Appendix S1

SUPPLEMENTARY MATERIALS AND METHODS

Definition of index and reference groups

HCTZ users represent the index group and were defined as using a minimum of 292 days of HCTZ monotherapy or HCTZ combination preparations. This agrees with an average of 80% use in one year (1). The first reference group "starters of other non-HCTZ antihypertensives" was defined as starting with a minimum of 2 prescriptions of non-thiazide containing antihypertensive drugs (ACE-inhibitors, angiotensin II receptor blockers, calcium channel blockers, beta blockers, combined alpha and beta blockers, other agents RAAS system, antihypertensives). Diuretics with photosensitizing properties, such as potassium-sparing diuretics, have also been excluded from this reference group as several studies have shown these are associated with an increased risk of skin cancer (2–5). The second reference group "starters of non-antihypertensive long-term medication" was defined as starting with a minimum of 2 prescriptions within the first year of a non-antihypertensive chronic drug for a chronic disease that requires regular prescriptions (acid related disorders, diabetes, functional gastrointestinal disorders, bile and liver disorders, cardiovascular disease, anemia, thyroid disorders, pancreatic disorders, bone disease, psychiatric disease, obstructive airway disease and renal disease). Photosensitizing drugs have been excluded from this reference group (5). The ATC codes used in the formation of the three study groups are listed in Table S1. Follow-up initiated on the index date and ended on the moment of skin cancer diagnosis, date of death if applicable or end of follow-up, which was 31 December 2020.

Outcomes and possible confounders

The primary outcomes of interest were development of any skin cancer, BCC, SCC (combined as KC), malignant melanoma and melanoma in situ (combined as melanoma), Merkel cell carcinoma and malignant adnexal skin tumors. Skin cancer outcomes were only confirmed after pathological diagnosis, which were retrieved from PALGA.

To investigate a potential dose-response relationship, patients in the index group (HCTZ users) were divided into two subcategories: lower cumulative use, <5000 DDD and high cumulative use, ≥5000 DDD, in which 1 DDD is equal to 25 mg HCTZ, based on the total amount of DDD of HCTZ prescribed during the study period (data available from index date until 31 December 2019). High cumulative use in our study was equal to ≥125 000 mg, within the range of other studies defining high cumulative use as 100 000 mg(6) and 200 000 mg (7).

We included information from the Lifelines cohort questionnaire data and IADB.nl about the following potential risk factors or confounders: age at index date, gender (8), smoking status (9), immunosuppressant drug use (10,11), use of oral glucocorticoids (3,12), use of (other) diuretics (2–5), statins (13), comorbidities such as diabetes, which were self-reported and captured at baseline (14), education level, subdivided into the categories “low”, “middle” and “high”, which were calculated based on provided answers regarding the highest obtained degree questions in Lifelines questionnaires (15,16), UV-exposure, defined as the number of days spent outdoors (odd jobs, garden, exercise, walking in leisure time, cycling) for at least 30 minutes a day over a period of 2 weeks (17), ever outdoor profession, defined as ever having an outdoor profession that is possibly associated with an increased risk of skin cancer and was captured at any time (Table S2) (18), and coffee consumption, defined as the average cups of coffee per week (19). Drug prescription records were obtained from the IADB.nl database and were only considered if at least two prescriptions were given during the study period. ATC codes used to determine the use of specific drug types can be found in Table S3.

Statistical analysis

To evaluate whether the proportional hazard assumption was met, survival curves were evaluated in a visual way.

Table SI – ATC codes used for determination of study groups

		ATC codes
Hydrochlorothiazide use (exposure group)	Hydrochlorothiazide (single)	C03AA03
	Hydrochlorothiazide and potassium	C03AB03
	Hydrochlorothiazide, combinations	C03AX01
	Hydrochlorothiazide and potassium-sparing agents	C03EA01
Antihypertensive drug use (reference group 1)	Anti-hypertensives	C02A, C02C, C02DB, C02DC, C02DD, C02DG, C02K
	Beta blockers	C07A, C07E, C07F
	Calcium channel blockers	C08C, C08D, C08E
	ACE-inhibitors	C09AA, C09BB, C09BX01, C09BX02, C09BX04, C09BX05, QC09BX90
	Angiotensin II receptor blockers	C09CA, C09DB, C09DX02, C09DX04, C09DX05
	Other agents RAAS-system	C09XA01, 09XA02, C09XA53
Non-antihypertensive long-term medication use (reference group 2)	Acid related disorders	A02A, A02BA, A02BB, A02BC, A02BX
	Functional gastrointestinal disorders	A03
	Bile and liver therapy	A05, V03AC, M01CC01, N03AA02, A16AX12
	Diabetes therapy	A10A
	Antithrombotic agents	B01
	Antihemorrhagics	B02
	Antianemic preparations	B03, B06AX, A16AA03
	Cardiac therapy	C01A, C01C, C01D

	Peripheral vasodilators	C04
	Thyroid therapy	H03
	Pancreatic hormones	H04
	Bone disease	M05
	Analgesics	N02
	Psycholeptics & analeptics	N05B, N05C, N06B, N06D
	Obstructive airway disease	R03AA, R03AB, R03AC, R03BB, R03C
	Renal disease	H01BA, A12BA02, G04CA, C03XA
ACE, Angiotensin-converting-enzyme; RAAS, Renin-Angiotensin-Aldosterone System		

Table SII – Outdoor occupations with possible increased risk of skin cancer

		ISCO-08 code
Outdoor occupations with possible increased risk of skin cancer	Aircraft pilots and related associate professionals	3153
	Flight attendants	5111
	Firefighters	5411
	Police officers	5412
	Protective services workers not elsewhere specified	5419
	Skilled agricultural, forestry and fishery workers	6000
	Market gardeners and crop growers	6111, 6112, 6113, 6114
	Animal producers	6120
	Mixed animal and crop producers	6130
	Forestry and related workers	6210
	Inland and coastal waters fishery workers	6222
	Deep-sea fishery workers	6223

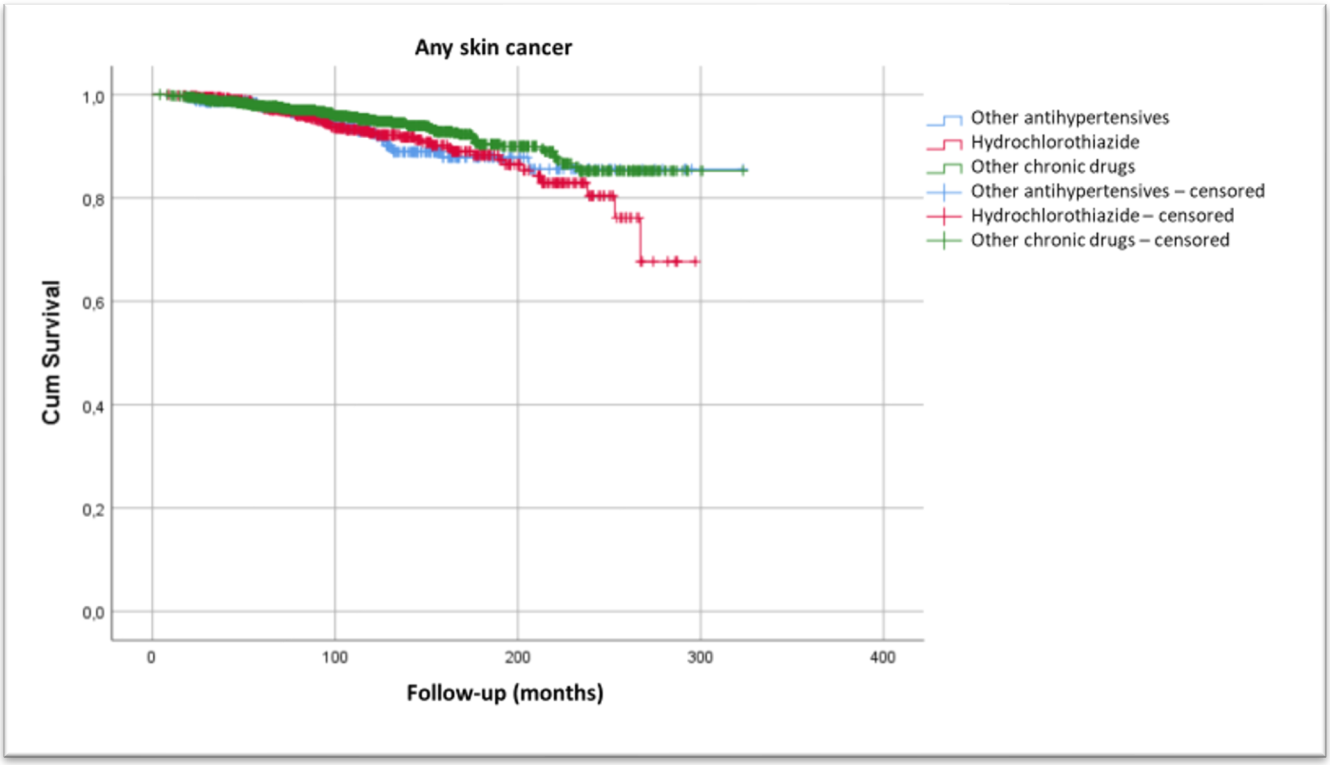
	Hunters and trappers	6224
	Subsistence crop farmers	6310
	Subsistence livestock farmers	6320
	Mixed subsistence crop and livestock farmers	6330
	Subsistence fishers, hunters, trappers and gatherers	6340
	Craft and related trades workers	
	Building and related trades workers	7111, 7112, 7121
	Welders and flame cutters	7212
	Fumigators and other pest and weed controllers	7544
	Ships' deck crews and related workers	8350
	Elementary occupations	
	Agricultural, forestry and fishery labourers	9211-9216
	Building construction labourers	9313
	Refuse workers and other elementary workers	9611, 9613
	Armed forces occupations	0110, 0210, 0310

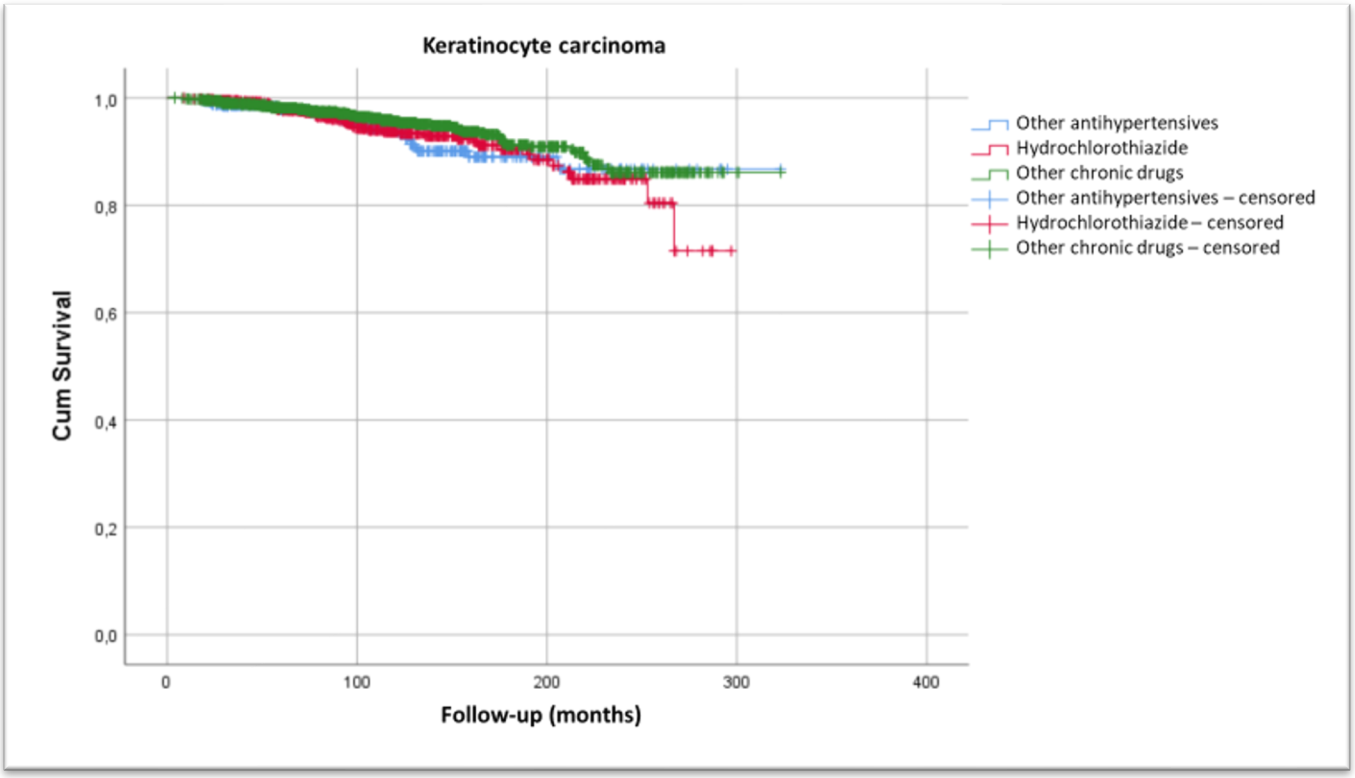
Table SIII – ATC codes used to determine usage of medication considered to have an effect on the risk of developing skin cancer

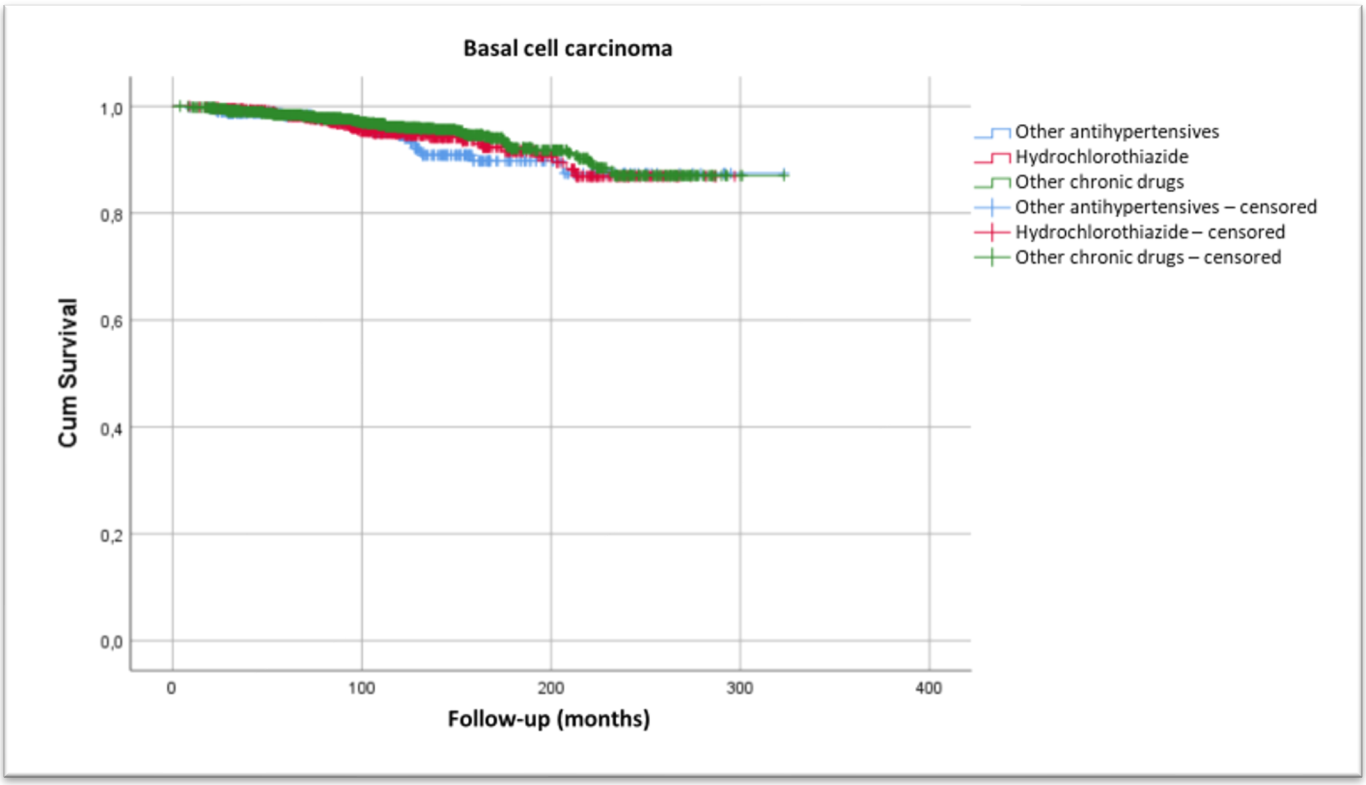
		ATC codes
Immunosuppressive drugs	Immunosuppressants (incl. azathioprine, cyclosporine)	L04A
	Tacrolimus	D11AH01
Oral glucocorticoids		H02AB
Other diuretics	Low-ceiling diuretics, excl. thiazide	C03B
	High-ceiling diuretics	C03C
	Potassium-sparing agents	C03D
	High-ceiling diuretics and potassium-sparing agents	C03EB
	Other diuretics	C03X
	Perindopril, amlodipine and indapamide	C09BX01
	Rosuvastatin, perindopril and indapamide	C10BX13
Other drugs	Statins	C10AA

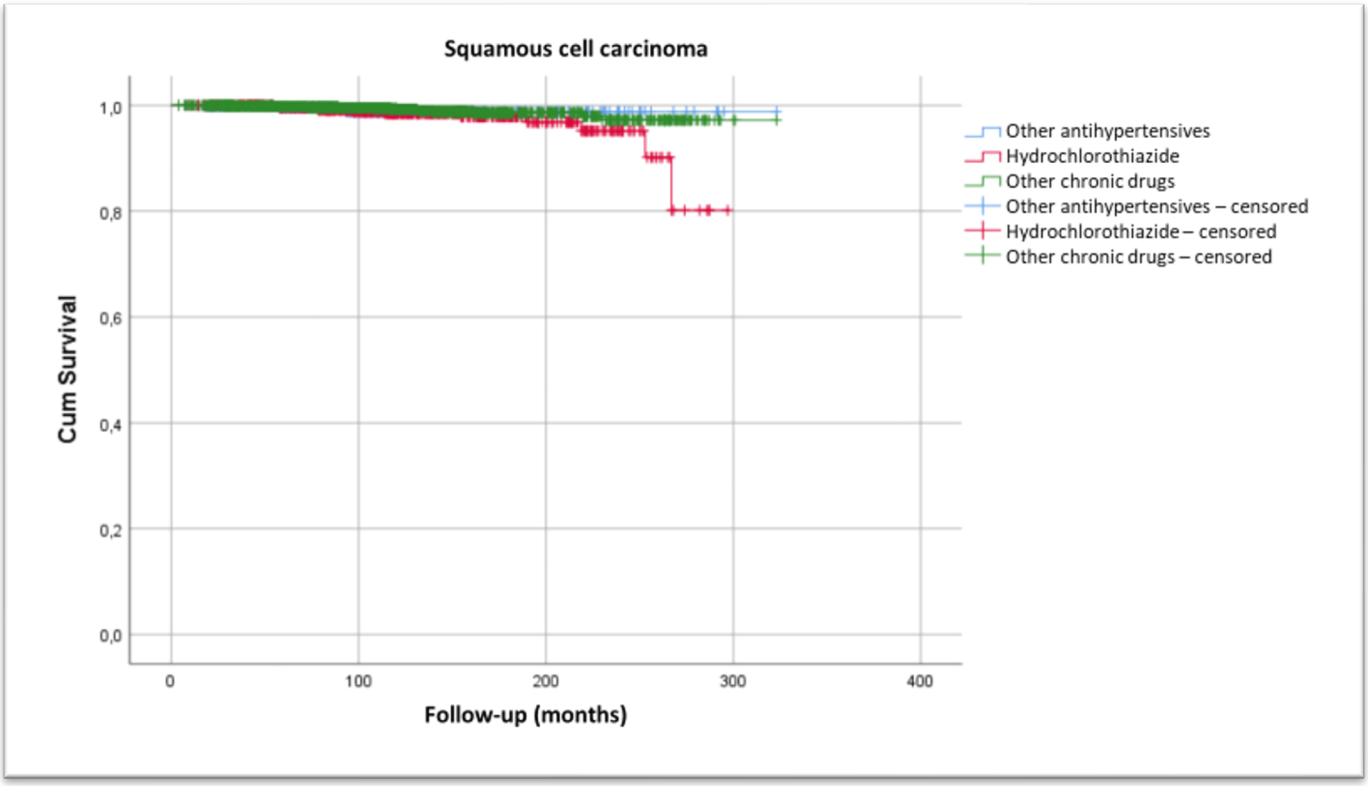
SUPPELEMENTARY RESULTS

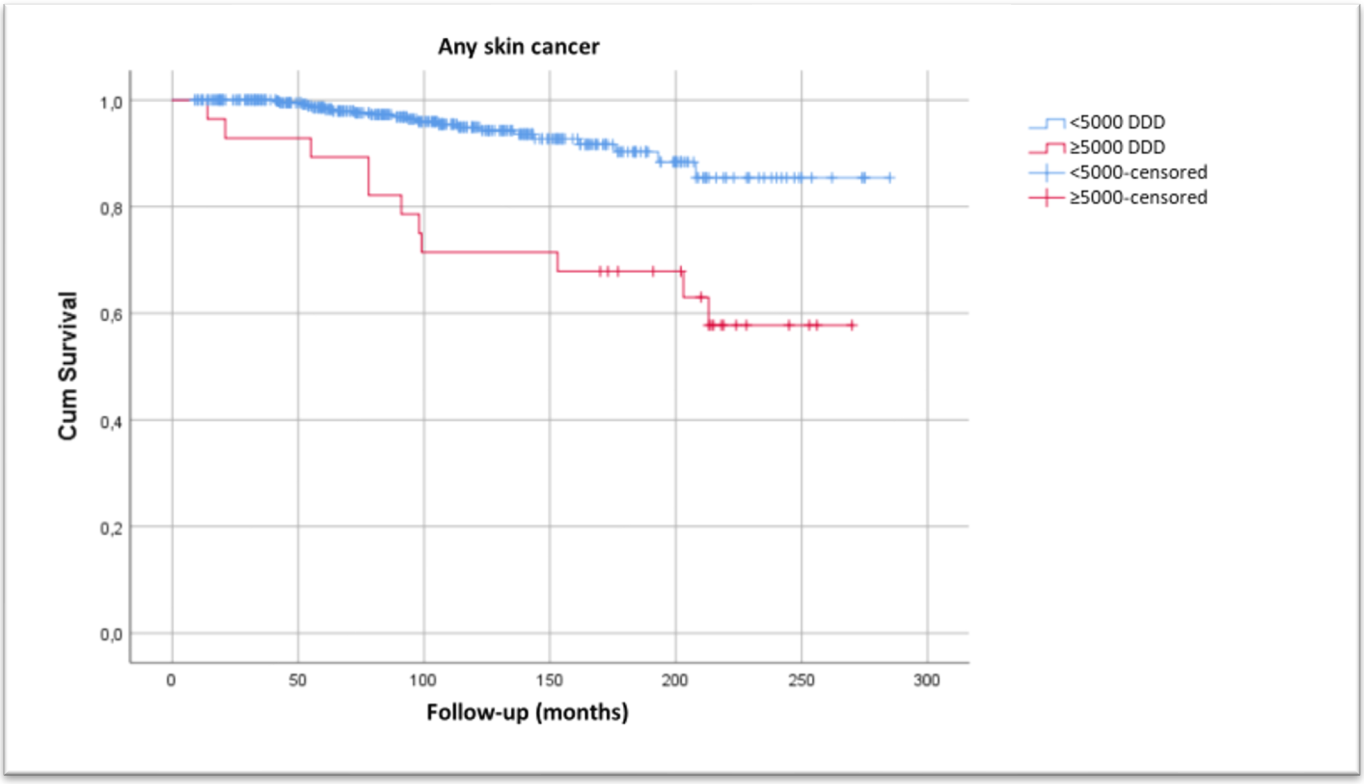
Figure S1 – Kaplan-Meier curves



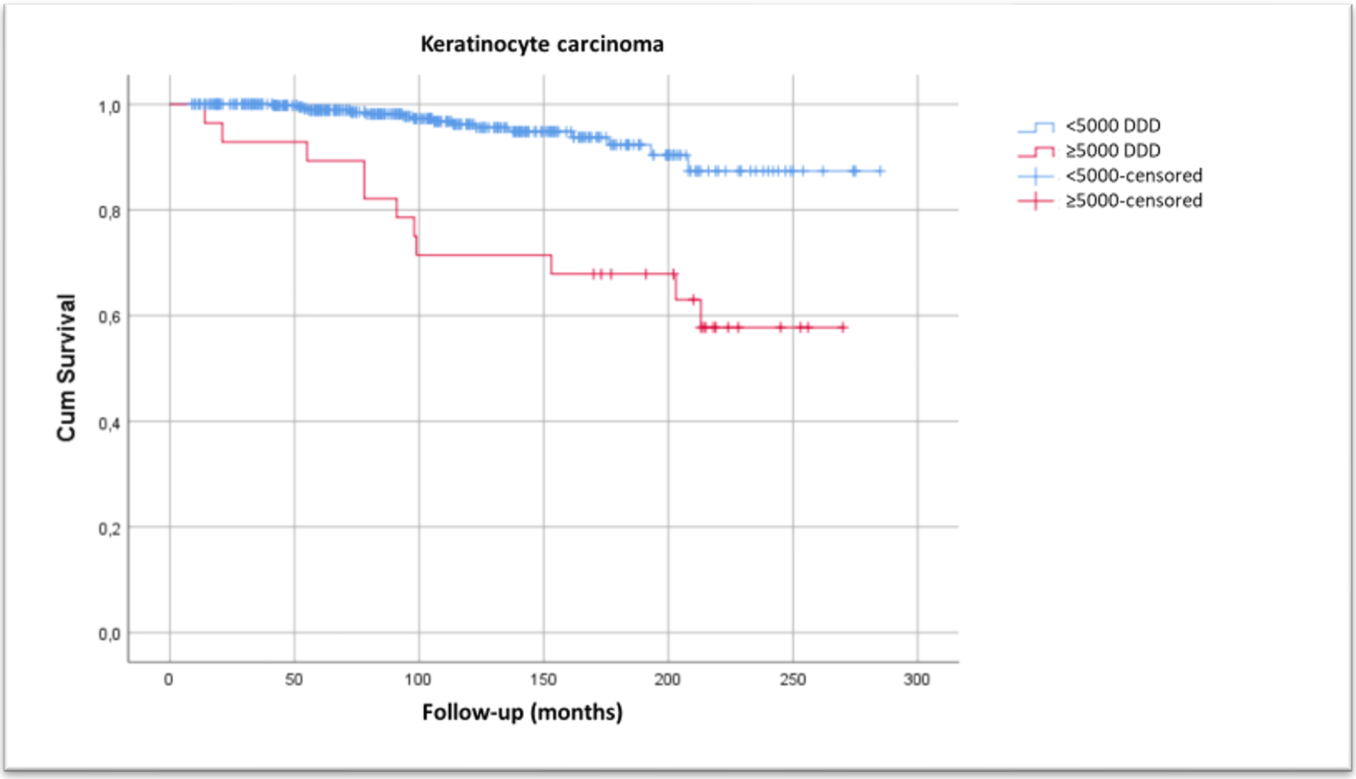

Keratinocyte carcinoma
Cum Survival
1,0
0,8
0,6
0,4
0,2
0,0
0
100
200
300
400
Follow-up (months)
Other antihypertensives
Hydrochlorothiazide
Other chronic drugs
Other antihypertensives – censored
Hydrochlorothiazide – censored
Other chronic drugs – censored


Basal cell carcinoma
Cum Survival
1,0
0,8
0,6
0,4
0,2
0,0
0
100
200
300
400
Follow-up (months)
Other antihypertensives
Hydrochlorothiazide
Other chronic drugs
Other antihypertensives – censored
Hydrochlorothiazide – censored
Other chronic drugs – censored

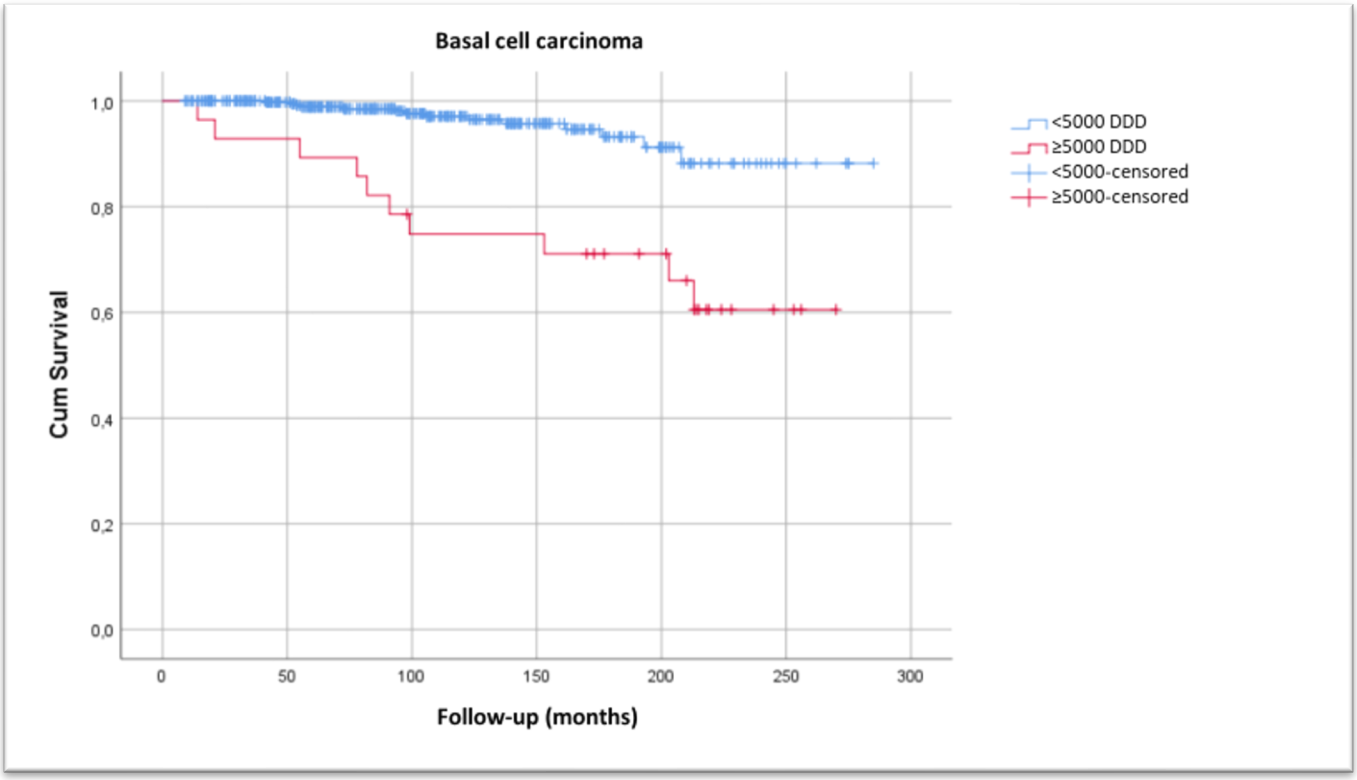

Squamous cell carcinoma
Cum Survival
1,0
0,8
0,6
0,4
0,2
0,0
0
100
200
300
400
Follow-up (months)
Other antihypertensives
Hydrochlorothiazide
Other chronic drugs
Other antihypertensives – censored
Hydrochlorothiazide – censored
Other chronic drugs – censored



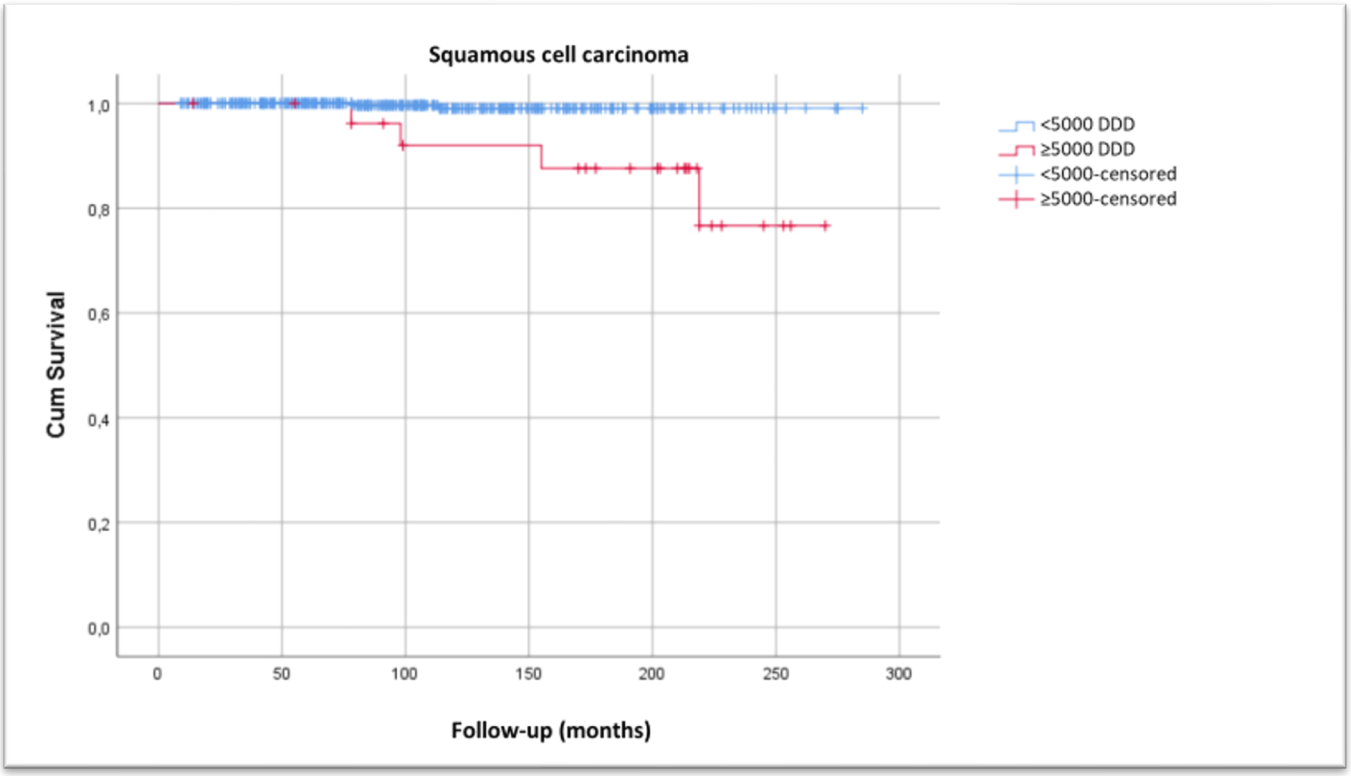
DDD, defined daily dose



DDD, defined daily dose



DDD, defined daily dose



DDD, defined daily dose

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