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Research Article

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Photosensitizing Medication Use and Risk of Skin Cancer

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Abstract

Background: Many commonly used medications, including both medications for long-term (daily) use and short-term use (treatment courses of finite duration), have photosensitizing properties. Whether use of these medications affects skin cancer risk, however, is unclear.

Methods: Using a cohort of all Danish residents ≥15 years old in 1995 to 2006 (n = 4,761,749) and information from Danish national registers, we examined associations between use of photosensitizing medications and risk of basal cell carcinoma, cutaneous malignant melanoma, Merkel cell carcinoma, and squamous cell carcinoma.

Results: Users of only 2 of 19 medications for long-term use (methyldopa and furosemide) had both a ≥20% increased risk of skin cancer (compared with nonusers) and an increase in risk with increasing duration of use; these effects were limited to basal cell carcinoma and squamous cell carcinoma, respectively. In contrast, 8 of 10 medications for short-term use were associated with both a ≥20% increased risk of skin cancer and an increase in risk with increasing use for at least one of the four cancers.

Conclusion: We found little evidence of an increased risk of skin cancer among users of photosensitizing medications for long-term daily use, but could not rule out the possibility that users of some photosensitizing medications for short-term use may have an increased risk of skin cancer.

Impact: Previous studies have been limited to specific medication types (e.g., antidiuretics). Our study examined the effect of a wide range of photosensitizing medications on skin cancer risk and suggests that future work should focus on photosensitizing medications for short-term use. *Cancer Epidemiol Biomarkers Prev; 19(11); 2942–9. ©2010 AACR.*

Introduction

Many drugs, including psoralens, tetracyclines, fluoroquinolones, nonsteroidal anti-inflammatory agents, and amiodarone, are known to have photosensitizing properties (1-6). There is evidence that photosensitization of the skin followed by exposure to UV radiation (UVR) enhances the risk of sunburns and photo damage to the skin, which might increase the risk of skin cancer (2, 5). Drug-induced photosensitivity causing skin reactions and the subsequent development of skin cancer has been observed in psoriasis patients treated with psoralens in combination with UV light A (PUVA); PUVA therapy increases the risk of squamous cell carcinoma (SCC; refs. 2, 7, 8) and cutaneous malignant melanoma (CMM) (9). Furthermore, photosensitizing diuretics have been shown to increase the risk of skin malignancies in humans (4), and fluoroquinolone antibiotics have been shown to induce skin lesions (5), SCCs in particular, in mice exposed to UVR (10).

Despite the frequency with which photosensitizing medications are used (prevalence of use in the Danish population, 2006: <0.01-6.1%, depending on the medication—see Appendix; ref. 11) and their potential to increase the risk of UVR-related skin cancers, very few epidemiologic studies have addressed the question of a possible association of photosensitizing medication use with skin cancer (4, 12-14), and the results of these studies have often been equivocal. Furthermore, skin cancers are not a single entity but different diseases with different sun exposure–related risk factors; for example, early, intermittent overexposure to the sun is thought to be most important for the development of CMM and basal cell carcinoma (BCC; refs. 15-17), whereas cumulative sun exposure is thought to be more relevant to SCC (18). Consequently, the skin cancers should be considered individually, rather than as a group (as has been done in some previous studies), because we might reasonably expect to see associations between photosensitizing medications and some forms of skin cancer but not others.

We conducted a large population-based cohort study to determine whether (*a*) any use of photosensitizing medications (medications for long- and short-term use considered in two separate groups) increases the risk of BCC, CMM, Merkel cell carcinoma (MCC), and/or SCC,

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with a dose-response relationship required over and above a positive effect of any use (versus no use) as evidence of a possible causal relationship, and (*b*) use of specific photosensitizing medications increases the risk of BCC, CMM, MCC, and/or SCC.

Materials and Methods

Danish Civil Registration System

All residents in Denmark are registered in the Civil Registration System (CRS), a computerized national civil register established in 1968 (19). The CRS records demographic information on all individuals, and updates vital status, emigration, or disappearance from Denmark on a daily basis. The CRS and the personal identification number assigned to each Danish resident permit virtually complete follow-up of study subjects living in Denmark, as well as linkage of information from Denmark's population-based health registers.

Identification of cancer cases

The Danish Cancer Register is considered close to complete for incident cases of malignant neoplasm diagnosed in Denmark since 1943 (20). Physicians in hospitals and outpatient settings report cancer cases, along with primary site and stage, to the Cancer Register at the time of diagnosis. Information is also received when a patient first receives treatment. In addition, both pathology and forensic medicine departments report cancer information to the register. All cancer-specific autopsy information is registered, regardless of whether the deceased was known to have cancer or the cancer was first noted at autopsy. Finally, information from the Danish Hospital Discharge Register and the Danish Causes of Death Register is added annually.

All incident skin cancer cases registered in the Cancer Register with International Classification of Diseases, 10th revision, codes C43 and C44 from 1995 until the end of 2006 were identified. The skin cancers were then categorized based on WHO histology codes, as follows: BCC (C44, histology codes 80903-80933), CMM (C43), MCC (C44, histology code 82473), and SCC (C44, histology codes 80513-80523, 80703-80763, 80943, or 85603).

Information on photosensitizing medications

The medications included in this study were selected based on a list on photosensitizing medications taken from Litt's Drug Eruption Reference Manual (pp. 480-2; ref. 21). These medications are listed by therapeutic class and generic name, with the corresponding Anatomical Therapeutic Chemical codes, in the Appendix.

Information on the use of photosensitizing medications in cohort members was obtained from the Danish Register of Medicinal Product Statistics. This register was established in 1995 and contains individual-level information on all prescriptions filled at nonhospital pharmacies in Denmark. Each record contains the date of purchase, the pharmacy, the prescriber, and an account of the medication purchased, including brand name, dose, and amount of medication purchased. Use of the CRS personal identification number enables the compilation of longitudinal medication histories and the linkage of prescription data to information from other Danish population-based registers. The register is considered close to complete for prescriptions reimbursed by the state (22). With the exception of ibuprofen in 200-mg packages, all of the photosensitizing medications listed in Appendix 1 are reimbursable prescription medications in Denmark.

Statistical methods

Using the CRS, we constructed a cohort of all persons born in Denmark and resident there at some point during the period 1995 to 2006. Follow-up for each of the skin cancers (BCC, CMM, MCC, and SCC) began on January 1, 1995 or a person's 15th birthday, whichever came later, and continued until the point at which the skin cancer under consideration was first diagnosed, emigration, death, or December 31, 2006, whichever came first. For each cohort member, we used the Register of Medicinal Product Statistics to identify all prescriptions for photosensitizing medications filled during the follow-up period. Cohort members were considered to have used a photosensitizing medication from the first date a prescription for a photosensitizing medication was filled. Associations between a history of photosensitizing medication use and risk of the four skin cancers were expressed using incidence rate ratios (IRRs). The IRRs were estimated using log-linear Poisson regression models with number of skin cancer cases as the outcome and the logarithm of person-years at risk as the offset. IRR estimates were adjusted for attained age (1-year categories), calendar period (1-year categories), sex, and education (categorized by duration in seven categories); history of photosensitizing medication use, age, and period were treated as time-dependent variables. To examine the effect of confounding by other photosensitizing medications when evaluating the effects of specific medications, we initially adjusted our "any use" specific medication analyses for use of any of the other 28 photosensitizing medications (e.g., inclusion of 28 other yes/no variables in the regression). Because adjustment for use of other photosensitizing medications in our models did not change our results appreciably, the specific medication results presented are not adjusted for use of other photosensitizing medications. Increase in risk per 5 years of use or per five additional courses of treatment (i.e., trend) was estimated by including years of use or number of courses of treatment as a continuous variable in our models. All analyses were done using SAS (version 9.2).

Results

The cohort included 4,761,749 individuals, of whom 3,407,099 had filled at least one prescription for photosensitizing medication. We observed 35,328 BCC cases

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during 23.2 million person-years of follow-up, 7,254 CMM cases during 23.5 million person-years of follow-up, 95 MCC cases during 23.6 million person-years of follow-up, and 6,550 SCC cases during 23.6 million person-years of follow-up. Photosensitizing medications were divided into two groups: (*a*) medications for long-term daily use (typically medications used to treat chronic conditions, referred to hereafter as LT medications), and (*b*) medications for short-term use (typically medications for courses of treatment of defined, short duration, referred to hereafter as ST medications).

Effect of LT photosensitizing medication use on the risk of skin cancer

Among users of any LT medication, we found a modestly increased risk of MCC, whereas BCC, CMM, and SCC risks were only slightly elevated (Table 1). However, when we estimated skin cancer risk per 5 years of use among users of any LT medication, we found no trend in BCC or CMM risk with increasing duration of medication use (Table 2), and slight trends in MCC and SCC risk (Table 2). The same was true when we restricted the analyses to individuals for whom LT medication use was first registered after July 1, 1995 (i.e., individuals most likely initiating use of LT medication after the creation of the Register of Medicinal Product Statistics at the beginning of 1995; data not shown). In additional analyses, we restricted the analyses of any LT medication use to only include follow-up time more than 1 year after the first registration of a prescription for LT medication and observed similar results (data not shown).

Although any use of many individual LT photosensitizing medications was associated with an increased risk of one or more skin cancers (Table 1), there was evidence of a trend of increased risk with increasing duration of use for only few of these medications (Table 2). Among

Table 1. IRR of BCC, CMM, MCC, and SCC according to any use of specific photosensitizing medications for LT daily use

Medications for LT daily use	BCC		CMM		MCC		SCC	
	No. cases	IRR (95% CI)*	No. cases	IRR (95% CI)*	No. cases	IRR (95% CI)*	No. cases	IRR (95% CI)*
Any use of LT medications	30,885	1.07 (1.05-1.08)	6,276	1.06 (1.02-1.10)	90	1.58 (1.08-2.31)	5,912	1.16 (1.12-1.22)
Diuretic agents								
Bendroflumethiazide	444	1.0 (1.0-1.1)	89	1.3 (1.0-1.6)	1	0.7 (0.1-5.1)	93	1.0 (0.8-1.2)
Bumetanide	438	1.0 (0.9-1.1)	61	0.9 (0.7-1.1)	3	1.8 (0.6-5.8)	125	1.2 (1.0-1.4)
Furosemide	7,339	1.0 (1.0-1.0)	1,129	1.0 (1.0-1.1)	46	2.0 (1.3-2.8)	2,404	1.4 (1.3-1.4)
Nonsteroidal anti-inflammatory drugs								
Diclofenac	9,997	1.1 (1.1-1.1)	2,157	1.0 (1.0-1.1)	27	1.5 (0.9-2.3)	1,646	1.1 (1.0-1.1)
Ibuprofen	17,302	1.0 (1.0-1.1)	3,821	1.0 (1.0-1.1)	43	1.2 (0.8-1.7)	2,939	1.0 (1.0-1.1)
Indomethacin	991	1.0 (1.0-1.1)	179	1.0 (0.9-1.1)	7	2.8 (1.3-5.9)	236	1.2 (1.1-1.4)
Cardiovascular medications								
Amiodarone	247	1.2 (1.0-1.3)	38	1.2 (0.9-1.6)	1	1.6 (0.2-11)	61	1.2 (0.9-1.5)
Atenolol	1,525	1.0 (1.0-1.1)	264	1.0 (0.9-1.1)	7	1.8 (0.8-3.8)	285	1.0 (0.9-1.1)
Captopril	657	1.0 (1.0-1.1)	85	0.9 (0.7-1.1)	4	2.0 (0.7-5.4)	175	1.2 (1.0-1.4)
Enalapril	2,869	1.0 (1.0-1.0)	540	1.1 (1.0-1.2)	8	1.0 (0.5-2.1)	664	1.1 (1.0-1.2)
Methyldopa	88	1.3 (1.0-1.6)	20	1.5 (1.0-2.3)	1	3.7 (0.5-27)	20	1.3 (0.8-2.0)
Simvastatin	2,742	1.0 (1.0-1.1)	486	1.0 (0.9-1.1)	16	3.6 (2.0-6.4)	523	1.1 (1.0-1.2)
Sotalol	1,084	1.2 (1.2-1.3)	161	1.2 (1.0-1.4)	3	1.1 (0.4-3.6)	226	1.1 (1.0-1.3)
Verapamil	1,980	1.2 (1.1-1.3)	275	1.1 (1.0-1.2)	6	1.0 (0.5-2.4)	450	1.1 (1.0-1.3)
Hypoglycemics								
Metformin	825	0.8 (0.7-0.8)	170	0.9 (0.8-1.1)	4	1.5 (0.6-4.2)	235	1.1 (1.0-1.3)
Tolbutamide	311	0.9 (0.8-1.0)	51	1.0 (0.8-1.3)	1	0.8 (0.1-6.0)	84	1.0 (0.8-1.3)
Anticonvulsants								
Carbamazepine	722	1.1 (1.0-1.2)	125	1.0 (0.9-1.2)	3	1.7 (0.5-5.3)	168	1.3 (1.1-1.5)
Valproate	379	1.3 (1.1-1.4)	61	1.0 (0.8-1.3)	1	1.2 (0.2-8.7)	79	1.3 (1.1-1.6)
Cytotoxic medications								
Methotrexate	17	1.9 (1.2-3.1)	6	2.9 (1.3-6.5)	0	—	2	1.7 (0.4-7.0)

Abbreviation: 95% CI, 95% confidence interval.

*Adjusted for age, period, sex, and education. The reference group is never users of the specific photosensitizing medication.

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Table 2. IRR of BCC, CMM, MCC, and SCC per 5 y of treatment with specific photosensitizing medications for LT daily use, among users of such medications

Medications for LT daily use	IRR (95% CI)*			
	BCC	CMM	MCC	SCC
Any LT medication use	0.99 (0.99-1.00)	0.99 (0.98-1.01)	1.08 (1.00-1.17)	1.03 (1.02-1.04)
Diuretic agents				
Bendroflumethiazide	0.9 (0.7-1.2)	1.3 (0.8-2.2)	—	1.5 (0.9-2.4)
Bumetanide	1.0 (0.8-1.2)	1.4 (0.8-2.2)	—	1.3 (0.9-1.8)
Furosemide	0.9 (0.9-1.0)	1.0 (0.8-1.1)	1.6 (0.9-2.7)	1.1 (1.0-1.2)
Nonsteroidal anti-inflammatory drugs				
Diclofenac	1.0 (0.9-1.1)	0.8 (0.6-1.1)	0.4 (0.02-6.8)	0.8 (0.6-1.1)
Ibuprofen	0.9 (0.9-1.0)	0.9 (0.7-1.0)	0.1 (0.01-1.4)	1.0 (0.8-1.1)
Indomethacin	0.9 (0.7-1.1)	1.3 (0.8-2.0)	0.3 (0.01-12)	1.2 (0.9-1.8)
Cardiovascular medications				
Amiodarone	1.0 (0.7-1.4)	1.6 (0.8-3.2)	—	1.4 (0.8-2.5)
Atenolol	1.0 (1.0-113)	1.2 (1.0-1.4)	1.3 (0.4-4.5)	1.3 (1.1-1.5)
Captopril	0.9 (0.8-1.0)	1.0 (0.7-1.5)	0.7 (0.1-5.5)	0.9 (0.7-1.2)
Enalapril	1.0 (0.9-1.1)	1.0 (0.8-1.1)	4.9 (1.9-13)	1.1 (1.0-1.3)
Methyldopa	1.7 (1.2-2.5)	1.1 (0.4-2.9)	—	0.4 (0.1-1.3)
Simvastatin	1.0 (1.0-1.1)	0.8 (0.7-1.0)	0.5 (0.1-2.1)	1.2 (1.0-1.5)
Sotalol	1.0 (0.8-1.1)	0.9 (0.7-1.3)	2.2 (0.4-14)	0.9 (0.7-1.2)
Verapamil	0.9 (0.9-1.0)	1.0 (0.8-1.2)	0.8 (0.2-4.2)	1.1 (0.9-1.2)
Hypoglycaemics				
Metformin	1.0 (0.9-1.2)	1.3 (0.9-1.7)	1.0 (0.1-8.2)	0.8 (0.6-1.1)
Tolbutamide	0.8 (0.6-1.0)	0.8 (0.5-1.5)	—	1.0 (0.7-1.6)
Anticonvulsant				
Carbamazepine	0.9 (0.8-1.1)	0.7 (0.5-1.0)	0.8 (0.1-10)	0.8 (0.6-1.2)
Valproate	1.1 (0.9-1.4)	0.9 (0.5-1.5)	—	0.8 (0.5-1.4)
Cytotoxic medications				
Methotrexate	1.3 (0.3-4.9)	0.2 (0.01-14)	—	—

*Adjusted for age, period, sex, and education.

LT medications for which any use was associated with at least a 20% significant increase in the risk of one or more skin cancers, only two also exhibited a significant increase in skin cancer risk per 5 years of use: methyldopa (effect on BCC risk) and furosemide (effect on SCC risk; Tables 1 and 2).

Effect of ST photosensitizing medication use on the risk of skin cancer

Among those who had used any ST medication, we observed modestly increased risks of BCC, MCC, and SCC, and a slightly increased risk of CMM (Table 3). Furthermore, we found an increase in the risk of BCC, CMM, and SCC with additional courses of treatment among users of any ST medication (Table 4). Restricting the analyses to follow-up time more than 1 year after the first registration of a prescription for ST medication did not change our results appreciably (data not shown). In addition, when we examined the effect of any ST medication use by season of use, we found no difference in risk of any of the four skin cancers for those who had ever used an ST medication during the summer months (June, July, or August) and those whose ST medication use fell outside these months (data not shown).

We found that any use of many individual ST photosensitizing medications significantly increased the risk of one or more skin cancers by at least 20% (Table 3). In addition, the risk of one or more skin cancers per five additional courses of treatment was also significantly increased for users of 8 of the 10 ST medications (Table 4): use of ciproflaxacin, ketoconazole, sulfamethazole, and tetracycline increased the risk of BCC, hydroxychloroquine use increased the risk of CMM, and use of doxycycline, sulfamethazole, acitretin, and isotretinoin increased the risk of SCC (Tables 3 and 4).

Discussion

In this population-based cohort study, we found little evidence that photosensitizing medications for LT use, as a group, increase the risk of skin cancer. Furthermore,

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Table 3. IRR of BCC, CMM, MCC, and SCC according to any use of specific photosensitizing medications for ST use

Medications for ST use	BCC		CMM		MCC		SCC	
	No. cases	IRR (95% CI)*	No. cases	IRR (95% CI)*	No. cases	IRR (95% CI)*	No. cases	IRR (95% CI)*
Any use of ST medications	12,831	1.34 (1.31-1.37)	2,558	1.11 (1.06-1.16)	30	1.42 (0.93-2.15)	2,332	1.47 (1.40-1.54)
Antimicrobials								
Acyclovir	1,954	1.3 (1.3-1.4)	368	1.1 (1.0-1.2)	4	1.1 (0.4-2.9)	408	1.5 (1.4-1.7)
Ciprofloxacin	3,170	1.2 (1.1-1.2)	557	1.0 (0.9-1.1)	11	1.4 (0.8-2.7)	709	1.3 (1.2-1.4)
Doxycycline	1,744	1.3 (1.2-1.3)	365	1.1 (1.0-1.2)	4	1.5 (0.5-4.0)	280	1.3 (1.2-1.5)
Ketoconazole	4,056	1.5 (1.4-1.5)	754	1.1 (1.0-1.2)	9	1.5 (0.7-2.9)	741	1.5 (1.4-1.7)
Levofloxacin	36	1.5 (1.1-2.1)	3	0.6 (0.2-1.9)	0	—	5	1.0 (0.4-2.3)
Sulfamethazole with trimethoprim	416	1.1 (1.0-1.2)	66	1.0 (0.8-1.2)	1	1.0 (0.1-6.9)	121	1.7 (1.4-2.0)
Tetracycline	1,723	1.3 (1.3-1.4)	371	1.1 (1.1-1.3)	2	0.8 (0.2-3.1)	305	1.5 (1.4-1.7)
Antimalarials								
Hydroxychloroquine	2,629	1.4 (1.3-1.4)	601	1.2 (1.1-1.3)	2	0.9 (0.2-3.6)	300	1.4 (1.3-1.6)
SDA								
Acitretin	63	1.1 (0.8-1.4)	14	1.2 (0.7-2.0)	1	7.8 (1.1-56)	41	4.1 (3.0-5.6)
Isotretinoin	132	2.0 (1.7-2.4)	55	1.3 (1.0-1.8)	1	22.6 (3.1-166)	10	2.1 (1.1-3.8)

Abbreviation: SDA, systemic dermatologic agents.

*Adjusted for age, period, sex, and education. The reference group is never users of the specific photosensitizing medication.

although any use of many individual LT photosensitizing medications was associated with an increased risk of one or more skin cancers, there was only evidence of a trend of increased risk with increasing duration of use for BCC in users of methyldopa and SCC in users of furosemide. Because one would expect to see a dose-response relationship between total duration of use of photosensitizing agents and skin cancer risk if

Table 4. IRR of BCC, CMM, MCC, and SCC per additional five treatments with specific photosensitizing medications for ST use, among users of such medications

Medications for ST use	IRR (95% CI)*			
	BCC	CMM	MCC	SCC
Any ST medication use	1.11 (1.08-1.13)	1.06 (1.01-1.12)	0.93 (0.47-1.82)	1.16 (1.11-1.22)
Antimicrobials				
Acyclovir	1.1 (1.0-1.1)	1.1 (0.9-1.2)	0.8 (0.03-27)	1.1 (1.0-1.3)
Ciprofloxacin	1.2 (1.1-1.2)	0.8 (0.6-1.1)	0.01 (0.0-22)	1.1 (0.9-1.3)
Doxycycline	1.0 (0.9-1.2)	1.2 (0.9-1.6)	1.2 (0.1-19)	1.3 (1.0-1.7)
Ketoconazole	1.1 (1.0-1.1)	1.1 (1.0-1.2)	0.7 (0.1-3.2)	1.0 (0.9-1.1)
Levofloxacin	1.7 (0.7-3.9)	1.5 (0.03-84)	—	1.5 (0.1-29)
Sulfamethazole with trimethoprim	1.3 (1.1-1.5)	0.7 (0.3-1.5)	—	1.7 (1.5-1.9)
Tetracycline	1.1 (1.0-1.2)	1.0 (0.8-1.2)	—	1.0 (0.9-1.2)
Antimalarials				
Hydroxychloroquine	1.0 (1.0-1.1)	1.2 (1.0-1.4)	—	1.1 (0.9-1.4)
SDA				
Acitretin	0.9 (0.7-1.2)	0.9 (0.5-1.5)	1.5 (0.9-2.5)	1.2 (1.0-1.4)
Isotretinoin	1.2 (0.9-1.5)	0.7 (0.4-1.5)	—	1.4 (1.0-2.1)

*Adjusted for age, period, sex, and education.

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photosensitizing medications were involved in a general way in increasing skin cancer risk, these results argue against a generalized effect of these medications on skin cancer risk and suggest rather that, if anything, only specific photosensitizing medications for LT use increase the risk of skin cancer.

In contrast, use of at least some ST photosensitizing medications may be associated with increased skin cancer risk. We observed both a significant 20% or greater increase in skin cancer risk in users compared with nonusers and a significant trend with amount of use for the following ST medications: ciproflaxacin, ketoconazole, sulfamethazole, and tetracycline for risk of BCC; hydroxychloroquine for risk of CMM; and doxycycline, sulfamethazole, acitretin, and isotretinoin for risk of SCC. Thus, our results suggest that the use of some ST photosensitizing medications might increase the risk of BCC, CMM, and SCC.

Our findings for certain individual photosensitizing medications deserve additional comment. We observed that use of the photosensitizing diuretic furosemide increased the risk of SCC. In contrast, a previous Danish study based on more limited material from a local North Jutland County prescription database failed to find an association between furosemide use and skin cancer risk, but did find an association between the use of amiloride (another photosensitizing diuretic) and the risk of both SCC and CMM (4). In our study, although ever use of the photosensitizing antiepileptics carbamazepine and valproate was associated with the risk of multiple skin cancers, there was no evidence of a dose-response relationship for either medication. These results are consistent with previous studies reporting valproate to have an antiproliferative activity against a variety of malignancies (23, 24), although Lerche and colleagues (25) found that valproate enhanced photocarcinogenic effects in mice. Finally, we found that use of the photosensitizing cardiovascular medication methyldopa increased the risk of BCC, which is inconsistent with a previous study of angiotensin-converting enzyme (ACE) inhibitors and cancer risk that reported no association between ACE inhibitor use and skin cancer (12).

The observed associations between use of particular medications and increased risk of skin cancer may be due, at least in part, to the underlying condition being treated (confounding by indication). Certain chronic conditions are associated with increased risks of BCC and SCC (26), and many of these conditions (e.g., chronic pulmonary disease and connective tissue disease) are treated with photosensitizing medications. Immunosuppressed patients often require treatment with antimicrobial medications, some of which are photosensitizing; in such cases, the increased risk of skin cancer may be due to the underlying immunosuppression rather than to the photosensitizing properties of the antibiotics in question. Finally, because both isotretinoin and acitretin are used to treat actinic keratoses, a precursor to SCC, the observed associations between use of these medications and risk of SCC may also be due to confounding by indication (5).

On the other hand, for many medications (the ST medications in particular), we observed not only an association between any use and the risk of skin cancer but also a dose-response relationship. We consider it unlikely that trend estimates for duration/amount of use were subject to confounding by indication, as they were estimated among users of photosensitizing medications only. Consequently, in discussing our results, we have focused on medications for which we observed increases in skin cancer risk for both any/never use and duration or amount of use, as a causal relationship between medication use and skin cancer risk cannot be completely ruled out for these medications.

We conducted a register-based study in a cohort comprising the entire population of Denmark and did follow-up using up-to-date vital status information from the Danish CRS, thus minimizing selection bias and loss to follow-up. Registration of cancer in Denmark is considered close to complete for most malignancies (20), although the completeness of reporting has been questioned for nonmelanoma skin cancers (including BCC and SCC), with the Danish National Board of Health reporting that as few as 60% of BCC cases may be registered in the Cancer Register (27-29). Reasons for incomplete registration include (*a*) a high cure rate, leading clinicians to regard these cancers as trivial and underreport them; (*b*) a large case burden, such that full reporting of cases would overwhelm both treating physicians and possibly existing surveillance systems; and (*c*) the low priority given to these malignancies when multiple cancers are reported simultaneously (30). Given these explanations for incomplete registration, underreporting of nonmelanoma skin cancers to the Cancer Register is likely to be nondifferential with respect to underlying illnesses requiring use of photosensitizing medications; in this case, our findings with respect to the effects of photosensitizing medication use on the risk of BCC and SCC could be underestimated. In contrast, if BCC and/or SCC are more likely to be reported in persons with underlying conditions that result in use of photosensitizing medications, we might have overestimated the effect of the relevant medications on BCC and SCC risk.

Use of photosensitizing medications was determined using a prescription drug register where all filled prescriptions are recorded at the time of purchase. We thereby avoided recall bias and made it very likely that only true users were classified as users in this study. However, our study relied on the use of filled prescriptions as a surrogate for actual intake of medication. Nevertheless, as the users had gone to the trouble of filling their prescriptions and paying for their medications, it seems reasonable to assume that filled prescriptions were a good proxy for intake, particularly given that most of the medications examined are prescribed for fairly serious conditions. Unfortunately, the register

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did not include information on use of photosensitizing medications before 1995, which could have led to misclassification of some users as nonusers and thereby resulted in underestimation of the effect of medication use on the risk of skin cancer. However, this misclassification is probably not very great for LT medication, because once initiated, use of these medications tends to continue throughout life. Consequently, use initiated before 1995 would most likely continue after 1995 and therefore be registered. The same cannot be argued for ST medications, but because registered users are most likely true users (i.e., high specificity), as argued above, and the prevalence of use of most such drugs is less than 5% to 10%, the bias induced by this misclassification will be small. (This will actually be true for both ST and LT use medications.) Finally, the lack of registration before 1995 could also have induced misclassification of duration of use in users who began using photosensitizing medication before the initiation of the register in 1995. However, in the additional analyses where we included only users of LT medication most likely to have initiated use after 1995, we observed similar associations. Thus, we do not think that the lack of prescription registration before 1995 induced the general lack of association between use of photosensitive medication and skin cancer risk.

Because our study was register based, we did not have access to individual-level data on sun exposure and sunburns, major risk factors for skin cancer. However, there is no reason to expect that photosensitizing medication users had more exposure to the sun than nonusers. In all likelihood, they either had similar amounts of sun exposure or less exposure and were more careful about sunburns, as photosensitizing medication users are routinely advised to avoid sun exposure by both their doctor and package inserts. If the former (similar amounts of sun exposure), there should be little or no confounding of our estimates by sun exposure. In the latter case (less exposure), confounding by sun exposure would have resulted in a protective effect for photosensitizing medication use, rather than the detrimental effects we observed for some medications. In addition, use of ST medications during the summer months was no more strongly associated with skin cancer risk than was use of these medications during the rest of the year. This adds weight to the suggestions that our results were not confounded by sun exposure and that photosensitizing medications as a group do not increase the risk of skin cancer (due to a general photosensitization of the skin), but that risk is limited to specific photosensitizing medications, possibly due to the fact that the UV absorption spectra for different medications have absorption maxima at different wavelengths.

In conclusion, we found little evidence that, in general, skin cancer risk is associated with photosensitizing medications for LT use, whereas we cannot exclude the possibility that some photosensitizing medications for ST use increase the risk of skin cancer.

Appendix. Photosensitizing medications listed by therapeutic class and generic name, with the corresponding Anatomical Therapeutic Chemical (ATC) codes and proportion of Danish residents using each medication in 2006

Photosensitizing drugs	ATC codes	Prevalence of use in 2006 (%)
Diuretic agents		
Bendroflumethiazide	C03AA01, C03AB01	6.1
Bumetanide	C03CA02, C03CB02	0.1
Furosemide	C03CA01	3.3
Nonsteroidal anti-inflammatory drugs		
Diclofenac	M01AB05	4.2
Ibuprofen	M01AE01, M01AE03	9.1
Indomethacin	M01AB01	0.1
Antimicrobials		
Acyclovir	J05AB01	1.1
Ciprofloxacin	J01MA02	1.2
Doxycycline	J01AA02	0.4
Ketoconazole	D01AC08, J02AB02	1.4
Levofloxacin	S01AX19	0.04
Sulfamethizole with trimethoprim	J01EE01	<0.01
Tetracycline	J01AA07	0.6
Cardiovascular medications		
Amiodarone	C01BD01	0.1
Atenolol	C07AB03	0.8
Captopril	C09AA01	0.1
Enalapril	C09AA02	2.5
Methyldopa	C02AB01	0.02
Sotalol	C07AA07	0.1
Simvastatin	C10AA01	6.0
Verapamil	C08DA01, C08DA51	0.6
Hypoglycaemics		
Metformin	A10BA02	1.4
Tolbutamide	A10BB03	0.04
Anticonvulsant		
Carbamazepine	N03AF01	0.3
Valproate	N03AG01	0.3
Antimalarials		
Hydroxychloroquine, chloroquine	P01BA02, P01BA01	0.2
Cytotoxic medications		
Methotrexate	L01BA01	0.01
Systemic dermatologic agents		
Acitretin	D05BB02	0.02
Isotretinoin	D10BA01	0.4

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No potential conflicts of interest were disclosed.

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