Use of antihypertensive drugs and risk of keratinocyte carcinoma: a meta-analysis of observational studies

Short title: Antihypertensive drugs and KC risk

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KEY POINTS

- Current epidemiological studies of the association between antihypertensive drugs and keratinocyte carcinoma (KC) risk offer inconsistent results.
- Use of diuretics might be associated with an increased risk of KC, while ACE inhibitors or ARBs might be associated with a decreased risk of KC in patients at high risk.
- Use of β-blockers and CCBs might be associated with an increased risk of BCC but not SCC.
- Further post-marketing surveillance studies are warranted to confirm our findings.

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ABSTRACT

Purpose Current epidemiologic evidence on the association between antihypertensive drugs and keratinocyte carcinoma (KC) risk is inconsistent. We sought to quantify this association by meta-analysis of observational studies.

Methods We systematically reviewed observational studies published through August 2016 and reported the KC risk (basal cell carcinoma/BCC and squamous cell carcinoma/SCC) associated with antihypertensive drugs, including diuretics, angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin II receptor blockers (ARBs), beta-adrenergic blocking agents (β-blockers), and calcium channel blockers (CCBs). Random-effects meta-analysis was used to estimate the odds ratio (OR) with 95% confidence interval (CI).

Results Ten eligible studies were included. Compared with non-use, diuretic use was significantly associated with increased risk of both BCC (OR, 1.10; 95% CI, 1.01 to 1.20) and SCC (OR, 1.40; 95% CI, 1.19 to 1.66). Use of β-blockers or CCBs was slightly associated with increased risk of BCC (but not SCC); the OR with β-blockers was 1.09 (95% CI, 1.04 to 1.15) and with CCBs was 1.15 (95% CI, 1.09 to 1.21). Use of ACE inhibitors or ARBs was associated with decreased risk of both BCC (OR, 0.53; 95%CI, 0.39 to 0.71) and SCC (OR, 0.58; 95%CI, 0.42 to 0.80) in high-risk individuals.

Conclusions Current evidence indicates that use of diuretics might be associated with an increased risk of KC, while ACE inhibitors or ARBs might be associated with a decreased risk in high-risk individuals. β-blockers or CCBs might be positively

associated with BCC risk. Further post-marketing surveillance studies and investigations to clarify the possible underlying mechanisms are warranted.

INTRODUCTION

Keratinocyte carcinoma (KC), the most common type of skin cancer, generally refers to basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). The incidence of NMSC has been increasing steadily, e.g., the US alone had an estimated incidence of 3.5 million in 2006, which grew to 5.4 million by 2012[1]. Although the mortality associated with KC is relatively low, the substantial associated morbidity translates to a considerable number of cases, and therefore an enormous burden in healthcare costs [2]. KC is caused mainly by exposure to ultraviolet radiation (UVR) [3, 4], though other postulated risk factors include fair skin, red hair, smoking, alcohol consumption, obesity, and drug use[5-8].

A number of antihypertensive drugs have been approved and widely used for treating hypertension, which affects up to 60 million people in the US[9]. Several classes of antihypertensive drugs (e.g., diuretics) are described as being photosensitizing [10, 11] and may also have phototoxic effects upon UVR exposure, increasing the risk of developing UVR-related KC [12]. However, the mechanism of action is poorly understood. Drug-induced photosensitivity is influenced by the chemical structure of the drug and determined by its capacity to modify an individual's sensitivity to UVR. Current findings regarding the risk of KC have been inconsistent across the classes of antihypertensive drugs. Elevated risk of BCC associated with diuretic use has been observed especially in overweight and obese individuals [13]. More recently, several case-control studies found that long-term use of diuretics was associated with increased risk of SCC [14, 15].. However, one cohort study in Danish patients found no association between increased risk of KC and long-term daily use of diuretics [17]. In contrast, reduced risk of KC has

been associated with the use of both angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers (ARBs) [18]. Little is known about the association between beta-adrenergic blocking agents (β-blockers) or calcium channel blockers (CCBs) and KC risk. The inconsistent results might be due to limited information from individual studies, including small sample size, short follow-up, and variation in geographic region. We therefore examined whether use of any of the following five major classes of antihypertensive drugs – ACE inhibitors, ARBs, β-blockers, CCBs, or diuretics – was associated with KC risk by meta-analysis of observational studies.

METHODS

The study was performed in accordance with the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines for reviews of observational studies [19]

Search strategy and study selection

We systematically searched PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) from inception to August 12, 2016 to identify observational studies (cohort studies and case-control studies) evaluating the association between exposure to antihypertensive drugs and risk of KC. Combined terms were used to search these databases without any restriction (**File S1**). We also manually checked the reference lists of relevant reviews and meta-analyses to identify additional studies. Two reviewers (HT and SF) independently selected the studies according to the following criteria: 1) clearly defined the exposure to antihypertensive drugs; 2) “no use of antihypertensive drug” as the reference; 3) reported the outcome of KC (including BCC or SCC); 4) reported the odds ratio (OR), risk ratio (RR), and hazard ratio (HR) with

corresponding 95% confidence intervals (CIs), or sufficient data to calculate; and 5) cohort studies or case-control studies. We excluded abstracts and unpublished studies due to lack of information about patient and study characteristics. For the same sample used in multiple reports, only the latest or longest follow-up study was included. In the case of any missing information, we contacted the original author for clarification.

Data extraction and quality assessment

Two reviewers (HT and SF) independently extracted data and assessed the quality of each study. We collected the following information: study design, region of study, drug use and reference, characteristics of participants, selection criteria, exposure definition, adjusted covariates, and the adjusted estimates of KC. In additional, we assessed the quality of studies using the Newcastle-Ottawa quality-assessment scale (NOS) based on the following three domains: selection, comparability, and exposure/outcome[20]. The total NOS score ranges from 0 to 9, with a higher score indicating greater quality. The studies with scores of 0 to 5, 6 to 7, and 8 to 9 were considered low, moderate, and high quality, respectively. Any disagreements were resolved by consensus or referral to a third reviewer (JH).

Statistical analysis

ORs with 95% CI were used to estimate the risk of KC associated with antihypertensive drugs. Considering heterogeneity across studies, a random-effects meta-analysis model was used to calculate the estimates separately for ACE inhibitors, ARBs, β-blockers, CCBs, and diuretics. The I^2 statistic was used to assess heterogeneity, with I^2 of <25%, ≥25% and <75%, and ≥75% indicating low, moderate, and high heterogeneity, respectively [21]. Subgroup analysis was used to assess the consistency of associations

between each class of antihypertensive drug and risk of KC within certain pre-specified subgroups: type of design (cohort study *vs.* case-controlled study), region of study (Europe *vs.* USA), study quality (high quality *vs.* moderate quality), adjusted for sun or UVR exposure (yes *vs.* no), and adjusted for smoking (yes *vs.* no) if there were sufficient data (at least six studies included[22]). We performed a cumulative meta-analysis to evaluate the development of evidence over time by adding one study at a time in the order of date of publication. A sensitivity analysis was carried out to assess the robustness of our findings by removing one study at a time. In addition, publication bias was assessed using Begg's and Egger's tests. All statistical analyses were performed with STATA (Version 14; Stata Corp., College Station, TX). A p value <0.05 was considered significant.

RESULTS

Of 2430 unique citations retrieved from electronic databases, ten observational studies, i.e., six cohort studies[13, 17, 18, 23-25] and four case-control studies[12, 14, 26, 27], met the eligibility criteria and were included in our meta-analysis (**Figure 1**). The basic characteristics of the included studies are presented in **Table 1**. Studies were published between 2008 and 2016; six were carried out in Europe and four in the United States. It should be noted that one study[25] was conducted among renal transplant recipients and another study[18] included veterans at high risk for BCC and SCC, which was defined as experiencing at least two BCCs and/or SCCs in the five years preceding the study period. Diuretics were analyzed in nine studies, ACE inhibitors in two, ARBs in two, ACE inhibitors or ARBs as a category in two, β-blockers in three, and CCBs in three. The included studies were of moderate or high quality, with five assessed as high

quality (8 out of 9 using NOS), and the other five studies were assessed as medium quality (NOS score from 6 to 7) (**Table S1**).

Use of diuretics and KC risk

Eight studies [12-14, 17, 18, 23, 24, 27] reported an association between diuretic use and risk of BCC. Meta-analysis of these studies showed that use of diuretics was significantly associated with an increased risk of BCC compared with non-use (OR, 1.10; 95% CI, 1.01 to 1.20) (**Figure 2A**). There was significant heterogeneity among studies (I^2 = 82.2%). The results from subgroup analysis are presented in **Table 2**. A significantly increased risk of BCC was observed in cohort studies (OR, 1.09; 95% CI, 1.04 to 1.13), studies of moderate quality (OR, 1.47; 95% CI, 1.04 to 2.07), or in studies with (OR, 1.07; 95% CI, 1.01 to 1.12) or those without adjusting for smoking status (OR, 1.14; 95% CI, 1.02 to 1.29). Our cumulative meta-analysis showed that the cumulative OR became significant when the study published by Nardone *et al.* in 2016 was added (**Figure 3A**). A sensitivity analysis excluding one study at a time indicated that our results are robust unless the study by Nardone *et al.* 2016 was excluded (**Figure S1A**). There was no evidence of publication bias based on Egger's test (*P* = 0.20) or Begg's test (*P* = 0.27).

Seven studies [12, 14, 17, 18, 24, 26, 27] provided estimates of the association between diuretics and SCC risk. Meta-analysis of these studies showed that use of diuretics was significantly associated with an increased risk of SCC compared to non-use (OR, 1.40, 95% CI, 1.19 to 1.66) (**Figure 2B**). There was significant heterogeneity among studies (I^2 = 81.8%). Our subgroup analysis did not found a significantly increased risk of SCC

in US populations, in studies adjusted for sun or UVR exposure, and studies adjusted for smoking status (**Table 2**). Our cumulative meta-analysis showed that the cumulative OR including the second study in 2008 became significant (OR, 1.19; 95% CI, 1.04 to 1.36) (**Figure 3B**). Since then, the cumulative OR remained significant and stable. In addition, a sensitivity analysis excluding one study at a time did not significantly affect the pooled estimates (**Figure S1B**). There was no evidence of publication bias based on Egger's test (P=0.30) or Begg's test (P=0.23).

Use of ACE inhibitors or ARBs and KC risk

Two studies [14, 24] reported on the association between ACE inhibitors and risk of BCC or SCC (**Figure 2**), one of which found a significantly increased risk [24]. However, when we conducted a pooled analysis of the data from these two studies, there was no significant association between ACE inhibitors and risk of BCC (OR, 1.50; 95% CI, 0.70 to 3.22) or SCC (OR, 1.42; 95% CI, 0.81 to 2.50). In addition, significant heterogeneity was detected for BCC (I^2 = 97.6%) and SCC (I^2 = 88.6%). Further analysis (e.g., subgroup analysis) was not possible due to the limited number of studies included.

Two studies [14, 24] examining the risk of BCC and SCC associated with ARBs had inconsistent results (**Figure 2**), one of which indicated significantly increased risk [24]. Pooled analysis of these two studies identified no significant association between use of ARBs and risk of BCC (OR, 1.75; 95% CI, 0.68 to 4.49) or SCC (OR, 1.54; 95% CI, 0.82 to 2.90). There was significant heterogeneity for both BCC (I^2 = 97.4%) and SCC (I^2 = 83.1%).

Two studies [18, 25] provided data on the association between use of ACE inhibitors or ARBs as a category and risk of KC in renal transplant recipients or patients at high risk for KC (**Figure 2**). Both studies found a lower risk of BCC and SCC among patients using ACE inhibitors or ARBs[18, 25]. Our meta-analysis showed that use of ACE inhibitors or ARBs was significantly associated with a decreased risk of both BCC (OR, 0.53; 95% CI, 0.39 to 0.71) and SCC (OR, 0.58; 95% CI, 0.42 to 0.80) as compared to non-use (**Figure 2**).

Use of β-blockers and KC risk

Three studies [14, 18, 25] presented adjusted estimates of the association between use of β-blockers and risk of BCC or SCC (**Figure 2**). When we performed a pooled analysis of these three studies, we found that β-blockers were significantly associated with increased risk of BCC compared with non-use (OR, 1.09; 95% CI, 1.04 to 1.15), while there was no significant association between use of β-blockers and risk of SCC (OR, 0.89; 95% CI, 0.69 to 1.16). We detected no heterogeneity across studies for BCC (I^2 = 0%) and only moderate heterogeneity for SCC (I^2 = 68.1%).

Use of CCBs and KC risk

Three studies [14, 18, 25] assessed the association between CCBs and risk of BCC or SCC (**Figure 2**). Based on their data, use of CCBs was significantly associated with increased risk of BCC compared with non-use (OR, 1.15; 95% CI, 1.09 to 1.21), with no evidence of heterogeneity (I^2 = 0%). However, there was no significant association between use of CCBs and risk of SCC (OR, 1.03; 95% CI, 0.88 to 1.21), with low evidence of heterogeneity (I^2 = 29.3%).

DISCUSSION

In this meta-analysis of ten observational studies, we found that use of diuretics was significantly associated with increased risk of KC, with a 10% increased risk for BCC and 40% increased risk for SCC. However, there was significant heterogeneity among studies in the overall and subgroup analyses. There was no significant association between diuretics and risk of KC (including SCC) in studies that adjusted for sun or UVR exposure. Our cumulative meta-analysis indicated that the cumulative OR of the association between use of diuretics and risk of SCC and BCC first became significant in 2008 and in 2016, respectively. There was some evidence of a slightly but significantly increased risk of BCC among patients using β-blockers or CCBs. The use of ACE inhibitors or ARBs might be associated with a decreased risk of KC in renal transplant recipients or patients at high risk for KC. However, the results of our meta-analysis should be interpreted with caution due to significant heterogeneity and the limited number of studies included.

Our findings are in agreement with several previous studies suggesting increased risk of KC among users of diuretics[14, 24]. Moreover, the cumulative meta-analysis showed that the increased risk of SCC was evident from 2008 onwards, and the effect was robust and unlikely to be a chance finding. A recent matched cohort study performed in a large electronic medical records repository of the Northwestern Medicine Enterprise Data Warehouse (NMEDW) found that use of thiazide diuretics was associated with increased OR for development of both BCC and SCC [24]. Similarly, a case-control study performed in northern Demark found a significantly increased risk of SCC and a borderline increase in risk of BCC among patients taking diuretics [14]. These findings

raise the possibility that KC risk is elevated among users of diuretics, especially thiazide diuretics. In addition, we found a non-significantly increased risk of KC (especially SCC) in studies that adjusted for sun or UVR exposure. It is well known that diuretics can act as co-carcinogens with UVR to promote KC development [12]. The photosensitizing reaction followed by sun or UVR exposure can exacerbate the risk of sunburn and photo-damage and ultimately increase risk of KC among patients taking diuretics[28]. However, the results from prior studies varied for BCC and SCC. A multicenter hospital-based case-control study in European populations found that users of diuretics had increased risk of SCC, but not BCC [27]. Another population-based case-control study showed a significant association between use of diuretics and development of SCC, but not BCC [12]. In our meta-analysis, we also found a stronger association with SCC (OR, 1.40) than with BCC (OR, 1.10) among patients taking diuretics, and our cumulative meta-analysis indicated that the significantly increased risk of SCC has been observed since 2008, while the increased risk of BCC became evident starting only in 2016. One possible explanation might be that chronic UV exposure is more strongly related to risk of SCC than BCC[29]. Further studies on effect modification of UV exposure on these drugs with skin cancer risk are warranted.

Though smoking is a well-known risk factor for many human cancers[30], findings regarding potential associations between smoking and KC risk remain inconsistent [31]. Our subgroup analysis found a significantly increased risk of BCC and a non-significantly increased risk for SCC in the studies adjusted for smoking status, indicating that smoking is not likely to be a major confounder for KC risk. Our stratified analysis by geographic region indicated that use of diuretics was significantly associated with

increased risk of SCC in European populations, but not in US populations. However, a non-significantly increased BCC risk was observed in both populations. Further large, well-conducted studies adequately adjusting and stratifying for major confounders (e.g., UVR exposure) are required to confirm our findings.

Our meta-analysis of three studies[14, 18, 25] found a slight but significant association between increased risk of BCC and use of β-blockers or CCBs. The underlying mechanism of action is unclear. Some specific drugs in the classes of β-blockers (e.g., sotalol) or CCBs (e.g., nifedipine) are considered photosensitizing agents [32] and therefore might increase KC development by acting as co-carcinogens with UVR. However, there was no significant difference between CCBs and β-blockers in terms of SCC risk. In addition to the fact that only three studies were included, it should be noted that the significant association was largely driven by one study performed by Schmidt et al[14]. The KC risk associated with CCBs or β-blockers remains uncertain and therefore requires exploration in more well-conducted studies.

Use of ACE inhibitors or ARBs might be associated with lower risk of KC in renal transplant recipients or patients at high risk for KC. No significant difference was observed in other populations. Little is known about the possible mechanisms underlying any carcinogenic risk associated with ACE inhibitors or ARBs. Some evidence from experimental studies and epidemiologic studies has suggested chemopreventive effects of ACE inhibitors and ARBs against cancer, with possible mechanisms of actions including inhibition of matrix metalloprotease activity, reduced expression of vascular endothelial growth factor, and interference with the renin-angiotensin system[33]. However, ACE inhibitors or ARBs have been reported to have

photosensitizing potential [32], and one matched-cohort study found significantly increased risk of KC among patients taking these drugs [24]. Therefore, future studies are warranted to clarify the association between use of ACE inhibitors or ARBs and development of KC.

Our study has two strengths. First, we systematically searched electronic databases to include all relevant studies. It is important to note that this is the first meta-analysis to address the association between antihypertensive drugs and risk of KC. Second, to confirm the robustness of our findings, pre-specified subgroup analysis and sensitivity analysis were performed if there were sufficient data. However, our meta-analysis also has several potential limitations. First, because there was a lack of information in the eligible studies about the common risk factors for KC, such as UVR exposure, ethnicity, and smoking status, we extracted the adjusted estimates for potential confounders (e.g., UVR exposure) whenever available and further conducted a subgroup analysis to minimize bias. Second, one potential confounder, health-seeking behaviors, may lead to detection bias. Individuals under hypertension management may be more likely to seek medical advice and be subject to increased surveillance, increasing the likelihood of disease diagnosis. However, we did not detect an increased risk of KC across all classes of antihypertensive drugs, which suggested that the increased risk might not be entirely due to increased scrutiny. Third, information about cumulative doses and cumulative durations were unavailable from the selected studies, preventing us from performing a further dose-response analysis. Finally, there was some evidence of significant heterogeneity across studies. Though we explored possible sources of heterogeneity by performing several subgroup analyses, we could not completely

exclude heterogeneity. Additionally, the limited number of studies included made us unable to perform this analysis for β-blockers, ACE inhibitors, ARBs, or CCBs.

In summary, this meta-analysis based on evidence from ten observational studies indicated that use of diuretics might be associated with increased risk of KC, while use of ACE inhibitors or ARBs might be associated with decreased risk in patients at high risk. In addition, use of β-blockers or CCBs might be associated with increased risk of BCC. Because our study was observational, these results should be interpreted with caution and are insufficient evidence to alter current clinical recommendations. Nevertheless, these data support continued investigation of the potential mechanisms underlying this relationship.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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ETHICS STATEMENT

The authors state that no ethical approval was needed.

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Table 1. Characteristics of included studies

Study	Study design	Data source	Follow-up (years)	No. of participants	Age (year)	Male (%)	Selection criteria	Exposure definition	Adjustment covariates
Jensen et al. 2008[12]	Case-control study	Danish Cancer Registry; North Jutland County; 1989 to 2003; Denmark	NR	MM: 1010; BCC: 594; SCC: 1129; Controls: 32,412	NR	NR	Patients registered with a first primary diagnosis of BCC, SCC, or MM, and four population controls selected for each case	Use of diuretics	Prior hospitalization for selected chronic diseases and use of glucocorticoids.
De Vries et al. 2012[27]	Case-control study	Multicenter, hospital-based, case–control study was carried out in Finland, Germany, Greece, Italy, Malta, Poland, Scotland, and Spain; NR; Europe	NR	MM:360; SCC:409; BCC:602; Controls:1550	67	56	Patients recently diagnosed with SCC, BCC, or MM (≥18 years) and matched controls	Use of thiazide diuretics at least for 3 months	Age, sex, phototype, and country
Robinson et al. 2013[26]	Case-control study	New Hampshire residents enrolled in the Center for Medicare and Medicaid Services; 1993 to 2000; 2001 to 2009; US	NR	BCC:1567; SCC:1599; Controls:1906	NR	56.4	BCC and SCC cases, matched controls identified from New Hampshire residents who speak English, have a listed telephone number, and were between 25 and 74 at diagnosis	Use of diuretics	Age, sex, number of painful sunburns, and study phase in final models; other confounder effects including the lifetime hours of warm months sun exposure, skin response to first hour of sun in summer, tanning lamp use, and radiation treatment did not alter estimates of photosensitizing medications effects and were not included in final models
Schmidt et al. 2015[14]	Case-control study	Northern Denmark using various registries linked by the CPR numbers; 1991 to 2010; Denmark	Maximum: 19	SCC: 2,282; BCC:17, 242, MM:3,660; controls:231, 743	67	46	Aged ≥20 years with a first-time diagnosis of SCC, BCC, or MM and 10 matched controls	Use of antihypertensive drugs	CCI score, hospital-diagnosed obesity, and use of systemic glucocorticoids, aspirin, non-aspirin NSAIDs, and statins
Christian et al. 2008[18]	Cohort study	Veterans Affairs Topical Tretinoin Chemoprevention (VATTC)	Median: 3.4 years	ACEi or ARB users: 532; non-users: 519	71	97	Enrolled 1131 veterans at high risk for BCC and SCC †; filled a prescription for at least	Use of ACEi or ARB	Age; sex; race; number of previous SCCs and BCCs in past 5 years; smoking history; sun sensitivity

		Trial;1998 to 2003;US					one medication during the study period		score; history of psoriasis, eczema, chemical peels, and 5-fluorouracil treatment; family history of skin cancer; education; arital status; number of actinic keratoses; CCI; and history of use of statins, H2 blockers, antidepressants, and other antihypertensive agents.
Moscarelli et al. 2010[25]	Cohort study	Renal Unit Careggi University Hospital; 1991 to 2005; Italy	median: 4.9 years	ACEi or ARB users 215; non-users 350	60	66.4	All renal transplant recipients admitted to Renal Unit Careggi University Hospital, Italy from July 1991 to December 2005	Use of ACEi or ARB for at least six months	Sex, white race, smoking history, history of a previous SC, duration of pre-transplant dialysis therapy, treatment for early acute rejection, age at transplant, number of years since transplantation, number of renal transplants, number of previous actinic keratosis, use of common antihypertensive medications, use of statins, histamine-H2 receptor antagonists, proton-pump inhibitors.
Ruiter et al. 2010[23]	Cohort study	Rotterdam Study-a large prospective, population-based follow-up study with coverage of prescription-only drugs from pharmacies;1986 to 2007; Netherlands	Maximum: 20 years	Use of high-ceiling diuretics:110; no users: 412	69	40	Patients received a prescription of diuretics before 1 April 1991	Use of diuretics	Gender, age, smoking status, self-reported tendency to sunburn, outdoor work, history of living in a country with a high sun exposure, ethnicity, natural hair color during childhood, natural hair color when adult, eye color, and cohort
Kaae et al. 2010[17]	Cohort study	Danish national registers;1995 to 2006; Denmark	NR	4,761,749 participants	NR	NR	Patients identified from Danish Cancer Registers filled at least one prescription for	Use of photosen sitizing medicatio n	Age, period, sex, and education

							photosensitizing medication	(diuretics)	
McDonald et al. 2014[13]	Cohort study	United States Radiologic Technologists (USRT) Study; US	8.7 years	diuretics:6859; no diuretics 50716	49	18	White participants from USRT study completed two questionnaires	Use of diuretics	Age, birth cohort, sex, continuous BMI, and UVR quartile
Nardone et al. 2016[24]	Cohort study	Northwestern Medicine Enterprise Data Warehouse; 2004 to 2015; US	4 years	ACEi: 27,134, Control:81,399; ARBs:13,818, Control:41,454;Thiazides: 15,166, Control: 45,498	NR	43.4	Patient age range 18-89 years, one or more written orders for an ACEi, ARB, or thiazides; 3 matched individuals with no documented order for any antihypertensive drug	Use of antihypertensive drugs (ACEi, ARB or thiazides)	Age, gender, race, and CCI

† high risk is defined as suffering from at least two BCCs and/or SCCs in the five years before the study periods.

MM, malignant melanoma; BCC, basal cell carcinoma; SCC, squamous cell carcinoma; NR, not reported; ACEi, angiotensin converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; β-blockers, beta-adrenergic blocking agents; CCBs, calcium channel blockers; NSAID, non-steroidal anti-inflammatory drug; CCI, charlson comorbidity index

Table 2. Subgroup analysis of use of diuretics and risk of KC

Group/ subgroup	BCC				SCC			
	No. of studies	OR (95% CI)	P value	I^2 (%)	No. of studies	OR (95% CI)	P value	I^2 (%)
Total	8	1.10 (1.01, 1.20)	0.02	82.2	7	1.40 (1.19, 1.66)	<0.01	81.8
Design								
Cohort	5	1.09 (1.04, 1.13)	<0.01	86	3	1.33 (1.24, 4.43)	<0.01	92.8
Case-control	3	1.02 (0.98, 1.06)	0.26	68.2	4	1.22 (1.12, 1.33)	<0.01	4.5
Region								
Europe	5	1.03 (0.98, 1.08)	0.24	54.3	4	1.26 (1.17, 1.36)	<0.01	27.9
USA	3	1.36 (0.94, 1.95)	0.10	87.9	3	1.78 (0.82, 3.87)	0.14	91.8
Quality								
High	5	1.03 (0.98, 1.07)	0.26	45.2	4	1.25 (1.18, 1.32)	<0.01	0
Moderate	3	1.47 (1.04, 2.07)	0.03	83.9	3	2.06 (1.08, 3.93)	0.03	87.5
Adjusted for sun or UVR exposure								
Yes	3	1.11 (1.00, 1.22)	0.05	50.1	2	1.17 (0.91, 1.51)	0.22	0
No	5	1.13 (0.99,1.29)	0.07	87.6	5	1.49 (1.22,1.82)	<0.01	87.4
Adjusted for smoking status								
Yes	2	1.07 (1.01, 1.12)	0.01	0	1	1.09 (0.79,1.51)	0.60	-
No	6	1.14 (1.02, 1.29)	0.03	87	6	1.46 (1.21, 1.75)	<0.01	84.3

Figure legends:

Figure 1. Flow chart of the identification of eligible studies

Figure 2. Meta-analysis of the association between use of antihypertensive drugs and risk of BCC (A) and SCC (B).

Figure 3. Cumulative meta-analysis of studies ordered by publication year for the association between use of diuretics and risk of BCC (A) and SCC (B). The studies are added at one time according to year of publication and the results are summarized as each new study is added.

Fig 1

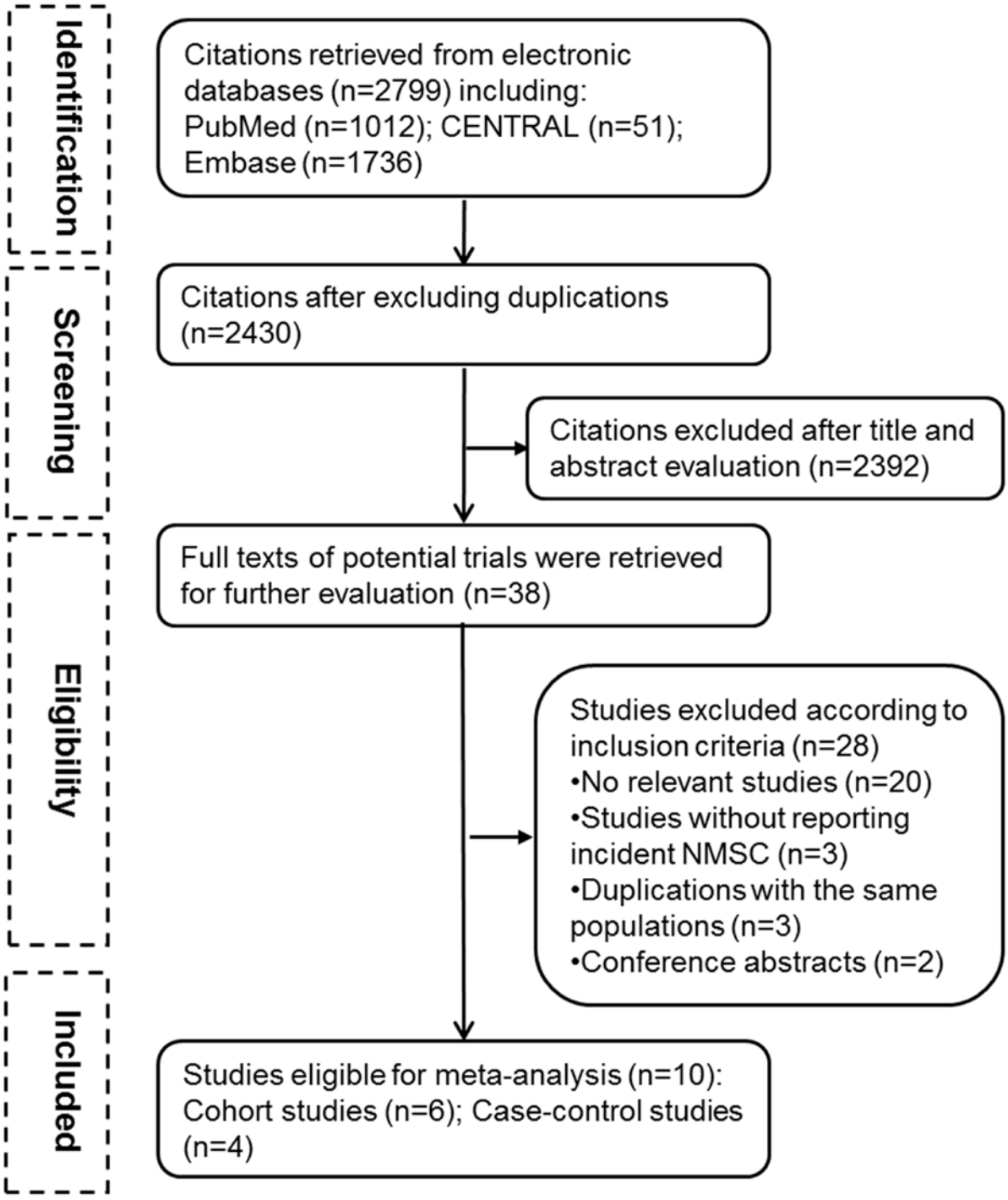

Identification
Screening
Eligibility
Included
Citations retrieved from electronic databases (n=2799) including: PubMed (n=1012); CENTRAL (n=51); Embase (n=1736)
Citations after excluding duplications (n=2430)
Citations excluded after title and abstract evaluation (n=2392)
Full texts of potential trials were retrieved for further evaluation (n=38)
Studies excluded according to inclusion criteria (n=28)
•No relevant studies (n=20)
•Studies without reporting incident NMSC (n=3)
•Duplications with the same populations (n=3)
•Conference abstracts (n=2)
Studies eligible for meta-analysis (n=10): Cohort studies (n=6); Case-control studies (n=4)

Fig 2.

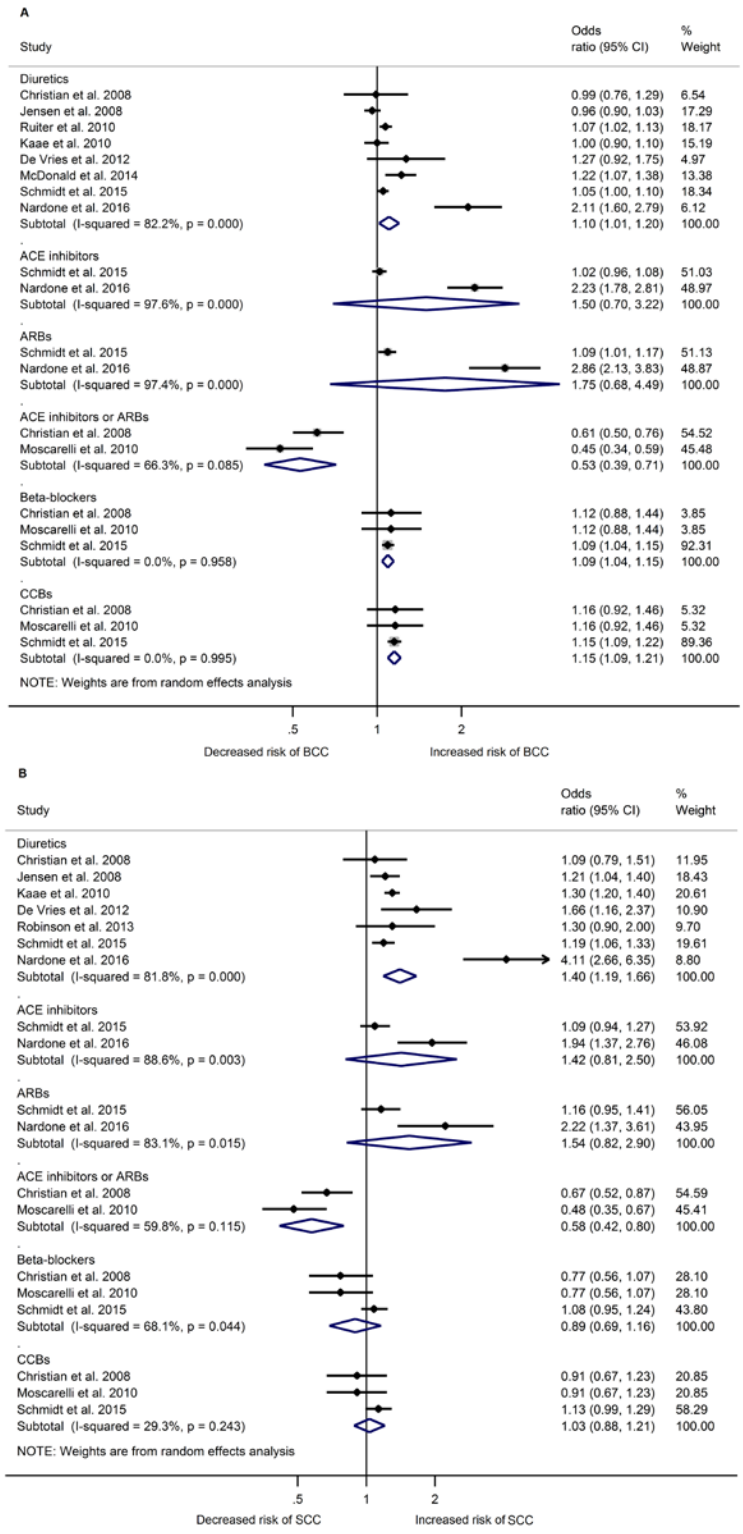
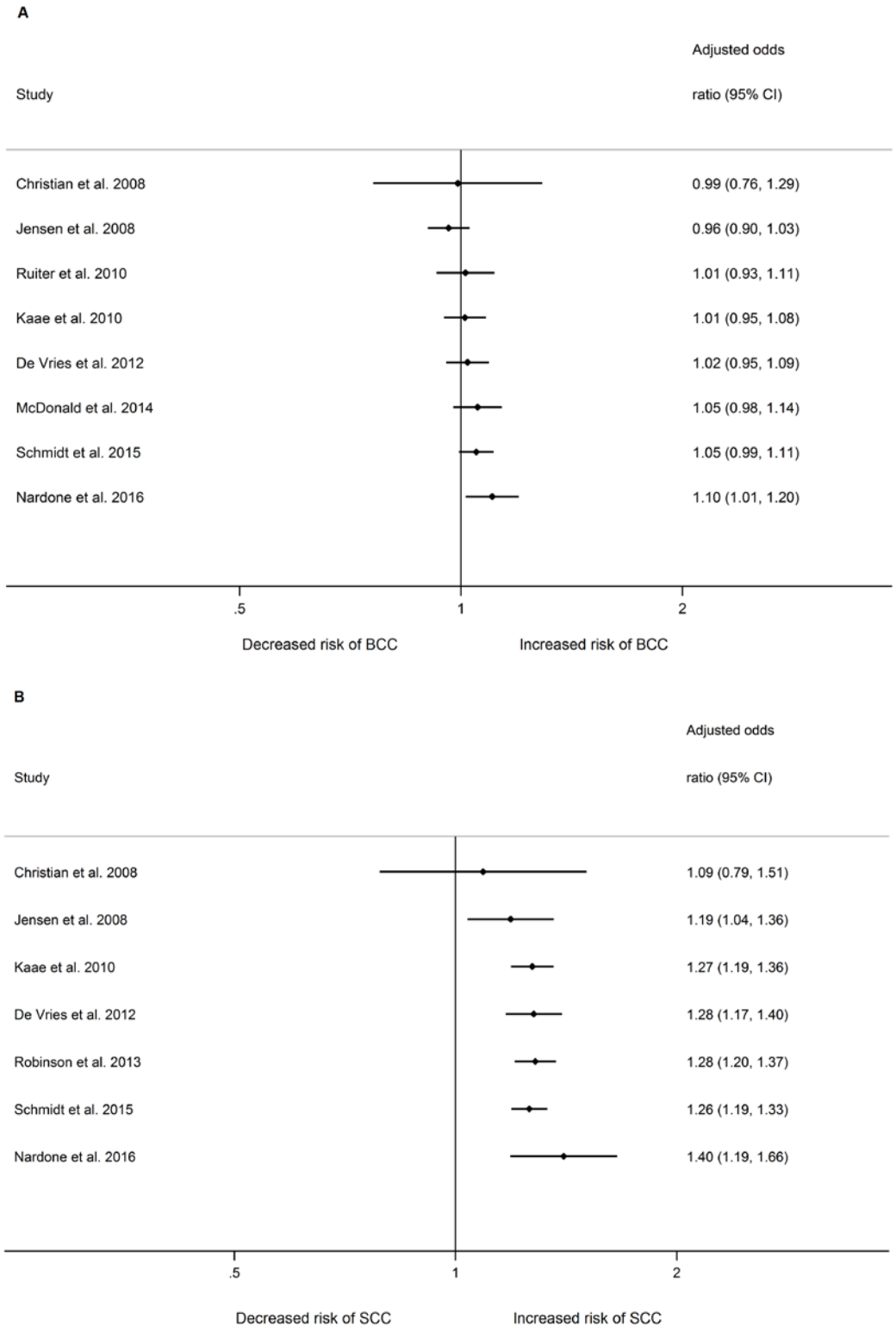

A
Study
Odds ratio (95% CI)
% Weight
Diuretics
Christian et al. 2008 0.99 (0.76, 1.29) 6.54
Jensen et al. 2008 0.96 (0.90, 1.03) 17.29
Ruiter et al. 2010 1.07 (1.02, 1.13) 18.17
Kaae et al. 2010 1.00 (0.90, 1.10) 15.19
De Vries et al. 2012 1.27 (0.92, 1.75) 4.97
McDonald et al. 2014 1.22 (1.07, 1.38) 13.38
Schmidt et al. 2015 1.05 (1.00, 1.10) 18.34
Nardone et al. 2016 2.11 (1.60, 2.79) 6.12
Subtotal (I-squared = 82.2%, p = 0.000) 1.10 (1.01, 1.20) 100.00
ACE inhibitors
Schmidt et al. 2015 1.02 (0.96, 1.08) 51.03
Nardone et al. 2016 2.23 (1.78, 2.81) 48.97
Subtotal (I-squared = 97.6%, p = 0.000) 1.50 (0.70, 3.22) 100.00
ARBs
Schmidt et al. 2015 1.09 (1.01, 1.17) 51.13
Nardone et al. 2016 2.86 (2.13, 3.83) 48.87
Subtotal (I-squared = 97.4%, p = 0.000) 1.75 (0.68, 4.49) 100.00
ACE inhibitors or ARBs
Christian et al. 2008 0.61 (0.50, 0.76) 54.52
Moscarelli et al. 2010 0.45 (0.34, 0.59) 45.48
Subtotal (I-squared = 66.3%, p = 0.085) 0.53 (0.39, 0.71) 100.00
Beta-blockers
Christian et al. 2008 1.12 (0.88, 1.44) 3.85
Moscarelli et al. 2010 1.12 (0.88, 1.44) 3.85
Schmidt et al. 2015 1.09 (1.04, 1.15) 92.31
Subtotal (I-squared = 0.0%, p = 0.958) 1.09 (1.04, 1.15) 100.00
CCBs
Christian et al. 2008 1.16 (0.92, 1.46) 5.32
Moscarelli et al. 2010 1.16 (0.92, 1.46) 5.32
Schmidt et al. 2015 1.15 (1.09, 1.22) 89.36
Subtotal (I-squared = 0.0%, p = 0.995) 1.15 (1.09, 1.21) 100.00
NOTE: Weights are from random effects analysis
.5
1
2
Decreased risk of BCC
Increased risk of BCC
B
Study
Odds ratio (95% CI)
% Weight
Diuretics
Christian et al. 2008 1.09 (0.79, 1.51) 11.95
Jensen et al. 2008 1.21 (1.04, 1.40) 18.43
Kaae et al. 2010 1.30 (1.20, 1.40) 20.61
De Vries et al. 2012 1.66 (1.16, 2.37) 10.90
Robinson et al. 2013 1.30 (0.90, 2.00) 9.70
Schmidt et al. 2015 1.19 (1.06, 1.33) 19.61
Nardone et al. 2016 4.11 (2.66, 6.35) 8.80
Subtotal (I-squared = 81.8%, p = 0.000) 1.40 (1.19, 1.66) 100.00
ACE inhibitors
Schmidt et al. 2015 1.09 (0.94, 1.27) 53.92
Nardone et al. 2016 1.94 (1.37, 2.76) 46.08
Subtotal (I-squared = 88.6%, p = 0.003) 1.42 (0.81, 2.50) 100.00
ARBs
Schmidt et al. 2015 1.16 (0.95, 1.41) 56.05
Nardone et al. 2016 2.22 (1.37, 3.61) 43.95
Subtotal (I-squared = 83.1%, p = 0.015) 1.54 (0.82, 2.90) 100.00
ACE inhibitors or ARBs
Christian et al. 2008 0.67 (0.52, 0.87) 54.59
Moscarelli et al. 2010 0.48 (0.35, 0.67) 45.41
Subtotal (I-squared = 59.8%, p = 0.115) 0.58 (0.42, 0.80) 100.00
Beta-blockers
Christian et al. 2008 0.77 (0.56, 1.07) 28.10
Moscarelli et al. 2010 0.77 (0.56, 1.07) 28.10
Schmidt et al. 2015 1.08 (0.95, 1.24) 43.80
Subtotal (I-squared = 68.1%, p = 0.044) 0.89 (0.69, 1.16) 100.00
CCBs
Christian et al. 2008 0.91 (0.67, 1.23) 20.85
Moscarelli et al. 2010 0.91 (0.67, 1.23) 20.85
Schmidt et al. 2015 1.13 (0.99, 1.29) 58.29
Subtotal (I-squared = 29.3%, p = 0.243) 1.03 (0.88, 1.21) 100.00
NOTE: Weights are from random effects analysis
.5
1
2
Decreased risk of SCC
Increased risk of SCC

Fig 3.


A
Study
Adjusted odds ratio (95% CI)
Christian et al. 2008
0.99 (0.76, 1.29)
Jensen et al. 2008
0.96 (0.90, 1.03)
Ruiter et al. 2010
1.01 (0.93, 1.11)
Kaae et al. 2010
1.01 (0.95, 1.08)
De Vries et al. 2012
1.02 (0.95, 1.09)
McDonald et al. 2014
1.05 (0.98, 1.14)
Schmidt et al. 2015
1.05 (0.99, 1.11)
Nardone et al. 2016
1.10 (1.01, 1.20)
.5
1
2
Decreased risk of BCC
Increased risk of BCC
B
Study
Adjusted odds ratio (95% CI)
Christian et al. 2008
1.09 (0.79, 1.51)
Jensen et al. 2008
1.19 (1.04, 1.36)
Kaae et al. 2010
1.27 (1.19, 1.36)
De Vries et al. 2012
1.28 (1.17, 1.40)
Robinson et al. 2013
1.28 (1.20, 1.37)
Schmidt et al. 2015
1.26 (1.19, 1.33)
Nardone et al. 2016
1.40 (1.19, 1.66)
.5
1
2
Decreased risk of SCC
Increased risk of SCC