HHS Public Access

Author manuscript

J Invest Dermatol. Author manuscript; available in PMC 2014 February 01.

Published in final edited form as:

J Invest Dermatol. 2013 August ; 133(8): 1950–1955. doi:10.1038/jid.2013.33.

Photosensitizing Agents and the Risk of Non-Melanoma Skin Cancer: A Population-Based Case-Control Study

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Abstract

It is well-known that ultraviolet (UV) light exposure and a sun sensitive phenotype are risk factors for the development of non-melanoma skin cancer (NMSC), including basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). In this New Hampshire population-based case-control study, we collected data from 5,072 individuals, including histologically-confirmed cases of BCC and SCC, and controls via a personal interview to investigate possible associations between photosensitizing medication use and NMSC. After adjustment for potentially confounding factors (e.g. lifetime number of painful sunburns), we found a modest increase in risk of SCC (OR = 1.2, 95% CI = 1.0–1.4) and BCC (OR = 1.2, 95% CI = 0.9–1.5), in particular early-onset BCC, (≤ 50 years of age) (OR = 1.5, 95% CI = 1.1–2.1) associated with photosensitizing medication use. For SCC the association was strongest amongst those with tendency to sunburn rather than tan. We also specifically found associations with BCC, and especially early-onset BCC, and photosensitizing antimicrobials. In conclusion, certain commonly prescribed photosensitizing medications may enhance the risk of developing SCC, especially in individuals with a sun sensitive phenotype, and may increase the risk of developing BCC and incidence of BCC at a younger age.

INTRODUCTION

Non-melanoma skin cancer (NMSC), a designation that includes both basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), is the most common type of cancer in Caucasians. Despite its widespread occurrence, relatively little is known about the exact

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CONFLICTS OF INTEREST

The authors state no conflict of interest.

incidence of NMSC in the United States because the population-based cancer surveillance systems generally do not track NMSC. It is well known that ultraviolet (UV) light plays a key role in the development of NMSC. Particular medications that are described as "photosensitizing," including those with known ability to induce either a phototoxic or photoallergic reaction upon UV exposure, increase the vulnerability of the skin to UV-induced damage that can lead to the development of NMSC (Stern, 1998). Such medications belong to a variety of pharmacological classes by composition and are used for an array of diverse conditions ranging from treatment of acute bacterial infections to long-term hypertension control (Gould *et al.*, 1995; Bellaney *et al.*, 1996; Stern 1998; Epstein 1999). Photosensitizing medications, with few exceptions, have not been well-studied with regard to their long-term damage, such as the later risk of NMSC. Exceptions include the research regarding oral psoralen and UV-A light treatment for psoriasis, which was found to increase risk of SCC incidence (Stern *et al.*, 1998; Lindelöf *et al.*, 1999). More recently, two record linkage studies from Denmark and one prospective study from Rotterdam investigated the association between select photosensitizing medications (namely specific classes of diuretics, antimicrobials, and retinoids) and NMSC with inconsistent results (Jensen *et al.*, 2008; Kaae *et al.*, 2010; Ruiter *et al.*, 2010).

In our investigation, as part of the larger New Hampshire Health Study, we conducted a population-based case-control study that allowed us to obtain detailed information on major skin cancer risk factors along with history of photosensitizing drug usage to determine whether risks of BCC, SCC, early-onset BCC (diagnosed at ≤ 50 years of age), or multiple BCC relate to the use of photosensitizing medications. This current study extends our preliminary work based on the early phase of our study (Karagas *et al.* in 2007).

RESULTS

A total of 5,072 participants were eventually enrolled and interviewed, and responded to questions concerning tanning device use during the all phases of our study, including 1,906 controls and 1,567 BCC cases and 1,599 SCC cases. SCC cases were older than BCC cases, and slightly more were men (Table 1). Both BCC and SCC cases reported having greater skin sensitivity to the sun than did the controls and reported a greater number of lifetime painful sunburns compared to controls (Table 1). SCC cases had a higher amount of reported cumulative sun exposure history (Table 1). Tanning lamp use and medical ionizing radiation exposure also were more common in cases than controls (Table 1). The majority of skin tumors were located in the head and neck anatomic region (Table 1). Additionally, more than 75% of SCC cases had severe solar elastosis and more than 40% had evidence of actinic keratoses, in the skin adjacent to the tumor (Table 1).

We found a modest increase in risk of SCC (OR = 1.2, 95% CI = 1.0–1.4) and BCC (OR = 1.2, 95% CI = 0.9–1.5) related to use of photosensitizing medications, and a 50% greater risk of early-onset BCC (OR = 1.5, 95% CI = 1.1–2.1) (Table 2). Results were similar in the analysis further restricted to phototoxic medications (Table 2). For SCC, the association appeared to be largely among those with a sun sensitive phenotype (OR = 1.5; 95% CI 1.1–2.0 for those with a tendency to sunburn, and OR = 1.0; 95% CI = 0.8–1.3 for those with a tendency to tan). We did not observe this overall for BCC, but there was a tendency towards

a higher OR among those with a sun sensitive phenotype for multiple BCCs (OR = 1.7; 95% CI 1.0–3.0 for those with a tendency to sunburn, and OR = 1.2; 95% CI = 0.7–2.1 for those with a tendency to tan). We did not find evidence of modification of risk by other factors we examined (e.g., by study phase, gender, skin reaction to first summer sun exposure, history of sunburns, or anatomic site of the tumor) (data not shown).

We then examined types of photosensitizing medications. Ever use of photosensitizing antimicrobials was associated with increased risks of BCC (OR = 1.9, 95% CI = 1.3–2.8) and specifically early-onset BCC (OR = 2.1, 95% CI = 1.3–3.5) (Table 2). These associations were strongest with longer use, i.e., for use > 1 year of use for both BCC (OR = 1.9, 95% CI = 1.0–3.7) and early-onset BCC (OR = 2.0, 95% CI = 0.9–4.2). In a further division of the antimicrobials, the tetracycline class of antibiotics was associated BCC (OR = 1.8, 95% CI = 1.2–2.8) and specifically early-onset BCC (OR = 2.0, 95% CI = 1.2–3.4) (Table 2), with evidence of a higher risk with longer duration (p-value for trend based on continuous duration for BCC = 0.075, and for early-onset BCC = 0.03). The primary reason for treatment was acne and skin rashes and within this subgroup associations were present for BCC and early-onset BCC (BCC OR = 2.6, 95% CI = 1.6–4.2; early-onset BCC OR = 2.3, 95% CI = 1.4–3.9).

We found a modest association between SCC and CV medication use (OR = 1.3, 95% CI = 1.0–1.6) (Table 2) with evidence of a higher risk with longer duration of use (OR = 1.4, 95% CI = 1.0–1.8). Odds ratios of SCC were specifically increased for diuretics (OR = 1.3, 95% CI = 0.9–2.0), thiazide diuretics (OR = 1.3, 95% CI = 0.7–2.4), and non-diuretic CV medications (OR = 1.3, 95% CI = 1.0–1.7). No relation was found between CV medication use and the risk of BCC (OR = 0.8, 95% CI = 0.5–1.3) (Table 2).

DISCUSSION

Our study of the association between the use of photosensitizing agents and NMSC provides some evidence that commonly used photosensitizing medications may enhance risk of both SCC and BCC. For BCC, associations were strong for early-onset disease (≤50 years), and for SCC among those with a sun sensitive phenotype (e.g., tendency to sunburn).

While the literature is sparse, as in our study, a study from Denmark likewise found an association between use of tetracyclines and BCC (incidence rate ratio (IRR) = 1.3, 95% CI = 1.3–1.4) and additionally found a relation with SCC (IRR = 1.5, 95% CI = 1.4–1.7) (Kaae *et al.*, 2010) that we did not detect. The study based in Denmark involved linkage between cancer registry and national pharmacy data, which limited their ability to assess sun sensitivity or sun exposure as potentially confounding or modifying factors. One possible explanation for our finding of an association with BCC but not SCC is that tetracyclines are commonly used for acne treatment during the teenage years, a period when UV exposure has been related to an increased risk of BCC (Gallagher *et al., 1995*) whereas chronic UV exposure appears to more strongly relate to risk of SCC (Armstrong and Kricker, 2001). In our study, the majority of BCC cases and controls reported antimicrobial use for acne and other skin conditions, which raises the possibility that acne or another form of treatment for acne, such as ionizing radiation, may be confounding the association between tetracycline

use and BCC. While acne is not a risk factor for BCC to our knowledge, there are reported associations with psoriasis and atopic dermatitis (Frentz and Olsen, 1999; Olesen *et al.*, 2005). The possibility of confounding by ionizing radiation treatment used for treatment of acne is unlikely because its use was uncommon after 1960, and therefore would not have contributed much to the incidence of early-onset BCC. Further, adjustment for ionizing radiation therapy did not appreciably alter our results.

Another category we studied was photosensitizing CV medications. While prior studies have investigated this topic, the results have varied for the different medications. A recently published U.S. based case-control study found longer durations of use of thiazide diuretics to be associated with increased odds ratios for development of carcinoma of the lip (Friedman *et al.*, 2012). A case-control study in Denmark found that users of the diuretic therapy combination of amiloride and hydrochlorothiazide had an increased risk of SCC with an IRR of 1.79 (95% CI = 1.45–2.21), but did not find statistically significant results for other diuretics or BCC (Jensen *et al.*, 2008). When we restricted our analysis to thiazide diuretics (i.e. hydrochlorothiazide or hydrochlorothiazide combination medications), we found a similar modest association with SCC. A population-based follow-up study based in The Netherlands found an association between loop diuretics (e.g. furosemide, bumetanide) and BCC with a hazard ratio of 1.07 (95% CI = 1.01–1.13) (Ruiter *et al.*, 2010). Another population-based cohort study from Denmark found a significant association between methyldopa and BCC, and an association between furosemide and SCC (Kaae *et al.*, 2010). These findings, along with our own, raise the possibility of an enhanced NMSC risk with certain CV medications, specifically diuretics and namely thiazide diuretics that will need further confirmation.

A major limitation of our study is that we relied on self-reported medication use. The phrasing of questions differed between the early and late phases of the study that we were able to take into account by including a random effect term for study period. We did not detect any statistically significant differences between the odds ratios by study phase. For our main finding on BCC and antibiotic use for example, the odds ratio in the early phase was 1.96 (95% CI = 1.11–3.45) and for the later phase was 1.83 (95% CI = 1.01–3.32). However, it is possible that we missed photosensitizing drugs that were used but not reported by subjects, especially in the early phase when the question relied on the subject supplying the name of the medication rather than choosing from a predetermined list. This misclassification was likely non-differential and thus could have biased our results towards the null as differential misclassification would have resulted in an increased risk associated with other similar medications where we observed a reduced risk (e.g., with NSAIDS)(Torti *et al* 2011). Another bias inherent in this study design is selection bias from non-participation, although it is unlikely that those who chose not to participate were different in meaningful ways (e.g., in terms of photosensitizing drug use, and/or NMSC risk) for the purposes of this study. Controls were matched to cases on age and sex to represent the population from which the cases arose. Overall 97% of cases 65 years of age or older were enrolled in Medicare, and 96% of cases <65 years held a valid driver's license. Additionally, despite our detailed personal interview, we consider that there could be residual confounding from unmeasured factors contributing to the modest odds ratios we observed. We note

however that given the magnitude of the skin cancer problem worldwide, use of the photosensitizing agents causing even small increases in the relative risks of basal cell or squamous cell carcinomas could translate into an appreciable number of new cases of these malignancies.

One advantage to our approach is that it allowed us to evaluate several types of medications in a large group of BCC and SCC cases and controls. The study was population-based and we had an active surveillance system in place to ensure that we were informed of new cases during the study period. To our knowledge, there is limited prior research on these medications in relation to NMSC in the United States population. Additionally, the personal interview allowed for collection of demographic information as well as baseline sun sensitivity (i.e. propensity to tan or burn), cumulative lifetime sun exposure, indication for use, and prior radiation treatment, among others. As expected, we observed stronger associations among those with a sun sensitive phenotype for SCC and to a lesser extent multiple BCCs, which is consistent with a finding reported from the Rotterdam cohort study for BCC (Ruiter *et al*., 2010). As to why our findings were stronger for early-onset BCC is unclear, but may relate to the fact that antibiotics used to treat acne are taken at a young age. Further studies will need to evaluate this possibility.

In conclusion, we found evidence that use of certain photosensitizing medications may enhance risks of SCC and BCC in the United States population, particularly among individuals with a sun sensitive phenotype, and for BCC, those with a young age at onset.

MATERIALS AND METHODS

Study Group

The cases for our study were identified by obtaining records of SCC and BCC diagnoses from dermatology, dermatopathology, and pathology practices throughout the state of NH that were histologically confirmed. To be eligible, cases and controls needed to be residents of New Hampshire, speak English, have a listed telephone number, and between the ages of 25 and 74 at the time of diagnosis (or for controls a matched “reference date”). During all periods: July 1993 through June 1995, July 1997 through March 2000, July 2001 through June 2002, and July 2007 through June 2009, we selected all eligible cases of invasive SCC that met our inclusion criteria. A total of 4026 cases were contacted, of which 3242 (81%) took part, for a total of 1,637 cases of SCC and 1,605 cases of BCC. During the first period, we sampled an approximately two-to-one ratio of BCC to SCC, and in the second period approximately a one-to-one ratio of BCC to SCC. In the third period, we selected all cases diagnosed before the age of 51 years (‘early-onset’), or with multiple concomitant BCCs. Cases included NMSC diagnoses from all anatomic sites excluding genital cancers.

The control subjects for our study were frequency matched, to the combined distribution of NMSC cases, in each study period, on age and sex from population lists of New Hampshire residents ages 25 to 74 years of age. Controls younger than 65 years of age were chosen from a list of New Hampshire residents provided by the New Hampshire Department of Transportation, while controls older than 65 years of age were chosen from New Hampshire residents enrolled in the Center for Medicare and Medicaid Services. These control subjects

were selected to match our cases by age and sex stratification. A total of 2797 controls were contacted of which 1952 (70%) enrolled.

Interview

Written informed consent was obtained from each participant in accordance with Committee for the Protection of Human Subjects at Dartmouth College, Hanover, NH and the Declaration of Helsinki protocols. The personal interviews, which were usually conducted at the home of the subject, took place between February 1994 and June 2011. The interview included collection of information regarding skin sensitivity upon acute exposure to the sun (i.e., whether the respondent's skin would tan or burn after first exposure to the sun in summer for one hour), lifetime number of painful or blistering sunburns, lifetime sun exposure (during warm months between 9am and 5pm, as well as during cool months), history of treatment involving radiation, and ever use of a tanning device. The interviewers were not aware of the case-control status of participants.

Determination of drug usage

During the first two recruitment periods (the "early phase"), we asked whether participants had used any medications that made their skin unusually sensitive to the sun. We then asked them to name the medication, the reason for use and duration of use. From this information, we coded any drugs that are known to have photosensitizing properties, based on a list compiled from a search of the literature (Gould *et al.*, 1995; Bellaney *et al.*, 1996; Stern 1998; Epstein 1999). After exclusion of the drugs without photosensitizing properties and the few that were not recognizable as drug names, we restricted the data to include only drugs used for duration of one month or longer.

During the last two recruitment periods (the "late phase") drug usage information was collected based on selection of medications by the participant from a prompted list of known photosensitizing medications, as well as other medications by category such as antibiotic, heart medication (e.g., anti-hypertensives), anti-anxiety medication, retinoid, chemotherapeutic, and pain mediation (e.g., NSAIDs). We restricted the duration of use of the drug to a minimum of 6 months and there was a minimum frequency of use of 4 times per week. Table 3 presents a summary of the frequency of use of reported medications across the entire study population.

Statistical analysis

We computed ORs and their 95% confidence intervals for all SCC, BCC, early onset BCC and multiple BCC case groups for the studied drugs using logistic regression with those who responded that they did not ever use the photosensitizing medications as the reference category. To adjust for potentially confounding factors, skin response first hour of sun exposure in summer (tan or mild burn followed by a tan, painful burn or burn with blistering), lifelong cumulative number of hours of sun exposure (≤ median hours exposure, > median hours exposure), tanning device use, radiation treatment for conditions other than skin cancer, anatomic site, the histologic presence of actinic keratosis (SCC only) and the histologic presence of solar elastosis were all included in preliminary models. But the inclusion of these variables did not appreciably influence our results and therefore were not

included in our final models. Subjects with missing covariates were omitted from the multivariate analysis. All final model risk estimates were adjusted by age, sex, and number of previous painful sunburns (none, 1–2, 3–15, and >15). Because of differences in the questionnaires between the early phase (1993–2000) and late phase (2001–2009), we included study phase as a random strata effect in all of our models (Derr 2000; Kuss 2002). We assessed the potential modifying effects of sex, study phase and UV-related factors (e.g., skin sensitivity to the sun exposure in summer and by lifetime number of painful sunburns), we computed odds ratios stratified by these factors.

We also examined duration of photosensitizing medication use (classified into non-users, > 1 month and < 7 years and ≥ 7 years overall, and non-user, < 1 year of use, > 1 year of use for specific mediations). Tests for trend were performed by modeling duration as a continuous variable in months of medication use (p-for trend continuous).

Pharmacological class was used to evaluate conditions for which drugs were being use. Additionally we analyzed specific conditions for which antimicrobials were use. Self-reported conditions were categorized into: 1) acne and other skin rashes, 2) non-skin infections and 3) arthritis (both rheumatoid and not otherwise specified) allowing analysis of photosensitizing medication risk in these subgroups of antibiotic condition. In addition to evaluating subgroups of tumors separately (SCC, BCC, and for BCC early-onset and BCC multiple tumors), we further analyzed subgroups of tumors according to presence or absence of actinic keratosis (SCC only), and the presence or absence of solar elastosis in the adjacent skin, as well as the anatomic site of the skin lesions. The statistical package SAS v9.2 was used for all the analyses.

Acknowledgments

We are indebted to the dermatologists comprising the New Hampshire Skin Cancer Study Group, the New Hampshire Dermatological Society, and the study staff and participants of the New Hampshire Health Study. This study was funded by Grant CA057494 of the National Cancer Institute, National Institutes of Health.

Abbreviations

NMSC	non-melanoma skin cancer
SCC	squamous cell carcinoma
BCC	basal cell carcinoma
UV	ultraviolet
OR	odds ratio
CI	confidence interval
CV	cardiovascular
IRR	incidence rate ratio

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Table 1

Demographics

	Controls N(%)	SCC[1] N(%)	BCC[2] N(%)
Phases			
Early (1993–2000)	1043 (54.7)	847 (53.0)	1110 (70.8)
Late (2001–2009)	863 (45.3)	752 (47.0)	457 (29.2)
Total	1906	1599	1567
Age			
< 40	155 (8.1)	19 (1.2)	184 (11.7)
41–50	319 (16.7)	114 (7.1)	489 (31.2)
51–60	362 (19.0)	346 (21.6)	297 (19.0)
61–70	728 (38.2)	705 (44.1)	413 (26.4)
70 +	342 (17.9)	415 (26.0)	184 (11.7)
Gender			
male	1078 (56.6)	987 (61.7)	794 (50.7)
female	828 (43.4)	612 (38.3)	773 (49.3)
Skin reaction to first hour of sun in summer			
tan	1274 (67.2)	908 (57.3)	838 (54.0)
burn	621 (32.8)	676 (42.7)	713 (46.0)
Lifetime warm month hours sun exposure 9am–5pm			
≤ 15676	887 (51.5)	597 (40.6)	896 (61.2)
> 15676	836 (48.5)	874 (59.4)	568 (38.8)
Lifetime number of painful sunburns			
0	556 (31.6)	362 (24.3)	369 (25.3)
1–2	451 (25.6)	299 (20.1)	278 (19.1)
3–15	399 (22.6)	369 (24.7)	342 (23.5)
≥ 16	356 (20.2)	461 (30.9)	468 (32.1)
Tanning lamp use			
never	1471 (79.9)	1190 (76.3)	1066 (70.3)
ever	369 (20.1)	370 (23.7)	450 (29.7)
Radiation treatment			
never	1751 (94.4)	1390 (89.9)	1422 (91.9)
ever	104 (5.6)	157 (10.1)	126 (8.1)
Anatomic site[3]			
Head/neck only		871 (56.5)	888 (59.0)
Other sites only		671 (43.5)	618 (41.0)
Solar elastosis			
absent		6 (0.7)	5 (0.8)
minimal		39 (4.5)	80 (12.2)
moderate		162 (18.6)	165 (25.1)
severe		665 (76.3)	407 (61.9)

	Controls N(%)	SCC[1] N(%)	BCC[2] N(%)
Actinic keratoses			
absent		564 (58.9)	
present		394 (41.1)	

Abbreviations SCC, Squamous cell carcinoma; BCC; Basal cell carcinoma.

[1] SCC cases and controls from study phases 1 through 4.

[2] BCC cases and controls from study phases 1 through 3.

[3] Anatomic site variables exclude 64 SCC cases with SCC to multiple sites.

[4] Variables with unknown values include skin reaction to the first hour of sun exposure in the summer (11 SCC controls and 15 SCC cases, 11 BCC controls and 16 BCC cases), painful sunburns (144 SCC controls and 108 SCC cases, 127 BCC controls and 110 BCC cases), radiation treatment (51 SCC controls and 52 SCC cases, 15 BCC controls, 19 BCC cases), hours sun exposure in warm months (183 SCC controls and 128 SCC cases, 141 BCC controls and 103 BCC cases), tanning lamp use (66 SCC controls and 39 SCC cases, 65 BCC controls and 51 BCC cases).

Table 2

Odds ratios

	Controls N (%)	SCC Cases N (%)	OR[1] (95% CI)	Controls N (%)	BCC Cases N (%)	OR[1] (95% CI)	Controls N (%)	Early-onset BCC Cases N (%)	OR[1] (95% CI)	Controls N (%)	Multiple BCC Cases N (%)	OR[1] (95% CI)
Photosensitizing medications												
No use	1385 (72.7)	1062 (66.5)	1.0 (ref)	1256 (85.2)	1303 (83.2)	1.0 (ref)	760 (87.8)	514 (76.4)	1.0 (ref)	1256 (85.2)	181 (71.2)	1.0 (ref)
Ever use	521 (27.3)	536 (33.5)	1.2 (1.0–1.4)	219 (14.8)	264 (16.8)	1.2 (0.9–1.5)	106 (12.2)	159 (23.6)	1.5 (1.1–2.1)	219 (14.8)	74 (28.8)	1.4 (1.0–2.1)
Phototoxic medications												
No use	1385 (75.8)	1062 (69.9)	1.0 (ref)	1256 (87.8)	1303 (86.1)	1.0 (ref)	760 (90.0)	514 (79.3)	1.0 (ref)	1256 (87.8)	181 (754)	1.0 (ref)
Ever use	441 (24.2)	458 (30.1)	1.1 (0.9–1.4)	174 (12.2)	211 (13.9)	1.1 (0.9–1.5)	84 (10.0)	134 (20.7)	1.5 (1.1–2.1)	174 (12.2)	59 (24.6)	1.4 (0.9–2.1)
Antimicrobial medications												
No use	1385 (96.0)	1062 (95.2)	1.0 (ref)	1256 (97.1)	1303 (93.5)	1.0 (ref)	760 (96.3)	514 (88.5)	1.0 (ref)	1256 (97.1)	181 (94.3)	1.0 (ref)
Ever use	57 (4.0)	54 (4.8)	1.4 (0.9–2.1)	38 (2.9)	90 (6.5)	1.9 (1.3–2.8)	29 (3.7)	67 (11.5)	2.1 (1.3–3.5)	38 (2.9)	11 (5.7)	1.6 (0.7–3.5)
Tetracyclines												
No use	1385 (97.0)	1062 (97.3)	1.0 (ref)	1256 (97.5)	1303 (94.4)	1.0 (ref)	760 (96.8)	514 (89.5)	1.0 (ref)	1256 (97.5)	181 (96.3)	1.0 (ref)
Ever use	43 (3.0)	29 (2.7)	1.0 (0.6–1.7)	32 (2.5)	77 (5.6)	1.8 (1.2–2.8)	25 (3.2)	60 (10.5)	2.0 (1.2–3.4)	32 (2.5)	7 (3.7)	1.2 (0.5–2.9)
Cardiovascular medications												
No use	1385 (87.7)	1062 (81.0)	1.0 (ref)	1256 (96.2)	1303 (96.9)	1.0 (ref)	760 (97.9)	514 (96.4)	1.0 (ref)	1256 (96.2)	181 (91.9)	1.0 (ref)
Ever use	195 (12.3)	249 (19.0)	1.3 (1.0–1.6)	49 (3.8)	41 (3.1)	0.8 (0.5–1.3)	16 (2.1)	19 (3.6)	1.7 (0.8–3.6)	49 (3.8)	16 (8.1)	1.2 (0.6–2.3)

[1]Adjusted by 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.

Table 3

Frequency of use of photosensitizing medications for total study population listed by pharmacological class.

Drug type	Frequency
Antimicrobials	
Tetracyclines (e.g. tetracycline, doxycycline)[2]	123
Sulfonamide antibiotics (e.g. trimethoprim/sulfamethoxazole)[2]	47
Fluroquinolones (e.g. ciprofloxacin)[2]	7
Cardiovascular	
Antihypertensives	
Thiazides (e.g. hydrochlorothiazide, including combination medication such as hydrochlorothiazide/triamterene)[2]	239
Loop diuretics (e.g. furosemide)[2]	46
Calcium channel blockers (e.g. diltiazem[2], nifedipine)	44
Potassium-sparing diuretics (e.g. triamterene)	29
Alpha-adrenergic agonists (e.g. methyldopa)	3
Other	
Antiarrhythmics (e.g. amiodarone, quinidine)[2]	11
Sulfonylureas (e.g. glipizide, glyburide)	3
Chemotherapeutics	
Antimetabolite (e.g. methotrexate)[2]	8
Antiestrogen (e.g. tamoxifen)[2]	6
Nonsteroidal anti-inflammatory drugs (NSAIDs)	
Salicylic acid derivatives (e.g. acetylsalicylic acid)[2]	623
Proprionic acid derivatives (e.g. ibuprofen, naproxen)[2]	432
Acetic acid derivatives (e.g. nabumetone)[2]	4
Enolic acid derivatives (e.g. piroxicam)	4
Psychiatric medications	
Benzodiazepines (e.g. alprazolam, diazepam)	112

Drug type	Frequency
Tricyclic antidepressants (e.g. amitriptyline)	13
Retinoids	
Topical (e.g. tretinoin)[2]	72
Oral (e.g. isotretinoin)[2]	12

[1] Photosensitizing medications were not listed in this table if only 1 or fewer usages.

[2] In addition to being photosensitizing, these drugs are also classified as having phototoxic effects.