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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

# Exposure to phototoxic NSAIDs and quinolones is associated with an increased risk of melanoma

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**Abstract**
*Purpose* Ultraviolet radiation exposure is the most important exogenous risk factor for cutaneous malignancies. It is possible that phototoxic drugs promote the development of cutaneous melanoma (CM) by intensifying the effect of ultraviolet light on the skin. We investigated the association between the use of common systemic phototoxic drugs and development of CM.
*Methods* This study was a case–control study in a Dutch population-based cohort. The drug dispensing data was obtained from PHARMO, a Dutch drug dispensing and hospital admissions registry, and linked to PALGA, the nationwide pathology network of the Netherlands. The cases were patients diagnosed with pathologically confirmed primary CM between 1991 and 2004. Controls were sampled from the PHARMO population. Exposure to systemic phototoxic drugs was measured and included antimicrobial agents, diuretics, antipsychotic drugs, antidiabetic drugs, cardiac drugs, antimalarials and nonsteroidal anti-inflammatory drugs (NSAIDs). A multivariate conditional logistic regression analysis was performed to study the association between exposure to phototoxic drugs and CM.
*Results* The study population included 1,318 cases and 6,786 controls. Any phototoxic drug during the study period was dispensed for 46 % of the cases and 43 % of the controls ($p$= 0.012). The use of quinolones [odds ratio (OR) 1.33, 95 % confidence interval (CI) 1.01–1.76] and propionic acid derivative NSAIDs (OR 1.33, 95 % CI 1.14–1.54) had a positive association with CM.
*Conclusions* Our study shows that the use of phototoxic drugs is associated with an increased risk of developing CM. Even a short-term use of phototoxic quinolones and propionic acid derivative NSAIDs may increase the risk for CM. Patient education to promote sun-protective behaviour is essential to avoid immediate adverse effects and possible long-term effects of phototoxic drugs.

**Keywords** Phototoxicity · Melanoma · NSAIDs · Quinolone · Carcinogenicity

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## Introduction

Both oral and topical drugs can trigger photosensitive cutaneous reactions when the skin is exposed to ultraviolet light. There are two types of photosensitizing reactions: (1)

photo*allergic* reactions that are immunologically mediated type IV hypersensitivity responses and (2) nonimmunologic photo*toxic* reactions [1–3]. Photo*allergic* reactions require prior sensitization and look clinically like contact dermatitis. Photo*toxic* reactions do not require prior sensitization, occur within hours after sunlight exposure and resemble exaggerated sunburn. Adverse photosensitivity responses to systemic drugs occur primarily as a dose-dependent phototoxic reaction which can be reversed by withdrawal of the drug [3–5].

Many commonly used systemic drugs, such as diuretics, antiarrhythmics, sulphonylureas and antimalarials, are known to be phototoxic [3]. The molecular structure of phototoxic agents (photosensitizers) usually includes a chromophore which is often a planar, tricyclic or polycyclic region containing heteroatoms, such as fluorine or sulphur [5]. Although the phototoxic mechanism is not fully understood, it is assumed that the chromophore absorbs ultraviolet (UVA/UVB) or visible light and induces a phototoxic inflammatory reaction in the cutaneous tissue [3] and damage to cell membranes and DNA [6]. Ultraviolet radiation exposure is the most important exogenous risk factor for cutaneous malignancies [7], and it is thus possible that phototoxic drugs promote skin cancer by intensifying the effect of ultraviolet light on skin [5, 8–11].

The association between PUVA-therapy (psoralen in combination with UVA-light) for psoriasis and the higher incidence of keratinocytic cancers and/or melanoma has been well documented [3, 11–14]. In contrast to the risks of PUVA, little is known about the association between the (chronic) use of systemic phototoxic drugs and UVA/UVB-induced cutaneous malignancies. An epidemiological study by Karagas et al. [15] showed an association between a reported use of a range of photosensitizing drugs and keratinocytic cancers but did not study cutaneous melanoma (CM). In another study limited to diuretics, the authors reported an increased risk of melanoma among users of indapamide and combined amiloride and hydrochlorothiazide therapy [16]. Kaae et al. suggested that short-term use of some photosensitizing medications may be associated with increased skin cancer risk [17]. Altogether, there is little observational evidence of the carcinogenic effects of phototoxic drugs on the skin.

Therefore, we investigated the association between the use of common systemic phototoxic drugs and CM by conducting a case–control study nested in a Dutch population-based cohort.

## Materials and methods

### Setting

The drug dispensing data for this study were obtained from the PHARMO Record Linkage System, a registry which includes data on drug dispensing and hospital admissions of approximately 2.5 million individuals in The Netherlands since 1986. These data were linked to PALGA, the nationwide network and registry of histo- and cytopathology in The Netherlands, as reported previously [18].

### Cases and controls

The case and control selection procedure has been described previously [19]. The cases included all patients over 18 years of age with a pathologically confirmed primary diagnosis of CM in PALGA between 1 January 1991 and 14 December 2004. For each eligible case, an average of five controls was sampled from the population available in PHARMO, matched for gender, date of birth (±2 years) and geographic region. The index date was defined as the date of pathologically confirmed diagnosis of CM (cases) or the index date of the case (controls). Potential cases were not selected as controls. Controls were excluded if in PHARMO the date of entry was unknown, if the individual was younger than 18 years at the index date, if the follow-up in the 3 years before the index date was incomplete or if the subject had a diagnosis of previous melanoma in PHARMO.

### Exposure

A list of commonly used systemic phototoxic drugs included in this study was compiled by the authors based on the published literature and the ATC [Anatomical Therapeutic Chemical (classification system)] index [20] (Table 1). In order not to compromise the sample size, the potentially phototoxic drugs were re-grouped in seven different categories based on the indication for use [20]: antimicrobial agents, diuretics, antipsychotic drugs, antidiabetic drugs, cardiac drugs, antimalarials and nonsteroidal anti-inflammatory drugs (NSAIDs).

Exposure to these drugs was measured in the 3 years before the index date, excluding the year immediately before the index date (Fig. 1). Thus, a 1-year lag time (induction/latent period for CM) was taken into account when defining exposure.

Ever-use (yes/no) of these drugs was measured (1) for each of the seven drug categories and (2) for any phototoxic drug (drug categories combined). The total duration of the drug use (cumulative exposure, days) was also calculated per drug category. If ever-use was significantly associated with CM in initial univariate analyses of the seven drug categories, the drug use from this category was further investigated per sub-category of the ATC fourth level (chemical subgroup) in multivariate analyses [20].

**Table 1** Categories of phototoxic drugs included in this study

| Drug category | ATC-code(s) | Reference(s) |
|---|---|---|
| Antimicrobial agents | | |
| Tetracyclines | J01AA | [1, 3, 5, 6, 8, 35] |
| Quinolones | J01MA, J01MB | [1, 3, 5, 6, 27, 35] |
| Sulfonamides | J01E, A07AB | [1, 3, 5] |
| Diuretics | | |
| Furosemide | C03CA01, C03CB01, C03EB01 | [1, 3, 5, 6, 16] |
| Thiazides | C03A, C07B, C07D | [1, 3, 5, 6, 15, 16] |
| Amiloride | C03DB01 | [16] |
| Spironolactone | C03DA01 | [16] |
| Bumetanide | C03CA02, C03CB02, C03EB02 | [3, 16] |
| Sulfonamides | C03BA, C03BB, C03BK, C03CA, C03CB | [3, 16] |
| Antipsychotics | | |
| Phenothiazines | N05AA, N05AB, N05AC | [1, 3, 5, 6, 8] |
| Antidiabetics | | |
| Sulfonamides | A10BB, A10BC | [3] |
| Cardiac drugs | | |
| Amiodarone | C01BD01 | [1, 3, 15, 35, 36] |
| Quinidine | C01BA01, C01BA51, C01BA71 | [1, 3, 6] |
| Calcium channel blockers | C08CA | [1, 3, 6] |
| Antimalarials | | |
| Aminoquinolines en methanolquinolines | P01BA, P01BC | [3] |
| Nonsteroidal anti-inflammatory drugs | | |
| Propionic acid derivatives | M01AE | [33, 37] |

ATC, Anatomical Therapeutic Chemical (classification system)

## Other covariates and potential confounders

Several other drugs may be associated with CM development. Prior exposure to these drugs was assessed as follows: ever-use (yes/no) of antineoplastic drugs (ATC-code: L01), coxibs (ATC-code: M01AH), statins (ATC-code: C10AA) and systemic glucocorticoids (ATC-code: H02AB) [21] for all cases and controls; ever-use (yes/no) of hormone-replacement therapy and anticonceptives (ATC-codes: G03CA, G03AA, G03AB) for all women. As a proxy for co-morbidity, the total number of unique ATC-codes (4th level, chemical subgroup) during the 2-year exposure measurement period (Fig. 1) in PHARMO was calculated, excluding the ATC-codes included in Table 1 as well as the ATC-codes of the above-mentioned covariates.

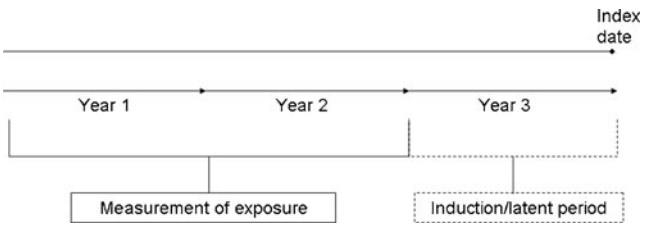


**Fig. 1** Definition of exposure measurement period for phototoxic drugs

## Data analysis

### *Univariate analyses*

The association between exposure to phototoxic drugs and CM was analysed for the total study population using chi-square statistics. Ever-use of drugs was analysed as a binary variable (yes/no) per drug category as presented in Table 1. The proxy for co-morbidity (the number of additional ATC-codes) was analysed as a continuous variable, and a paired *t* test was used to study differences between cases and controls.

### *Multivariate analyses*

A multivariate conditional logistic regression analysis was performed to calculate adjusted odds ratios (OR) and 95 % confidence intervals (CI) for the exposure to phototoxic drugs and CM. The drug categories that were significantly associated with the outcome ($p \leq 0.05$) in the univariate analysis were included in the multivariate model according to the fourth level of the ATC-code (chemical subgroup) in order to get a better picture of the actual associations. The other covariates significantly associated with the outcome ($p \leq 0.05$) in the univariate analysis were also included in the multivariate analysis.

*Sensitivity analyses*

Due to the observed gender differences in patterns of antimicrobial agent use and the possible role of oestrogens, the multivariate analyses were conducted not only for the whole study population but also separately for men and women. Furthermore, we conducted a sensitivity analysis assessing quinolone use during summer (May–September) and winter months (October–April).

*Dose–response relationship*

Subgroup analyses, including trend analyses, were conducted in order to study the dose–response relationship of drugs significantly associated with the outcome in the multivariate analyses. For these analyses, categories of cumulative duration of drug use were established as follows; for quinolones a cut-off of 10 days was used in order to make a distinction between those who received only one course of standard therapy and those who took quinolones for a longer period. For NSAIDs, the mean cumulative duration of use (8 days) was chosen as a cut-off.

## Results

The study population included 1,318 cases and 6,786 controls. The characteristics of the study population have been described previously [19]. Approximately 60 % of the cases and controls were female (Table 2).

Univariate analyses

The chi-square statistics of the differences in drug use between cases and controls are presented in Table 2. Only those co-variates that were significant in the univariate analyses were included in the multivariate analyses.

*Phototoxic drugs*

At least one prescription of any phototoxic drug during the study period was dispensed for 46 % of the cases and 43 % of the controls ($p$=0.012). Propionic acid derivative NSAIDs were significantly more often dispensed for cases (23 %) than for controls (19 %; $p$=0.001). A significantly larger proportion of cases than of controls were dispensed at least one prescription of any of the potentially phototoxic antimicrobial agents (24 vs. 21 %; $p$=0.017).

*Other covariates*

Of the other covariates studied, the use of antineoplastic agents (0.8 % of cases and 0.2 % of controls; $p$=0.005) and oestrogens (31 % of female cases and 25 % of female controls; $p$=0.001) were statistically significantly associated with CM in the univariate analyses.

Multivariate analyses of phototoxic drugs and CM

The results of the multivariate analyses of risk factors for CM included in this study are presented in Table 3.

*Quinolones*

The use of quinolones during the study period had a statistically significant positive association with CM ($OR_{adj}$ 1.33, 95 % CI 1.01–1.76, where $OR_{adj}$ is the adjusted odds ratio). The $OR_{adj}$ for quinolone use during the winter and summer months was 1.37 (95 % CI 0.95–1.99) and 1.28 (95 % CI 0.85–1.92), respectively. The gender-stratified analyses for quinolone use yielded $OR_{adj}$ for men and women of 1.67 (95 % CI 1.12–2.48) and 1.06 (95 % CI 0.71–1.56), respectively. When stratified by gender, the OR went in different directions, indicating effect modification by gender.

In our study 2.2 % ($n$=29) of the cases and 1.8 % ($n$=120) of the controls used quinolones for more than 10 days during the 2-year exposure measurement period (data not shown). Because of the sample size limitation, the dose–response relationship for quinolones was analysed further only in men. When no use of quinolones was used as a reference, the $OR_{adj}$ for quinolone use for 1–10 days was 1.53 (95 % CI 0.87–2.69), whereas the $OR_{adj}$ for the use of quinolones for >10 days was 1.80 (95 % CI 1.05–3.13) (data not shown). The trend analysis was statistically significant ($p$=0.012). Thus, a dose–response relationship was observed, and the risk of CM would appear to increase even after one course of quinolones.

*Propionic acid derivative NSAIDs*

The use of propionic acid derivative NSAIDs had a positive and statistically significant association with CM ($OR_{adj}$ 1.33, 95 % CI 1.14–1.54). When stratified by gender, the same association was observed, but the association was no longer statistically significant in men due to insufficient power. The dose–response relationship between the use of propionic acid derivative NSAIDs and CM was analysed further in women (data not shown). When no use of NSAIDs was used as a reference, the $OR_{adj}$ for 1–8 days and >8 days of use was 1.59 (95 % CI 1.24–2.06) and 1.26 (95 % CI 0.99–1.61). The trend analysis was statistically significant ($p$=0.004). The risk of CM would appear to increase even when these NSAIDs were used for only a short period of time.

**Table 2** Characteristics of the study population and the use of different drugs during the study period ($n$=8104)

| Characteristics of study population and drug use | Cases ($n$=1,318) | Controls ($n$=6,786) | $p$-value[a] |
|---|---|---|---|
| Female gender | 778 (59.0) | 4,072 (60.0) | 0.508 |
| Age at diagnosis (mean ± SD) | 55.3 (15.9) | 55.9 (15.5) | 0.181[c] |
| Number of concomitant drugs[b] (mean ± SD) | 5.1 (4.8) | 4.9 (5.0) | 0.120[c] |
| At least one prescription of any phototoxic drug | 610 (46.3) | 2,888 (42.6) | 0.012* |
| At least one prescription of 1 phototoxic drug | | | |
| Antimicrobial agents | 317 (24.1) | 1,432 (21.1) | 0.017 |
| Tetracyclines | 199 (15.1) | 953 (14.0) | 0.316 |
| Sulfonamides | 99 (7.5) | 432 (6.4) | 0.124 |
| Quinolones | 70 (5.3) | 278 (4.1) | 0.047* |
| Diuretics | 98 (7.4) | 527 (7.8) | 0.681 |
| Antipsychotics | 5 (0.4) | 30 (0.4) | 0.751 |
| Antidiabetics | 40 (3.0) | 186 (2.7) | 0.553 |
| Cardiac drugs | 56 (4.2) | 332 (4.9) | 0.317 |
| Antimalarials | 20 (1.5) | 91 (1.3) | 0.614 |
| Propionic acid derivative NSAIDs | 302 (22.9) | 1,283 (18.9) | 0.001* |
| At least one prescription of other drugs | | | |
| Antineoplastic agents | 10 (0.8) | 16 (0.2) | 0.005*[d] |
| Coxibs | 26 (2.0) | 126 (1.9) | 0.777 |
| Statins | 92 (7.0) | 487 (7.2) | 0.800 |
| Systemic glucocorticoids | 80 (6.1) | 458 (6.7) | 0.365 |
| Oestrogens (% of women) | 239 (30.7) | 1,009 (24.8) | 0.001* |

*Statistically significant at $p \leq 0.05$, included in the multivariate analyses

SD, Standard deviation; NSAIDs, nonsteroidal anti-inflammatory drugs

Data are presented as the number of cases/controls, with the percentage given in parenthesis, unless indicated otherwise

[a]Chi-square statistics unless mentioned otherwise

[b]Based on the number of unique ATC-codes, excluding drugs mentioned elsewhere in this table

[c]$t$ test statistics

[d]Fisher's exact test

*Other covariates*

The use of antineoplastic agents was statistically significantly associated with CM ($OR_{adj}$ 3.46, 95 % CI 1.50–7.94) and the same positive association was observed in men ($OR_{adj}$ 2.76, 95 % CI 0.79–9.65) and women ($OR_{adj}$ 4.34, 95 % CI 1.41–13.4). The use of oestrogens was positively associated with CM ($OR_{adj}$ 1.34, 95 % CI 1.10–1.63).

## Discussion

The results of our study show that the use of any phototoxic drug in the 3 years prior to diagnosis is associated with an increased risk of developing CM when taking into account a 1-year induction/latent period. Of all the phototoxic drugs studied in our analyses, quinolones and propionic acid derivative NSAIDs seem to have the strongest positive association with CM.

Quinolones

This is the first human study to suggest that the photocarcinogenic properties of quinolones observed in the laboratory may be relevant in clinical practice. Quinolones have been proven to be photomutagenic/phototumorigenic in human keratinocytes and other mammalian cells in vitro and on mouse skin in vivo [22–24]. However, epidemiological evidence on the association between the use of these drugs and CM is limited to one previous publication [17].

**Table 3** Multivariate conditional logistic regression analyses of the association between phototoxic drug use and cutaneous melanoma

| Risk factors for CM | Adjusted odds ratio (95 % CI) | | |
|---|---|---|---|
| | All patients | Men | Women |
| Phototoxic drug category | | | |
| Quinolones | 1.33 (1.01–1.76) | 1.67 (1.12–2.48) | 1.06 (0.71–1.56) |
| Propionic acid derivative NSAIDs | 1.33 (1.14–1.54) | 1.18 (0.92–1.52) | 1.40 (1.16–1.69) |
| Covariates | | | |
| Antineoplastic agents | 3.46 (1.50–7.94) | 2.76 (0.79–9.65) | 4.47 (1.46–13.7) |
| Oestrogens | N/A | N/A | 1.34 (1.10–1.63) |

CM, Cutaneous melanoma; N/A, not analysed; CI, confidence interval

It has been speculated in the literature that the photocarcinogenic properties of quinolones might not be relevant in clinical practice because antimicrobial agents are usually prescribed for only a short period of time [25, 26]. The earlier data on human melanocytes in vitro suggest, however, that the melanin in melanocytes and keratinocytes accumulates quinolone, thereby increasing its tissue concentration in the basal epidermis [27]. This mechanism may contribute to long-lasting phototoxicity. In our data, the use of quinolones seemed to be related to a higher risk of developing a CM, even when used for a short period of time corresponding to one course of standard therapy and even when used during the winter period (October–April; data not shown). It would be interesting to study the incidence of CM among patients who may be at higher risk, such as those treated with quinolones for longer time periods for cystic fibrosis or prostatitis.

### Propionic acid derivative NSAIDs

In our study, the use of propionic acid derivative NSAIDs was associated with a higher risk of developing CM. The results of previous studies on the association between the use of NSAIDs and CM have been contradictory [28–31, 32]. However, these studies did not separately analyse NSAIDs with different phototoxic properties. We chose to include only the propionic acid derivatives (ATC-code: M01AE) in the analyses because these compounds have been reported to be more photoactive than the other NSAIDs in vitro [33]. Some of the other NSAIDs, such as acetylsalicylic acid, have been reported to be chemoprotective for CM, especially when used in low doses for a longer period of time [28, 29] although this finding has recently been contradicted [32]. Due to the differences in phototoxic properties between NSAID classes, it would be interesting to analyse different groups of NSAIDs separately in any future studies on the association between NSAID use and the development of cutaneous malignancies if the sample size allows this stratification.

### Other covariates and stratified analyses

A strong positive association was detected between the use of antineoplastic agents and CM. Although we only had information on outpatient antineoplastic use in our data, the use of antineoplastic agents was included in the multivariate analyses as a covariate because of the potential for confounding by indication. It is possible that these patients have other (solid/hematologic) malignancies and are being treated with antineoplastic agents. Alternatively, these agents themselves might be carcinogenic.

Due to the differences in patterns of use of antimicrobial agents for men and women and the possible role of oestrogens, we decided to analyse the data for men and women separately. After stratification by gender we may not have had enough power for subgroup analyses, possibly explaining why the observed positive associations are not statistically significant. However, the OR for quinolones in men was statistically significant and even higher than that in the initial analyses of all patients. We can only speculate why this association seems to be stronger in men. It is possible that women are more likely to follow the advice of the doctor or a pharmacist and avoid ultraviolet light exposure when taking these drugs and might therefore have a lower risk for photocarcinogenesis [34].

### Strengths and limitations

The cases and controls in our study were sampled from the PALGA and PHARMO registries, which are representative of the Dutch general population [18]. The exposure data (pharmacy data) were collected prospectively based on a drug dispensing database (and not a questionnaire) which excludes recall bias.

We limited our study to the effects of phototoxic drug use in the 3 years prior to the diagnosis of CM, excluding the year immediately prior to the index date. The time period may have been too short, but it was chosen so as not to exclude too many patients. Restricting the analyses to patients with at least 5 years of follow-up in PHARMO would have reduced the number of cases from 1,318 to 931. On the other hand, all patients included in this study had a complete follow-up and co-medication data for the 3 years before diagnosis of CM. We did not study drug use beyond this 3-year period and thus do not have information on the cumulative duration of drug use before the start of the exposure measurement period.

In this linkage-study of two existing registries, we did not have information available on lifestyle factors, such as family history of melanoma, exposure to ultraviolet light or other melanoma-specific risk factors prior to and/or during drug exposure. This is a limitation of our study, and we cannot rule out residual biases or confounding factors as a possible explanation for our findings. The phototoxic properties of the drugs included in the analyses are generally known, and it can be assumed that (some of) the patients have been advised to stay out of the sun during a treatment period. If the patients using phototoxic drugs follow this advice and are then less likely to be exposed to ultraviolet light (exposure misclassification), the result would be an underestimation rather than an overestimation of the true effect size.

When designing the study, we did not have previous information on the length of the relevant latent/induction period for CM. In general, there is still an insufficient understanding of the time frames that should be used to study drug use and melanoma risk and/or chemoprevention for melanoma [31]. We conducted a lag analysis allowing a

latent/induction period of a minimum of 1 year in order to minimize the possibility of the latent/induction period overlapping with the exposure period. Such an overlap or a latent/induction period that is too long would result in non-differential misclassification and underestimate the actual effect of the drug use. It is therefore possible that for some of the drugs studied in our analysis the lag time was too long or too short for a true positive association with CM to be detected. Furthermore, a variation in exposure prevalence over time might bias the association, but we do not expect this to be a problem in our study because the exposure measurement period was only 2 years.

## Conclusions

Based on our results, we suggest that even a short-term use of some phototoxic drugs may increase the risk for cutaneous melanoma. However, the associations observed in our study should be investigated in further epidemiological analyses with a long follow-up and with information on sun exposure. Nevertheless, it continues to be important to advise patients to avoid ultraviolet light while taking phototoxic drugs and to report any phototoxic reactions to their doctor. Patient education to promote sun-protective behaviour is essential—not only to avoid any immediate adverse effects of phototoxic drugs but also to minimize the risk of possible long-term effects.

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**Conflicts of interest** None.

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