Published in final edited form as:

Br J Dermatol. 2018 November ; 179(5): 1088–1094. doi:10.1111/bjd.16713.

Photosensitizing Antihypertensive Drug Use and Risk of Cutaneous Squamous Cell Carcinoma

K.A. Su^{1,2}, L.A. Habel³, N.S. Achacoso³, G.D. Friedman³, and M.M. Asgari^{1,2}

¹Department of Dermatology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

²Department of Population Medicine, Harvard Pilgrim Health Care Institute, Harvard Medical School, Boston, MA

³Division of Research, Kaiser Permanente Northern California, Oakland, CA

Summary

Background—Many antihypertensive drugs (ADs) are photosensitizing, heightening reactivity of the skin to sunlight. Photosensitizing ADs have been associated with lip cancer, but whether they impact cutaneous squamous cell carcinoma (cSCC) risk is unknown.

Objectives—To examine the association between AD use and cSCC risk among a cohort of non-Hispanic whites with hypertension enrolled in a comprehensive integrated healthcare delivery system in northern California (n=28,357).

Methods—Electronic pharmacy data were used to determine exposure to ADs, which were classified, based on published literature, as photosensitizing (alpha-2 receptor agonists and diuretics [loop, potassium-sparing, thiazide, and combination]), non-photosensitizing (alpha-blockers, beta-blockers, central agonists, and angiotensin receptor blockers), or unknown (angiotensin converting enzyme inhibitors, calcium channel blockers, vasodilators, and other combinations). We identified patients who developed a cSCC during follow-up (n=3,010). We used Cox modeling to estimate adjusted hazard ratios (aHR) and 95% confidence intervals (CI). Covariates included age, sex, smoking, comorbidities, history of cSCC and actinic keratosis, survey year, healthcare utilization, length of health-plan membership, and prior history of photosensitizing AD use.

Results—Compared with non-use of ADs, risk of cSCC was increased with ever use of photosensitizing ADs (aHR=1.17, 95% CI 1.07–1.28) and ever use of ADs of unknown photosensitizing potential (aHR=1.11, 95% CI 1.02–1.20), whereas no association was seen with ever use of non-photosensitizing ADs (aHR=0.99; 95% CI, 0.91–1.07). In addition, there was a modest increased risk with increasing number of prescriptions for photosensitizing ADs (aHR=1.12, 95% CI 1.02–1.24, aHR=1.19, 95% CI 1.06–1.34, aHR=1.41, 95% CI 1.20–1.67 for 1–7, 8–15 and 16+ fills, respectively).

Corresponding Author: Maryam M. Asgari MD, MPH, Department of Dermatology, Massachusetts General Hospital, 50 Staniford Street, Suite 230A, Boston, Massachusetts 02114, (617) 643-6812 (phone), (617) 726-9133 (fax), masgari@partners.org. MS KATHERINE A. SU (Orcid ID : 0000-0002-2743-2079)

Conflict of Interest: The authors have no other potential conflicts of interest to disclose.

Conclusions—These findings provide moderate support for an increased cSCC risk among individuals treated with photosensitizing ADs.

Introduction

Many commonly used medications, including certain antihypertensive drugs (ADs), are photosensitizing, heightening reactivity of the skin to sunlight.^{1–7} The photosensitizing properties of medications are related to their distinct chemical structures that allow for the absorption of ultraviolet radiation (UVR).^{7–10} In the presence of UVR, photosensitizing medications may act as carcinogens by triggering phototoxic reactions, which cause acute DNA damage, and photoallergic reactions, which produce chronic inflammation.⁸ Phototoxic reactions, which occur shortly after medication administration, result from radiation-induced production of reactive oxygen species.⁸ Photoallergic reactions, which occur after a latent period of days to months, result from radiation-induced formation of antigens that elicit a delayed T-cell mediated hypersensitivity reaction.⁸ The ensuing chronic inflammation may promote cutaneous carcinogenesis.¹¹ Given the association between UVR, DNA damage, chronic inflammation, and development of cutaneous squamous cell carcinoma (cSCC), photosensitizing medications may increase cSCC risk.¹² A common malignancy with a rapidly rising incidence, cSCC is associated with substantial morbidity and cost.¹³

Epidemiologic data on the association between photosensitizing drug use and cSCC risk remain limited. Photosensitizing ADs have been associated with lip cancers, the majority of which are mucosal squamous cell carcinomas (SCC).^{14,15} Whether photosensitizing AD use affects cSCC risk, however, is unclear. Previous observational studies have produced conflicting results,^{16–24} and limitations have included small samples sizes,²² reliance on self-reported medication history,²³ confounding by indication, incomplete capture of cases,^{19,20,24} and lack of pathologic verification.^{19,20,22,24} In this study, we examined the association between AD use and cSCC risk among 28,357 non-Hispanic white (NHW) patients with hypertension in a closed healthcare system in northern California with integrated electronic pharmacy records and pathologically verified cSCC cases.

Patients and Methods

The source population was the membership of Kaiser Permanente Northern California (KPNC). KPNC is a pre-paid, integrated healthcare delivery system that serves approximately 4 million members. All aspects of medical care provided through KPNC's facilities, including pharmacy and pathology records, are captured electronically. The study cohort consisted of participants in KPNC's Research Program in Genes and Environmental Health (RPGEH), details of which have previously been published.²⁵ Participants were initially enrolled in the RPGEH cohort through participation in mailed surveys of adult KPNC members conducted in 2002–2003 and 2007–2009. Eligible individuals were those who at cohort entry reported NHW race/ethnicity, were at least 18 years of age, had KPNC pharmacy benefits, had no diagnostic codes for rare genetic disorders associated with cSCC risk,²⁵ had no history of infection with human immunodeficiency virus or history of a solid organ transplant, and had two or more records for a diagnosis of hypertension (International

Statistical Classification of Diseases and Related Health Problems, 9th revision (ICD-9) codes 401.0, 401.1, and 401.9) in the five years prior to study entry (n=28,357). At least five years of KPNC health plan membership prior to cohort entry were required to provide sufficient health and medication history. The study was limited to NHWs because cSCCs arise almost exclusively in fair-skinned individuals. We identified cohort members who developed a new, pathologically-verified invasive or in-situ cSCC from survey date to end of follow-up (December 31, 2012) (n=3,010). Cases of cSCC were identified through review of KPNC's pathology database. All cases of biopsy-proven cSCC in the RPGEH cohort were previously validated.²⁵

Electronic pharmacy data were used to determine exposure to ADs. A computerized prescription record system has tracked all prescriptions dispensed within KPNC since August 1994. ADs were classified as photosensitizing (alpha-2 receptor agonists and diuretics [loop, potassium-sparing, thiazide, and combination]), non-photosensitizing (alpha-blockers, beta-blockers, central agonists, and angiotensin receptor blockers [ARBs]), or unknown (angiotensin converting enzyme [ACE] inhibitors, calcium channel blockers [CCBs], vasodilators, and other combinations) based on a review of the literature.¹⁻⁷ Exposure was defined as two or more filled prescriptions for a given medication during the study period. While a single prescription for a photosensitizing AD could theoretically increase cSCC risk, two or more fills were required to minimize the chance of including patients who filled a prescription but never took the medication. Drug exposure after baseline was treated as time-varying. Person-time from the start of follow-up until first use of a given medication was classified as never use for that medication. For ever use, once a patient met the exposure definition (2 fills), he or she was considered exposed from that point forward, even if they later discontinued the medication. For exposure based on number of prescriptions, once a patient met the criteria for a category of fills, he or she was considered exposed to that category until they met the next higher category.

We used Cox modeling to estimate hazard ratios (HR) with 95% confidence intervals (CI) associating AD use with cSCC. Non-users of any ADs after cohort entry served as the reference group. We adjusted for variables associated with increased cSCC risk, including age, sex, smoking (current, former, never, unknown), comorbidities (Charlson Comorbidity Index [CCI] score 0, 1-2, or 3), history of cSCC and actinic keratosis (AK), and prior history of photosensitizing AD use (all in the five years prior to baseline). We also adjusted for survey year, length of KPNC health plan membership, baseline healthcare utilization, and surveillance measure. Smoking history was based on self-report at cohort entry. CCI is a weighted score of 17 conditions which predicts the risk of 10-year mortality for patients with a range of these diagnosis-based comorbid conditions.²⁶ History of cSCC was determined from pathology reviews, history of AK was captured using ICD-9 code 702.0, and prior photosensitizing AD use was determined based on pharmacy records. Healthcare utilization was defined as the average annual number of ambulatory visits in the 5 years prior to cohort entry, and the surveillance measure was defined as the average annual number of dermatology visits in the five years prior to cohort entry. All analyses were performed with SAS software version 9.3 (SAS Institute, Cary, NC) and all statistical tests were two-sided. This study was approved by the Institutional Review Board, Kaiser Foundation Research Institute.

Results

We identified a cohort of 28,357 NHW members of the RPGEH with hypertension who were followed for a mean of 5.09 years after cohort entry. Table 1 shows the baseline demographic characteristics of cohort members. The mean age at cohort entry was 69.1 years (standard deviation, 10.6 years) and was similar across the treatment groups. Women constituted 56.3% of the cohort and 59.5% of users of photosensitizing ADs. After baseline, 17,946 patients used photosensitizing ADs, 19,092 patients used non-photosensitizing ADs, 17,345 patients used ADs with unknown photosensitizing potential, and 1,530 patients did not use any ADs. There was considerable overlap between the treatment groups; many patients received prescriptions for multiple different classes of ADs after cohort entry. CCI score was higher among users of unknown photosensitizing ADs after cohort entry and lower among non-users of ADs after cohort entry. Prior cSCC and AK were more common among non-users of ADs after cohort entry (prior cSCC, 14.2%; prior AK, 40.1%) compared to the overall cohort (prior cSCC, 7.9%; prior AK, 35.2%). Prior photosensitizing AD use was less common among non-users of ADs after cohort entry (51.7%) compared to the overall cohort (74.0%).

We identified 3,010 cSCCs over 144,215 person-years of follow-up. Table 2 summarizes the HRs for cSCC among those exposed to ADs compared to no AD use. Compared with non-use of ADs, the adjusted hazard ratio (aHR) for ever use of photosensitizing ADs after baseline was 1.17 (95% CI, 1.07–1.28). The increase in cSCC risk associated with ever use of photosensitizing ADs was driven in large part by combination thiazide diuretics (aHR, 1.32; 95% CI, 1.19–1.46). Alpha-2 receptor agonists (aHR, 1.30; 95% CI, 0.62–2.74), potassium-sparing diuretics (aHR, 1.24; 95% CI, 0.96–1.61), loop diuretics (aHR 1.10; 95% CI, 0.98–1.24), and thiazide diuretics (aHR, 1.09; 95% CI, 0.99–1.19) all had HRs above 1.0. The aHR for ever use of non-photosensitizing ADs was 0.99 (95% CI, 0.91–1.07). Alpha blockers (aHR, 0.93; 95% CI, 0.83–1.03), beta blockers (aHR, 1.04; 95% CI, 0.96–1.12), central agonists (aHR, 1.07; 95% CI, 0.85–1.34), and ARBs (aHR, 0.97; 95% CI, 0.87–1.08) had HRs very close to 1.0.

The aHR for ever use of ADs with unknown photosensitizing potential was 1.11 (95% CI, 1.02–1.20). The increase in cSCC risk associated with ever use of ADs with unknown photosensitizing potential was driven by ACE inhibitors (aHR, 1.10; 95% CI, 1.01–1.19). CCBs had a HR very close to 1.0 (aHR, 1.06; 95% CI, 0.98–1.15). Vasodilators (aHR, 0.96; 95% CI, 0.76–1.21) and other combinations (aHR, 0.81; 95% CI, 0.64–1.03) were infrequently prescribed and not associated with increased cSCC risk.

Table 3 summarizes dose-response analyses based on number of prescriptions for ADs. There was a modest increase in risk of cSCC with increasing number of prescriptions for photosensitizing ADs (1–7 fills: aHR, 1.12; 95% CI, 1.02–1.24; 8–15 fills: aHR, 1.19; 95% CI, 1.06–1.34; 16+ fills: aHR, 1.41; 95% CI, 1.20–1.67). In contrast, no dose-response was observed with use of non-photosensitizing ADs (1–7 fills: aHR, 0.99; 95% CI, 0.89–1.09; 8–15 fills: aHR, 1.02; 95% CI, 0.92–1.14; 16+ fills: aHR, 0.95; 95% CI, 0.83–1.07) or unknown photosensitizing ADs (1–7 fills: aHR, 1.12; 95% CI, 1.02–1.23; 8–15 fills: aHR, 1.12; 95% CI, 1.01–1.25; 16+ fills: aHR, 1.06; 95% CI, 0.93–1.21).

Consistent with the main results, when outcomes were restricted to invasive disease, users of photosensitizing ADs had a very modest increased risk of invasive cSCC compared to non-users (aHR, 1.14; 95% CI, 1.02–1.27); users of unknown photosensitizing ADs also had a very modest increased risk of invasive cSCC (aHR, 1.08; 95% CI, 0.99–1.19). In contrast, users of non-photosensitizing ADs had a very modest decreased risk of invasive cSCC (aHR, 0.92; 95% CI, 0.84–1.02).

The association of photosensitizing ADs with risk of cSCC did not vary by history of actinic lesions (aHR, 1.16; 95% CI, 1.05–1.28 among those with history; aHR, 1.17; 95% CI, 0.97–1.41 among those without history). There was an increased risk of cSCC among users of unknown photosensitizing ADs with a past history of actinic lesions (aHR, 1.15; 95% CI, 1.05–1.26), but not those without a past history of actinic lesions (aHR, 0.99; 95% CI, 0.84–1.16).

Table 4 summarizes the results of additional subgroup analyses of new users of ADs after cohort entry and non-users of photosensitizing ADs before cohort entry. Analyses of new users of ADs after cohort entry were inconclusive because of small numbers of new users (n=405). Compared with non-use of ADs, new users of photosensitizing ADs had an elevated cSCC risk (aHR, 1.46; 95% CI, 0.70–3.02); new users of non-photosensitizing ADs had a reduced cSCC risk (aHR, 0.49; 95% CI, 0.19–1.30); and risk for new users of ADs with unknown photosensitizing potential fell in-between photosensitizing and non-photosensitizing new users (aHR, 0.92; 95% CI, 0.42–2.00). Due to the small number of new users, we were unable to demonstrate statistically significant differences in cSCC risk in the different exposure categories.

Analyses restricted to individuals without use of photosensitizing ADs prior to baseline (n=7,363) showed that users of photosensitizing and unknown photosensitizing ADs during follow-up had an increased cSCC risk compared with users of non-photosensitizing ADs during follow-up, though the results were not statistically significant (use of photosensitizing ADs during follow-up: aHR, 1.20; 95% CI, 0.97–1.48; use of unknown photosensitizing ADs during follow-up: aHR 1.16; 95% CI, 0.97–1.39).

Discussion

In this large cohort study conducted in a community-based comprehensive integrated healthcare delivery system, we found a 17% increase in risk of cSCC in NHW hypertensive patients who received photosensitizing ADs during follow-up compared to nonusers of ADs during follow-up. Each class of photosensitizing ADs showed small increases in risk, but combination thiazide diuretics were the only class to attain statistical significance. In addition, there was a modest increase in risk with increasing number of prescriptions of photosensitizing ADs. Risk of cSCC was increased among users of photosensitizing ADs regardless of history of actinic lesions. Use of unknown photosensitizing ADs was associated with a statistically significant 11% increase in risk and non-photosensitizing ADs were not associated with increased risk of cSCC. Findings among new users of these drugs were generally consistent with those of all users but statistical significance was not evident due to small numbers of new users.

Results of previous studies of ADs and risk of skin cancer have been inconsistent.^{24,23,20,19,22,18,17,21} While some have shown increased risk with use of potassium-sparing and combination diuretics,^{19,24} but not loop or thiazide diuretics,^{19,20,24} several studies, including one at KPNC, have shown a significant association between thiazide diuretic use and increased SCC risk.^{14,15,18,22} ACE inhibitors and ARBs have been associated with a reduced risk of keratinocyte cancers in some studies^{17,21} and an increased risk in others.^{22,24} Beta-blockers, which are not widely recognized as photosensitizing,^{1–5} have been associated with increased risk of lip cancer and SCC in some studies.^{14,20} To our knowledge, the present study is the first to examine cSCC risk associated with use of alpha blockers and central agonists. A recent meta-analysis of observational studies examining use of ADs and risk of keratinocyte carcinoma found that diuretics are associated with increased SCC risk, while ACE inhibitors and ARBs are associated with decreased SCC risk in high-risk individuals, and CCBs and beta-blockers are not associated with SCC risk.²⁷

The chemical structures of photosensitizing drugs permit the absorption of UVR,^{8–10} the primary risk factor for SCC.²⁸ They promote sunburn and may be carcinogenic by triggering phototoxic or photoallergic reactions.⁸ These effects in turn may induce DNA damage and chronic inflammation. Observed differences in cSCC risk among various photosensitizing drugs may be due to differences in their biological effects, as well as differences in study design.

Strengths of this study include its conduct in a comprehensive health care system with unified electronic patient records which allowed ascertainment of physicians' diagnosis of hypertension, pathological verification of the diagnosis of cSCC, and documentation of dispensing of the pharmaceutical drugs studied, thus eliminating the possibility of patients' recall bias. We could also document and attempt to account for health care utilization as possibly influencing our findings.

However, the main associations that we observed, although statistically significant, were quite small in magnitude and could have been affected by the study's limitations. Although we adjusted for several baseline characteristics, residual confounding could have affected our findings. We were unable to adjust for sun exposure but could ascertain and control for prior AKs, which may be viewed as sun-exposure-related risk factors for cSCC. Although drug related acute adverse reactions to sunlight could influence the choice of ADs or lead to switching them, it seems unlikely that this would have a major effect on our findings or that differences in sun exposure, would be generally related to which ADs are prescribed. While our use of prescriptions filled at KPNC pharmacies as a surrogate for medication use could have led to exposure misclassification, it is unlikely that those with pharmacy benefits would have filled their prescriptions elsewhere. There was considerable overlap between the treatment groups, and concurrent use of ADs from multiple different classes after cohort entry may have influenced the cSCC risk observed in each treatment group.

In conclusion, we observed a modest association between increasing exposure to photosensitizing ADs and increasing risk of cSCC. Additional studies, including those that control for potential confounding factors, such as sun exposure, are needed to confirm our findings and further evaluate risk associated with specific drug classes. In the meantime,

patients taking photosensitizing ADs may benefit from education on safe sun practices and closer screening for cSCC given the potential public health implications associated with widespread use of these common medications.

Acknowledgments

Funding: This study was supported by grants from the National Institutes of Health (R01 CA166672 and K24 AR069760 to MA and R01 CA098838 to LH).

Dr. Asgari has received research funding to her institution from Pfizer Inc. and Valeant Pharmaceuticals, but these associations are unrelated to and not affecting the present study.

References

1. Levine JJ. Medications that Increase Sensitivity to Light: A 1990 Listing. US Department of Health and Human Services; 1990.
2. Drucker AM, Rosen CF. Drug-induced photosensitivity: culprit drugs, management and prevention. *Drug Saf.* 2011; 34:821–837. [PubMed: 21879777]
3. Frishman WH, Brosnan BD, Grossman M, Dasgupta D, Sun ADK. Adverse dermatologic effects of cardiovascular drug therapy: part I. *Cardiol Rev.* 2002; 10:230–246. [PubMed: 12144734]
4. Quintero B, Miranda MA. Mechanisms of photosensitization induced by drugs: A general survey. *Ars Pharm.* 2000; 41:27–46.
5. Elias J, Fernandez G. Guidance on minimising photosensitivity / phototoxicity reactions between medication and sunlight. Sussex Partnership, NHS Foundation Trust; 2016.
6. Gould JW, Mercurio MG, Elmetts CA. Cutaneous photosensitivity diseases induced by exogenous agents. *J Am Acad Dermatol.* 1995; 33:551–573. quiz 574–576. [PubMed: 7673488]
7. Moore DE. Drug-induced cutaneous photosensitivity: incidence, mechanism, prevention and management. *Drug Saf.* 2002; 25:345–372. [PubMed: 12020173]
8. Zuba EB, Koronowska S, Osmola-Ma kowska A, Jenerowicz D. Drug-induced Photosensitivity. *Acta Dermatovenerol Croat.* 2016; 24:55–64. [PubMed: 27149132]
9. US Department of Health and Human Services. S10 Photosafety Evaluation of Pharmaceuticals: Guidance for Industry. 2015
10. O’Gorman SM, Murphy GM. Photosensitizing medications and photocarcinogenesis. *Photodermatol Photoimmunol Photomed.* 2014; 30:8–14. [PubMed: 24393207]
11. Elinav E, Nowarski R, Thaïss CA, Hu B, Jin C, Flavell RA. Inflammation-induced cancer: crosstalk between tumours, immune cells and microorganisms. *Nat Rev Cancer.* 2013; 13:759–771. [PubMed: 24154716]
12. Stern RS. Photocarcinogenicity of drugs. *Toxicol Lett.* 1998; 102–103:389–392.
13. Rogers HW, Weinstock MA, Harris AR, Hinckley MR, Feldman SR, Fleischer AB, et al. Incidence estimate of nonmelanoma skin cancer in the United States, 2006. *Arch Dermatol.* 2010; 146:283–287. [PubMed: 20231499]
14. Friedman GD, Asgari MM, Warton EM, Chan J, Habel LA. Antihypertensive drugs and lip cancer in non-Hispanic whites. *Arch Intern Med.* 2012; 172:1246–1251. [PubMed: 22869299]
15. 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; doi: 10.1111/joim.12629
16. Arnspang S, Gaist D, Johannesdottir Schmidt SA, Hölmich LR, Friis S, Pottegård A. Hydrochlorothiazide use and risk of non-melanoma skin cancer: A nationwide case-control study from Denmark. *J Am Acad Dermatol.* 2017; doi: 10.1016/j.jaad.2017.11.042
17. Christian JB, Lapane KL, Hume AL, Eaton CB, Weinstock MA. VATTC Trial. 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. [PubMed: 18728281]

18. 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(Suppl 2):1–13.
19. Jensen AØ, Thomsen HF, Engebjerg MC, Olesen AB, Sørensen 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. [PubMed: 18813314]
20. 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. [PubMed: 20861398]
21. 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. [PubMed: 20497756]
22. Nardone B, Majewski S, Kim AS, Kiguradze T, Martinez-Escala EM, Friedland R, et al. Melanoma and Non-Melanoma Skin Cancer Associated with Angiotensin-Converting-Enzyme Inhibitors, Angiotensin-Receptor Blockers and Thiazides: A Matched Cohort Study. *Drug Saf*. 2017; 40:249–255. [PubMed: 27943160]
23. Robinson SN, Zens MS, Perry AE, Spencer SK, Duell EJ, Karagas MR. Photosensitizing agents and the risk of non-melanoma skin cancer: a population-based case-control study. *J Invest Dermatol*. 2013; 133:1950–1955. [PubMed: 23344461]
24. Schmidt SAJ, Schmidt M, Mehnert F, Lemeshow S, Sørensen HT. Use of antihypertensive drugs and risk of skin cancer. *J Eur Acad Dermatol Venereol*. 2015; 29:1545–1554. [PubMed: 25640031]
25. Asgari MM, Wang W, Ioannidis NM, Itnyre J, Hoffmann T, Jorgenson E, et al. Identification of Susceptibility Loci for Cutaneous Squamous Cell Carcinoma. *J Invest Dermatol*. 2016; 136:930–937. [PubMed: 26829030]
26. Charlson ME, Charlson RE, Peterson JC, Marinopoulos SS, Briggs WM, Hollenberg JP. The Charlson comorbidity index is adapted to predict costs of chronic disease in primary care patients. *J Clin Epidemiol*. 2008; 61:1234–1240. [PubMed: 18619805]
27. 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; doi: 10.1002/pds.4384
28. Madan V, Lear JT, Szeimies R-M. Non-melanoma skin cancer. *Lancet Lond Engl*. 2010; 375:673–685.

Bulleted Statements**What's already known about this topic?**

- Certain antihypertensive drugs (ADs) are photosensitizing, heightening reactivity of the skin to sunlight.
- Photosensitizing ADs may act as carcinogens by triggering phototoxic reactions, which cause acute DNA damage, or photoallergic reactions, which produce chronic inflammation.
- Photosensitizing ADs have been associated with lip cancer, but whether they impact cutaneous squamous cell carcinoma (cSCC) risk is unclear.

What does this study add?

- This large cohort study of members of a managed care population with hypertension examined the association between AD use and cSCC risk.
- This study suggests that use of photosensitizing ADs is associated with a 17% higher risk of cSCC compared with non-use of ADs.
- These results suggest that patients taking photosensitizing ADs may benefit from education on safe sun practices and closer screening for cSCC.

Table 1

Baseline characteristics of RPGEH cohort with hypertension (n=28,357)

Characteristics	Treatment Group ^a				
	Overall (n=28,357)	Photosensitizing ADs (n=17,946) ^b	Non- photosensitizing ADs (n=19,092) ^b	Unknown photosensitizing ADs (n=17,345) ^b	Non-use of ADs (n=1,530)
Age (at cohort entry): Mean (±SD)	69.1 (10.6)	69.3 (10.4)	69.9 (10.2)	70.1 (10.2)	67.9 (12.7)
Sex, n (%)					
Male	12,382 (43.7)	7,268 (40.5)	8,952 (46.9)	8,193 (47.2)	652 (42.6)
Female	15,975 (56.3)	10,678 (59.5)	10,140 (53.1)	9,152 (52.8)	878 (57.4)
Cigarette use, n (%)					
Current	2,219 (7.8)	1,397 (7.8)	1,475 (7.7)	1,379 (8.0)	122 (8.0)
Former	13,247 (46.7)	8,408 (46.9)	9,292 (48.7)	8,386 (48.4)	682 (44.6)
Never	12,217 (43.1)	7,737 (43.1)	7,912 (41.4)	7,177 (41.4)	663 (43.3)
Unknown	674 (2.4)	404 (2.3)	413 (2.2)	403 (2.3)	63 (4.1)
Charlson Comorbidity Index, n (%)					
0	12,870 (45.4)	8,175 (45.6)	8,040 (42.1)	6,857 (39.5)	789 (51.6)
1-2	11,600 (40.9)	7,100 (39.6)	8,011 (42.0)	7,539 (43.5)	581 (38.0)
3	3,887 (13.7)	2,671 (14.9)	3,041 (15.9)	2,949 (17.0)	160 (10.5)
Healthcare utilization: Mean (±SD) ^c	10.8 (8.7)	10.9 (8.8)	11.2 (8.6)	11.3 (9.0)	11.2 (9.1)
Surveillance measure: Mean (±SD) ^d	0.6 (2.1)	0.7 (2.3)	0.6 (2.0)	0.6 (2.2)	0.8 (1.8)
Length of health plan membership: Mean (±SD)	9.8 (1.7)	9.8 (1.7)	9.8 (1.7)	9.8 (1.7)	9.9 (1.6)
Survey year, n (%)					
2002	831 (2.9)	571 (3.2)	656 (3.4)	629 (3.6)	15 (1.0)
2003	1,203 (4.2)	782 (4.4)	958 (5.0)	895 (5.2)	27 (1.8)
2007	22,286 (78.6)	14,169 (79.0)	14,867 (77.9)	13,418 (77.4)	1,235 (80.7)
2008	3,719 (13.1)	2,248 (12.5)	2,419 (12.7)	2,222 (12.8)	226 (14.8)
2009	318 (1.1)	176 (1.0)	192 (1.0)	181 (1.0)	27 (1.8)
Prior cutaneous squamous cell carcinoma, n (%) ^e					

Characteristics	Treatment Group ^a				
	Overall (n=28,357)	Ever use of			Non-use of ADs (n=1,530)
		Photosensitizing ADs (n=17,946) ^b	Non- photosensitizing ADs (n=19,092) ^b	Unknown photosensitizing ADs (n=17,345) ^b	
Yes	2,228 (7.9)	1,329 (7.4)	1,487 (7.8)	1,352 (7.8)	217 (14.2)
No	26,129 (92.1)	16,617 (92.6)	17,605 (92.2)	15,993 (92.2)	1,313 (85.8)
Prior actinic keratosis, n (%)^f					
Yes	9,972 (35.2)	6,181 (34.4)	6,844 (35.9)	6,161 (35.5)	614 (40.1)
No	18,385 (64.8)	11,765 (65.6)	12,248 (64.2)	11,184 (64.5)	916 (59.9)
Prior photosensitizing AD use, n (%)^g					
Yes	20,994 (74.0)	16,189 (90.2)	14,244 (74.6)	12,921 (74.5)	791 (51.7)
No	7,363 (26.0)	1,757 (9.8)	4,848 (25.4)	4,424 (25.5)	739 (48.3)

^a. Patients were divided into treatment groups based on antihypertensive drug (AD) use after cohort entry.

^b. Treatment groups are not mutually exclusive. Patients may contribute to multiple treatment groups due to receipt of prescriptions for more than one AD. Therefore, counts do not sum to overall.

^c. Healthcare utilization was the average annual number of emergency department and outpatient visits in the 5 years prior to cohort entry.

^d. Surveillance measure was the average annual number of dermatology visits in the 5 years prior to cohort entry.

^e. Prior cutaneous squamous cell carcinoma was determined by review of electronic pathology records.

^f. Prior actinic keratosis was determined based on ICD-9 codes.

^g. Prior photosensitizing AD use was determined based on pharmacy records between 1997 and cohort entry.

Table 2

Hazard ratios for cutaneous squamous cell carcinoma in RPGEH cohort with hypertension

Treatment Group ^a	cSCC cases, n (%)	Person-years of follow-up	Unadjusted HR (95% CI)	Adjusted HR (95% CI) ^b
Overall (n=28,357)	3,010 (100)	144,215		
Non-use of ADs after cohort entry (n=1,530)	371 (12.3)	19,222	1.00 (Reference)	1.00 (Reference)
Ever use of photosensitizing ADs after cohort entry (n=17,946) ^c	1,720 (57.1)	76,881	1.21 (1.12, 1.31)	1.17 (1.07, 1.28)
Loop diuretics (n=4,118)	403 (13.4)	12,581	1.47 (1.31, 1.65)	1.10 (0.98, 1.24)
Potassium-sparing diuretics (n=618)	63 (2.1)	1,872	1.36 (1.05, 1.77)	1.24 (0.96, 1.61)
Thiazide diuretics (n=10,449)	935 (31.1)	44,876	1.05 (0.97, 1.14)	1.09 (0.99, 1.19)
Combination thiazide diuretics (n=6,265)	579 (19.2)	26,313	1.20 (1.09, 1.32)	1.32 (1.19, 1.46)
Alpha-2 receptor agonists (n=61)	7 (0.2)	224	1.32 (0.63, 2.77)	1.30 (0.62, 2.74)
Ever use of non-photosensitizing ADs after cohort entry (n=19,092) ^c	1,862 (61.9)	83,414	1.23 (1.14, 1.33)	0.99 (0.91, 1.07)
Alpha-blockers (n=3,579)	450 (15.0)	14,735	1.50 (1.35, 1.66)	0.93 (0.83, 1.03)
Beta-blockers (n=15,792)	1,520 (50.5)	68,396	1.11 (1.03, 1.20)	1.04 (0.96, 1.12)
Central agonists (n=902)	80 (2.7)	3,427	0.91 (0.72, 1.14)	1.07 (0.85, 1.34)
Angiotensin receptor blockers (n=5,251)	426 (14.2)	19,877	1.00 (0.89, 1.11)	0.97 (0.87, 1.08)
Ever use of unknown photosensitizing ADs after cohort entry (n=17,345) ^c	1,717 (57.0)	73,300	1.35 (1.25, 1.46)	1.11 (1.02, 1.20)
Angiotensin converting enzyme inhibitors (n=11,658)	1,140 (37.9)	50,299	1.14 (1.05, 1.24)	1.10 (1.01, 1.19)
Calcium channel blockers (n=9,383)	924 (30.7)	36,483	1.25 (1.15, 1.35)	1.06 (0.98, 1.15)
Vasodilators (n=869)	75 (2.5)	2,562	1.07 (0.84, 1.35)	0.96 (0.76, 1.21)
Other combinations (n=1,161)	78 (2.6)	3,018	0.98 (0.78, 1.24)	0.81 (0.64, 1.03)

^a. Patients were divided into treatment groups based on antihypertensive drug (AD) use after cohort entry.

^b. Adjusted for age, sex, smoking, comorbidities, history of cutaneous squamous cell carcinoma and actinic keratosis, survey year, healthcare utilization, surveillance measure, length of health plan membership, and prior history of photosensitizing AD use.

^c. Treatment groups are not mutually exclusive. Patients may contribute to multiple treatment groups due to receipt of prescriptions for more than one AD. Therefore, counts do not sum to overall.

Table 3

Hazard ratios for cutaneous squamous cell carcinoma based on number of prescriptions for antihypertensive drugs filled

Treatment Group ^a	cSCC cases, n (%)	Person-years of follow-up	Unadjusted HR (95% CI)	Adjusted HR (95% CI) ^b
Non-use of ADs after cohort entry	371 (12.3)	19,222	1.00 (Reference)	1.00 (Reference)
Use of photosensitizing ADs after cohort entry				
1–7 fills	862 (28.6)	40,173	1.17 (1.06, 1.28)	1.12 (1.02, 1.24)
8–15 fills	610 (20.3)	27,071	1.21 (1.09, 1.35)	1.19 (1.06, 1.34)
16+ fills	248 (8.2)	9,637	1.42 (1.21, 1.66)	1.41 (1.20, 1.67)
Use of non-photosensitizing ADs after cohort entry				
1–7 fills	768 (25.5)	36,284	1.18 (1.07, 1.30)	0.99 (0.89, 1.09)
8–15 fills	625 (20.8)	27,326	1.27 (1.14, 1.41)	1.02 (0.92, 1.14)
16+ fills	469 (15.6)	19,804	1.30 (1.14, 1.47)	0.95 (0.83, 1.07)
Use of unknown photosensitizing ADs after cohort entry				
1–7 fills	782 (26.0)	34,182	1.33 (1.21, 1.46)	1.12 (1.02, 1.23)
8–15 fills	561 (18.6)	23,649	1.37 (1.23, 1.53)	1.12 (1.01, 1.25)
16+ fills	374 (12.4)	15,469	1.38 (1.21, 1.57)	1.06 (0.93, 1.21)

^a. Patients were divided into treatment groups based on antihypertensive drug (AD) use after cohort entry.

^b. Adjusted for age, sex, smoking, comorbidities, history of cutaneous squamous cell carcinoma and actinic keratosis, survey year, healthcare utilization, surveillance measure, length of health plan membership, and prior history of photosensitizing AD use.

Table 4

Selected subgroup analyses

Treatment Group	cSCC cases, n (%)	Person-years of follow-up	Unadjusted HR (95% CI)	Adjusted HR (95% CI) ^a
New Use of ADs After Cohort Entry				
Non-use of ADs before or after cohort entry (n=817)	35 (1.2)	2,878	1.00 (Reference)	1.00 (Reference)
New use of photosensitizing ADs after cohort entry (n=231)	11 (0.4)	845	1.14 (0.56, 2.28)	1.46 (0.70, 3.02)
New use of non-photosensitizing ADs after cohort entry (n=169)	5 (0.2)	609	0.61 (0.23, 1.60)	0.49 (0.19, 1.30)
New use of unknown photosensitizing ADs after cohort entry (n=203)	9 (0.3)	655	1.26 (0.60, 2.67)	0.92 (0.42, 2.00)
No Use of Photosensitizing ADs Before Cohort Entry				
Use of non-photosensitizing ADs during follow-up (n=4,848)	419 (13.9)	22,554	1.00 (Reference)	1.00 (Reference)
Use of photosensitizing ADs during follow-up (n=1,757)	120 (4.0)	6,213	1.11 (0.90,1.37)	1.20 (0.97,1.48)
Use of unknown photosensitizing ADs during follow-up (n=4,424)	390 (13.0)	20,310	1.26 (1.05,1.50)	1.16 (0.97,1.39)

^a. Adjusted for age, sex, smoking, comorbidities, history of cutaneous squamous cell carcinoma and actinic keratosis, survey year, healthcare utilization, surveillance measure, and length of health plan membership.