
	≥ 2,000	1.04 (0.97–1.11)	0.238	1.07 (1.00–1.14)	0.068
Amlodipine	< 2,000	–	–	–	–
	≥ 2,000	1.15 (1.01–1.30)	0.032*	1.17 (1.03–1.33)	0.019*
Felodipine	< 2,000	–	–	–	–
	≥ 2,000	0.96 (0.84–1.10)	0.565	0.97 (0.84–1.12)	0.663
ß-blockers	< 2,000	–	–	–	–
	≥ 2,000	1.00 (0.93–1.06)	0.874	1.05 (0.98–1.12)	0.199

§Cumulative dose, depicted as number of prescribed Defined Daily Doses (pDDD). ‡Odds ratio (OR) for developing basal cell carcinoma in individuals treated with ≥ 2,000 pDDD in comparison with individuals treated with < 2,000 pDDD. Presented together with 95% confidence intervals (CI). †Odds ratio (OR) for developing basal cell carcinoma in individuals treated with ≥ 2,000 pDDD in comparison with individuals treated with < 2,000 pDDD, adjusted for co-medication (loop diuretics, amiodarone, acetylsalicylic acid, statins, metformin), comorbidity (ischaemic heart disease, heart failure, diabetes, chronic kidney failure), and socioeconomic status (gross salary, and highest educational level). **p*-value < 0.05 indicates a significant effect of the exposure variable on the odds of developing a basal cell carcinoma, given the matching strata.
pDDD: prescribed Defined Daily Dose, OR: odds ratio, CI: confidence interval, HCTZ: hydrochlorothiazide, BFTZ: bendroflumethiazide, ACEi: angiotensin-converting enzyme inhibitor, ARB: angiotensin II receptor blocker, CCB: calcium channel blocker, β-blockers: betablockers.

ACE inhibitors

Regarding ACEi, 21,369 BCC cases (16.0%) and 44,020 controls (17.1%) were prescribed the medication. Among ACEi users as a group, there was a slight but significantly decreased odds of BCC, which was maintained in the adjusted model (OR 0.98, CI 95% 0.96–1.00). Meanwhile, when studying the 2 variants of ACEi (enalapril and ramipril), neither showed a significant association in the adjusted model (see Fig. 2). Furthermore, no dose-dependent correlations were found (see Table III).

Angiotensin II receptor blockers

ARB as a group were used in 13,460 BCC cases (10.0%) and 28,845 controls (9.6%). Users of these medications had significantly increased odds of developing BCC, which was maintained in the adjusted model (OR 1.09, CI 95% 1.06-1.11) (see Fig. 2). No obvious linear dose-dependent risk trend could be detected (see Tables III and SI).

Calcium channel blockers

Use of CCB was registered in 21,782 (16.3%) cases and in 40,832 (15.8%) controls. Users of CCB had significantly increased odds of developing BCC (OR 1.09; CI 95% 1.07–1.11). A sub-analysis of the 2 most prescribed CCB (felodipine and amlodipine), showed significant associations with BCC regarding both variants (see Fig. 2). Furthermore, the odds of BCC increased further among users of ≥2,000 pDDD amlodipine (OR 1.17, CI 95% 1.03–1.33) (see Table III). Meanwhile, further classification of cumulative dose did not present a clear dose-dependent relationship (see Table SI).

Beta-blockers

ß-blocker use was registered in 33,833 (25.3%) BCC cases and 64,859 (25.2%) controls. In the adjusted model a significantly increased odds of BCC were found with ß-blocker use (OR 1.07; CI 95% 1.05–1.09) (see Fig. 2). We found no dose-dependent relationship (see Tables III and SI).

Sensitivity analyses showed results analogous with the numbers presented above.

DISCUSSION

Considering the steep continuous increase in incidence of skin cancer, it is essential to evaluate if commonly prescribed antihypertensive drugs, whether they have photosensitivity properties or not, could influence cancer risk. In this nationwide case-control study, we focused on BCC risk in relation to the use of antihypertensive medication. We found that treatment with several of the different medications were associated with risk of BCC, including CCB, ARB, ß-blockers, and thiazide-containing combinations. Meanwhile, no significant association with BCC risk was found after use of single-agent thiazide treatment. The associations with BCC found in our study were consistently quite small in risk, and a causal relationship was neither established nor denied. Therefore, these results should be interpreted with careful consideration to clinical relevance as mortality and morbidity due to hypertension and arterial disease are substantially higher than those due to BCC.

Published data on antihypertensive medications and skin cancer risk has foremost centred on thiazides, due to their photosensitizing properties. The International Agency for Research on Cancer (IARC) has classified HCTZ as possibly carcinogenic to humans (30). Furthermore, the Food and Drug Administration (FDA) in the United States has approved a label change regarding HCTZ, adding risk of non-melanoma skin cancer to the list of possible adverse reactions (31). These decisions have primarily been based on studies indicating an

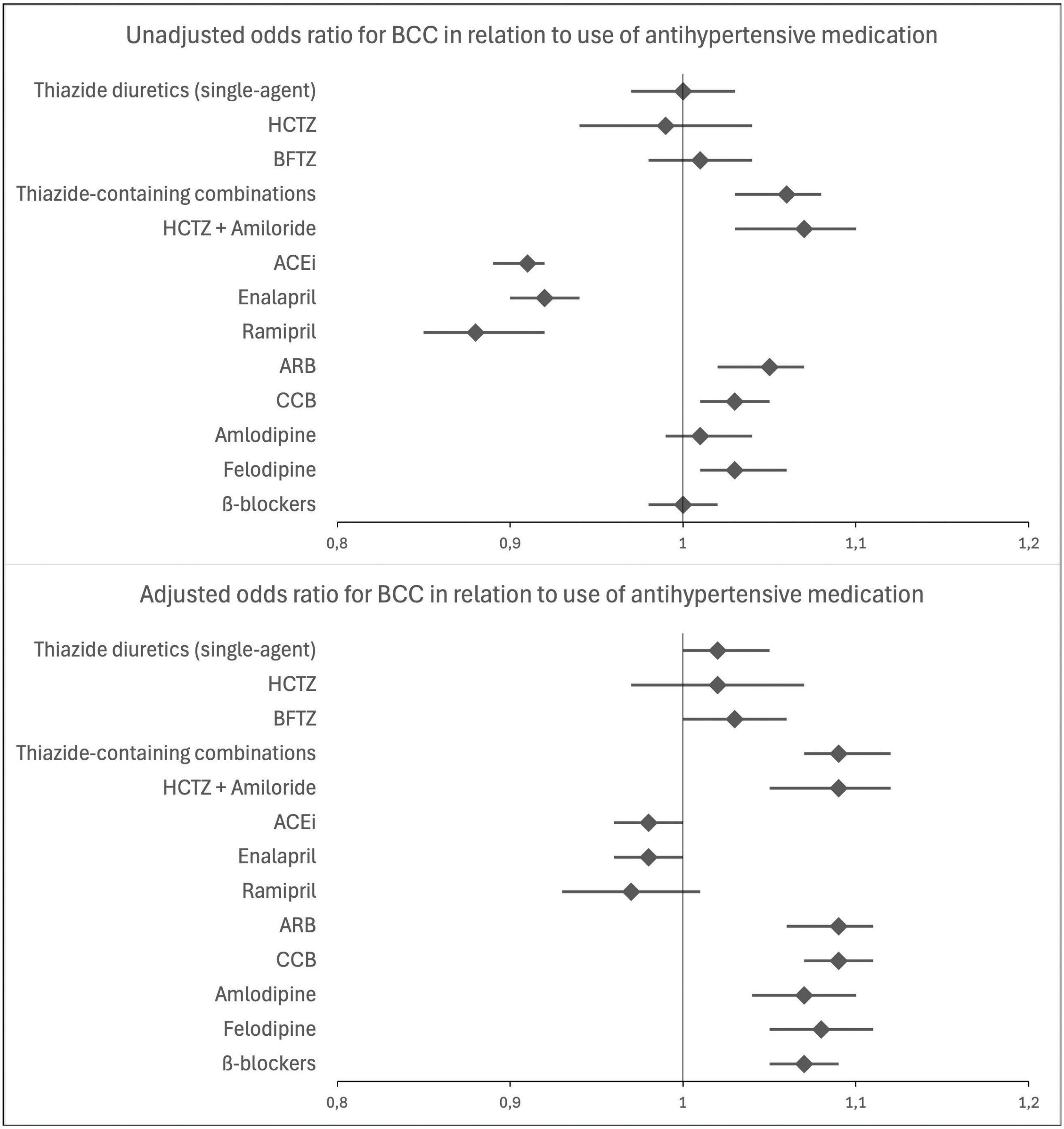

Fig. 2. Association between antihypertensive medication and the development of basal cell carcinoma, comparing ever-use with never-use, calculated using conditional logistic regression and depicted in a forest plot diagram. Numbers are presented unadjusted as well as adjusted for co-medication (loop diuretics, amiodarone, acetylsalicylic acid, statins, metformin), comorbidity (ischaemic heart disease, heart failure, diabetes, chronic kidney failure), and socioeconomic status (gross salary, and highest educational level).
BCC: basal cell carcinoma; HCTZ: hydrochlorothiazide; BFTZ: bendroflumethiazide; ACEi: angiotensin converting enzyme inhibitors; ARB: angiotensin II receptor blockers; CCB: calcium channel blockers; β-blockers: betablockers.

increased cSCC risk (5–10, 12, 32). However, the results regarding BCC have been more varied. In a registry-based study from Denmark by Pedersen et al., ever use of HCTZ was associated with a slight but significantly increased BCC risk (OR 1.08; CI 95% 1.05–1.10) (7). A similar risk estimate for HCTZ was also shown by Adalsteinsson et al. (OR 1.14; CI 95% 1.02–1.29), Morales et al. (OR 1.10; CI 95% 1.03 – 1.17), and Léon-Muñoz et al. (OR 1.06; CI 95% 1.03–1.10) (8–10), all registry-based case-control studies with only minor differences in methodology from our study. Meanwhile, studies by Kaae et al., Schneider et al., de Vries et al., and Jensen et al. could not find any significant relationship to BCC risk (11–14). These latter studies differed in methodology from ours, either by being based on surveys (13), by using differing lag-times (11–14), or by analysing only BFTZ (11, 13). Importantly, thiazides are often used in combination treatments. Published studies seldom separate risk estimates based on single-agent treatments and combination treatments (7–9, 19, 32). As an exception, Jensen et al. found an increased risk of cSCC with use of HCTZ in combination with amiloride, but not with HCTZ single-agent treatment (14). In another study of HCTZ and skin cancer risk, the exclusion of amiloride from the analysis did not affect the significantly increased risk estimate for BCC; however, the risk of cSCC decreased (10). In our study, single-agent use of thiazides as a group, as well as categorized by HCTZ and BFTZ, did not affect BCC risk. Meanwhile, use of thiazide-containing combinations was associated with a significantly increased BCC risk. This risk was further increased with exposure to a high cumulative dose. When further investigating the use of HCTZ in combination with amiloride, the same association was found. This indicates that adjunctive substances, such as amiloride, might be an important contributor to skin cancer risk when studying thiazide treatments. Further studies on amiloride-containing medications and skin cancer risk are warranted.

According to published literature, ACEi and ARB have a lower risk of photosensitivity reactions compared with thiazide diuretics, as do CCB and ß-blockers (33–35). Interestingly, cohort studies in selected high-risk populations have found a 40–50% decreased incidence rate ratio (IRR) for BCC in individuals treated with ACEi or ARB compared with subjects without these medications (16, 17). Meanwhile, in a population-based study in northern Denmark, no significant difference in BCC risk was shown with ACEi use, while ARB treatment was associated with a slightly increased BCC risk (OR 1.09) (15). In basic research studies, angiotensin-converting enzyme has been shown to activate cytokines pivotal to BCC carcinogenesis (36,37). Hence, it would be reasonable to suggest that earlier findings of a preventive role of ACEi in BCC development are possible. Indeed, our study showed a minimal, but statistically significant, decrease in BCC risk (OR 0.98). Meanwhile, in the unadjusted model, the risk reduction reached 9%, suggesting a common denominator that both decreases risk of BCC and increases the chance of ACEi use. Indeed, we found that both diabetes and chronic heart failure were less common in individuals with BCC. The mechanism linking these variables is worth examining more closely in future studies. Nonetheless, the slight preventive effect of ACEi in our material is likely to be of minor clinical relevance. Meanwhile, ARB was associated with a 9% increased BCC risk in our material, similar to the risk estimates published by Schmidt et al. (15). Thus, in our study, ACEi and ARB seem to have contrasting associations with BCC risk.

Calcium channel blockers are less studied than thiazides and ACEi in relation to BCC. In a meta-analysis from 2018 by Tang et al., a significantly increased BCC risk (OR 1.15; CI 95% 1.09–1.21) with use of CCB was shown (5). In our study, we estimated a similar risk increase with use of CCB. Furthermore, this risk increase was also found when studying the 2 most commonly prescribed variants of CCB. Overall, when considered in conjunction with the findings from earlier studies, CCB may be a potential risk factor for the development of BCC. That said, the risk increase was only modest and further studies on cSCC and melanoma would further aid in the risk assessment of this medication.

The use of ß-blockers has in earlier studies been associated with a possibly increased BCC risk (15–17). In the mentioned meta-analysis by Tang et al., an increased risk of BCC was shown (OR 1.09; CI 95% 1.04–1.15), in association with ß-blocker use (5). In our study, we found an increased BCC risk of similar size, albeit without an obvious dose-dependent relationship. This finding contradicts published preclinical data that suggest a protective effect of ß-blockers against skin cancer progression (38).

Strengths

Our case-control study was based on nationwide and population-based robust register data, making it possible to study individuals diagnosed with BCC in Sweden. Thanks to the unique personal identification number in Sweden, both cases and controls could be completely followed up and prescribed medications could be safely linked. Hence, selection bias was avoided. Information regarding prescribed and retrieved medications was available, indicating that the patients had used the medications. To minimize risk of confounding, analyses were adjusted by comorbidities, co-medications, and socioeconomic factors, based on information gathered from validated, nationwide high-standard registries.

Limitations

An essential limitation of this registry-based study was the lack of information regarding known pro-carcinogenic lifestyle factors, such as UV exposure. Moreover, no data were available on other possible risk-modifying factors, such as healthcare-seeking behaviour and phenotypic factors, that could be associated with a diagnosis of BCC. Furthermore, it was not possible to confirm that the included individuals consumed the prescribed and retrieved drugs. An inherent limitation of all observational studies is the risk of bias and confounding, such as surveillance bias, survivor bias, or a common denominator as discussed earlier. The presence of such confounding or biases in this study can neither be confirmed nor denied and might explain the similar associations between the use of several of the antihypertensive medications and the risk of BCC. Due to lack of data in the National Prescribed Drug Registry 1 January–30 June 2005, lag-time was restricted to 1.5–2 years for cases included from 1 January–30 June 2007, while the remaining cases had a lag-time of 2 years. This difference in lag-time is expected to have only a minor effect on the statistical outcome of our study.

Conclusion

In this nationwide study we found associations between BCC risk and the use of ARB, CCB, ß-blockers, and thiazide-containing drug combinations. Nevertheless, no significant effect of single-agent thiazide use was found, highlighting the need for further studies on adjunctive pharmaceuticals. These results cannot confirm a causal relationship; therefore, they should be interpreted with caution and with a focus on clinical relevance. For the prevention of BCC and considering the risk of stroke and ischaemic heart disease if patients cease their antihypertensive medication, our study suggests that a general discussion regarding UV protection is supported, rather than changing antihypertensive medications.

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REFERENCES

1. Verkouteren JA, Ramdas KH, Wakkee M, Nijsten T. Epidemiology of basal cell carcinoma: scholarly review. Br J Dermatol 2017; 177: 359–372. https://doi.org/10.1111/bjd.15321
2. Kappelin J, Green AC, Ingvar A, Ahnlide I, Nielsen K. Incidence and trends of basal cell carcinoma in Sweden: a population-based registry study. Br J Dermatol 2022; 186: 963–969. https://doi.org/10.1111/bjd.20964
3. Statistik om läkemedel 2021. 2022. [Accessed: 2023 October 25]. Available from: https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/statistik/2022-4-7842.pdf.
4. Statistik om läkemedel 2023. 2024. [Accessed: 2024 April 18]. Available from: https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/statistik/2024-4-9026.pdf.
5. Tang H, Fu S, Zhai S, Song Y, Asgari MM, Han J. Use of antihypertensive drugs and risk of keratinocyte carcinoma: a meta-analysis of observational studies. Pharmacoepidemiol Drug Saf 2018; 27: 279–288. https://doi.org/10.1002/pds.4384
6. Shin D, Lee ES, Kim J, Guerra L, Naik D, Prida X. Association between the use of thiazide diuretics and the risk of skin cancers: a meta-analysis of observational studies. J Clin Med Res 2019; 11: 247–255. https://doi.org/10.14740/jocmr3744
7. Pedersen SA, Gaist D, Schmidt SAJ, Holmich LR, Friis S, Pottegard A. Hydrochlorothiazide use and risk of nonmelanoma skin cancer: a nationwide case-control study from Denmark. J Am Acad Dermatol 2018; 78: 673–681 e679. https://doi.org/10.1016/j.jaad.2017.11.042
8. Adalsteinsson JA, Muzumdar S, Waldman R, Hu C, Wu R, Ratner D, et al. Association between hydrochlorothiazide and the risk of in situ and invasive squamous cell skin carcinoma and basal cell carcinoma: a population-based case-control study. J Am Acad Dermatol 2021; 84: 669–675. https://doi.org/10.1016/j.jaad.2020.08.025
9. Morales DR, Pacurariu A, Slattery J, Kurz X. Association between hydrochlorothiazide exposure and different incident skin, lip and oral cavity cancers: a series of population-based nested case-control studies. Br J Clin Pharmacol 2020; 86: 1336–1345. https://doi.org/10.1111/bcp.14245
10. León-Muñoz LM, Duarte-Salles T, Llorente A, Díaz Y, Puente D, Pottegård A, et al. Use of hydrochlorothiazide and risk of skin cancer in a large nested case-control study in Spain. Pharmacoepidemiol Drug Saf 2021; 30: 1269–1278. https://doi.org/10.1002/pds.5295
11. Kaae J, Boyd HA, Hansen AV, Wulf HC, Wohlfahrt J, Melbye M. Photosensitizing medication use and risk of skin cancer. Cancer Epidemiol Biomarkers Prev 2010; 19: 2942–2949. https://doi.org/10.1158/1055-9965.EPI-10-0652
12. Schneider R, Reinau D, Stoffel S, Jick SS, Meier CR, Spoendlin J. Risk of skin cancer in new users of thiazides and thiazide-like diuretics: a cohort study using an active comparator group. Br J Dermatol 2021; 185: 343–352. https://doi.org/10.1111/bjd.19880
13. de Vries E, Trakatelli M, Kalabalikis D, Ferrandiz L, Ruiz-de-Casas A, Moreno-Ramirez D, et al. Known and potential new risk factors for skin cancer in European populations: a multicentre case-control study. Br J Dermatol 2012; 167: 1–13. https://doi.org/10.1111/j.1365-2133.2012.11081.x
14. Jensen AO, Thomsen HF, Engebjerg MC, Olesen AB, Sorensen HT, Karagas MR. Use of photosensitising diuretics and risk of skin cancer: a population-based case-control study. Br J Cancer 2008; 99: 1522–1528. https://doi.org/10.1038/sj.bjc.6604686
15. Schmidt SA, Schmidt M, Mehnert F, Lemeshow S, Sorensen HT. Use of antihypertensive drugs and risk of skin cancer. J Eur Acad Dermaol Venereol 2015; 29: 1545–1554. https://doi.org/10.1111/jdv.12921
16. Christian JB, Lapane KL, Hume AL, Eaton CB, Weinstock MA, Trial V. Association of ACE inhibitors and angiotensin receptor blockers with keratinocyte cancer prevention in the randomized VATTC trial. J Natl Cancer Inst 2008; 100: 1223–1232. https://doi.org/10.1093/jnci/djn262
17. Moscarelli L, Zanazzi M, Mancini G, Rossi E, Caroti L, Rosso G, et al. Keratinocyte cancer prevention with ACE inhibitors, angiotensin receptor blockers or their combination in renal transplant recipients. Clin Nephrol 2010; 73: 439–445. https://doi.org/10.5414/CNP73439
18. Basal Cell Carcinoma in Sweden 2004–2008. 2009. [Accessed: 2023 May 23]. Available from: https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/statistik/2009-12-12.pdf.
19. Pottegård A, Hallas J, Olesen M, Svendsen MT, Habel LA, Friedman GD, et al. Hydrochlorothiazide use is strongly associated with risk of lip cancer. J Intern Med 2017; 282: 322–331. https://doi.org/10.1111/joim.12629
20. Defined Daily Dose (DDD). [Accessed: 2024 April 19]. Available from: https://www.who.int/toolkits/atc-ddd-toolkit/about-ddd.
21. Ruiter R, Visser LE, Eijgelsheim M, Rodenburg EM, Hofman A, Coebergh JW, et al. High-ceiling diuretics are associated

with an increased risk of basal cell carcinoma in a population-based follow-up study. Eur J Cancer 2010; 46: 2467–2472. https://doi.org/10.1016/j.ejca.2010.04.024
22. Siiskonen SJ, Koomen ER, Visser LE, Herings RM, Guchelaar HJ, Stricker BH, et al. Exposure to phototoxic NSAIDs and quinolones is associated with an increased risk of melanoma. Eur J Clin Pharmacol 2013; 69: 1437–1444. https://doi.org/10.1007/s00228-013-1476-x
23. Hou A, Li Y, Shadyab AH, Han J, Eaton CB, Qureshi A, et al. Photosensitizing antihypertensive medication and risk of skin cancer among postmenopausal women. J Dtsch Dermatol Ges 2024; 22: 186–194. https://doi.org/10.1111/ddg.15281
24. Brøndum-Jacobsen P, Nordestgaard BG, Nielsen SF, Benn M. Skin cancer as a marker of sun exposure associates with myocardial infarction, hip fracture and death from any cause. Int J Epidemiol 2013; 42: 1486–1496. https://doi.org/10.1093/ije/dyt168
25. Birkeland SA, Løkkegaard H, Storm HH. Cancer risk in patients on dialysis and after renal transplantation. Lancet 2000; 355: 1886–1887. https://doi.org/10.1016/S0140-6736(00)02298-4
26. Tseng HW, Shiue YL, Tsai KW, Huang WC, Tang PL, Lam HC. Risk of skin cancer in patients with diabetes mellitus: a nationwide retrospective cohort study in Taiwan. Medicine (Baltimore) 2016; 95: e4070. https://doi.org/10.1097/MD.0000000000004070
27. Corazza M, Ferretti S, Scuderi V, Borghi A. Socioeconomic status and skin cancer incidence: a population-based, cohort study in the province of Ferrara, northern Italy. Clin Exp Dermatol 2021; 46: 1285–1289. https://doi.org/10.1111/ced.14599
28. Kiiski V, de Vries E, Flohil SC, Bijl MJ, Hofman A, Stricker BH, et al. Risk factors for single and multiple basal cell carcinomas. Arch Dermatol 2010; 146: 848–855. https://doi.org/10.1001/archdermatol.2010.155
29. R Core Development Team. R: A language and environment for statistical computing. Vienna: R Foundation for Statistical Computing, 2021.
30. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Some drugs and herbal products. 2015; 108. IARC Monogr Eval Carcinog Risks Hum 2016: 108: 7–419.
31. FDA approves label changes to hydrochlorothiazide to describe small risk of non-melanoma skin cancer . 2020. [Accessed: 2023 November 21]. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-approves-label-changes-hydrochlorothiazide-describe-small-risk-non-melanoma-skin-cancer.
32. Rouette J, Yin H, Pottegård A, Nirantharakumar K, Azoulay L. Use of hydrochlorothiazide and risk of melanoma and nonmelanoma skin cancer. Drug Saf 2021; 44: 245–254. https://doi.org/10.1007/s40264-020-01015-1
33. Steckelings UM, Artuc M, Wollschläger T, Wiehstutz S, Henz BM. Angiotensin-converting enzyme inhibitors as inducers of adverse cutaneous reactions. Acta Derm Venereol 2001; 81: 321–325. https://doi.org/10.1080/000155501317140007
34. Alrashidi A, Rhodes LE, Sharif JCH, Kreeshan FC, Farrar MD, Ahad T. Systemic drug photosensitivity: culprits, impact and investigation in 122 patients. Photodermatol Photoimmunol Photomed 2020; 36: 441–451. https://doi.org/10.1111/phpp.12583
35. Götzinger F, Reichrath J, Millenaar D, Lauder L, Meyer MR, Böhm M, et al. Photoinduced skin reactions of cardiovascular drugs: a systematic review. Eur Heart J Cardiovasc Pharmacother 2022; 8: 420–430. https://doi.org/10.1093/ehjcvp/pvac017
36. Koronellos N, Yapijakis C, Katoulis A, Avgoustidis D, Vylliotis A, Papakosta V, et al. Association study indicates combined effect of interleukin-10 and angiotensin-converting enzyme in basal cell carcinoma development. Arch Dermatol Res 2021; 313: 373–380. https://doi.org/10.1007/s00403-020-02113-x
37. Yapijakis C, Koronellos N, Spyridonidou S, Vylliotis A, Avgoustidis D, Goutas N, et al. Association of angiotensin-converting enzyme gene insertion/deletion polymorphism with decreased risk for basal cell carcinoma. Arch Dermatol Res 2013; 305: 333–339. https://doi.org/10.1007/s00403-012-1312-7
38. Batalla-Covello J, Ali S, Xie T, Amit M. β-Adrenergic signaling in skin cancer. FASEB Bioadv 2022; 4: 225–234. https://doi.org/10.1096/fba.2021-00097