Summary

Background Cutaneous malignant melanoma (CMM) is a highly immunogenic tumour. Patients with an impaired immune system have an enhanced risk for CMM and a worse prognosis. Methotrexate (MTX) is an anti-inflammatory and immunosuppressive drug frequently used to treat patients with psoriasis. An association between MTX and risk of CMM has previously been demonstrated in patients with rheumatoid arthritis.

Objectives To investigate whether MTX increases the risk of CMM among patients with psoriasis.

Methods A nested case–control investigation from a Swedish cohort of patients with psoriasis was conducted. Data were obtained from available Swedish registers and included 395 patients with psoriasis who had previously been cancer-free and had a first CMM in the time period from 1 January 2010 to 31 December 2016. A total of 10 randomly selected cancer-free patients with psoriasis were matched per case with respect to age (same birth year) and sex. The accumulated MTX doses in both groups were obtained. Crude odds ratios (ORs) for the proportion of MTX in the respective group were calculated using conditional logistic regression analyses.

Results Of 395 patients with psoriasis who had CMM, 97 (25%) had filled a prescription of MTX; of 3950 controls, the corresponding number was 954 (24%). In a conditional logistic regression analysis, no association between MTX exposure (ever use) and risk for CMM was observed (OR 1.0, 95% confidence interval 0.8–1.3). Moreover, no indication of a dose–response association was observed.

Conclusions In this Swedish nested case–control study, the use of MTX was not associated with an enhanced risk for CMM. These findings are reassuring for dermatologists in everyday clinical practice.

What is already known about this topic?
- Methotrexate (MTX) treatment has been linked to an increased risk for cutaneous malignant melanoma (CMM) in an Australian cohort of patients with rheumatoid arthritis.
- In a previous retrospective Swedish cohort investigation, patients who had exclusively been prescribed MTX by a dermatologist did not have an enhanced risk for CMM compared with MTX-unexposed individuals. Nevertheless, this cohort did not specifically include patients with psoriasis.

What does this study add?
- This Swedish nested case–control investigation included 395 previously cancer-free patients with psoriasis who had CMM (cases) and 3950 matched cancer-free patients with psoriasis (controls).
Despite the noteworthy drug development and continuous introduction of novel pharmaceuticals including biologics, methotrexate (MTX) still constitutes one of the most important treatment options within dermatology in general, and for patients with psoriasis in particular. Although introduced more than 60 years ago, MTX is often the first systemic drug considered when topical treatment and phototherapy have failed or have been considered inappropriate or insufficient.

MTX has been linked to an increased risk of cutaneous malignant melanoma (CMM) in a cohort of patients with rheumatoid arthritis (RA). In a Swedish nationwide cohort investigation, a small but significant risk increase for CMM among MTX-exposed patients was observed compared with age- and sex-matched MTX-unexposed individuals. However, in a subanalysis, patients who exclusively had MTX prescribed by dermatologists did not have an enhanced risk compared with MTX-unexposed individuals. The evidence as to whether psoriasis per se enhances the risk for CMM is conflicting. Therefore, investigations within this cohort are important in order to avoid a possible confounding by indication.

MTX has been associated with an enhanced risk for squamous cell carcinoma and basal cell carcinoma among patients with RA and psoriatic arthritis (PsA). Furthermore, in an American cohort of patients with RA, long-term MTX use (defined as exposure > 1 year) increased the risk for a second nonmelanoma skin cancer.

In previous American and Danish investigations, no association between MTX treatment for psoriasis and the overall risk for malignancies has been observed. A recent double-blinded prospective trial, including 2391 patients randomized to low-dose MTX and 2395 patients randomized to placebo, investigated whether MTX protected against recurrent cardiovascular disease. Eligible patients included those who had a previous myocardial infarction or multivessel coronary disease in addition to either type 2 diabetes or metabolic syndrome. Overall, MTX failed to lower the risk for a subsequent cardiovascular event, but when addressing the adverse events, a significantly increased risk for nonbasal cell carcinoma skin cancer was observed. However, the specific subtypes of skin cancer were not presented.

In recent nationwide Danish investigations, the antihypertensive drug group of hydrochlorothiazides, has been linked to an increased risk for squamous cell carcinoma, lip cancer and CMM. The rationale behind this association is likely that hydrochlorothiazides have photosensitizing effects, which, in combination with ultraviolet (UV) radiation, induces DNA damage in skin cells. Although infrequently addressed in the literature, MTX has also been connected with photosensitivity reactions, which might further suggest an explanation for an association with an increased risk for cutaneous malignancies. Moreover, MTX is an anti-inflammatory and immunosuppressive drug, so bearing in mind that CMM is a highly immunogenic tumour that has a worse prognosis among patients with an impaired immune system, the following Swedish nested case–control investigation was performed. The aim was to elucidate a possible link between MTX exposure and CMM among patients with psoriasis.

**Patients and methods**

**Study cohort and data sources**

A cohort of patients aged ≥ 18 years with at least two outpatient diagnoses (primary healthcare not included) of psoriasis [defined as having an International Classification of Diseases, Tenth Revision (ICD-10) code starting with L40], with at least one of these diagnoses made by a dermatologist during the time period from 1 January 2001 to 31 December 2016, was obtained from Swedish registries (the population register and the National Board of Health and Welfare). The regional ethical review board in Gothenburg approved the study (approval number 911-17). Demographic data including civil status, country of birth, income and education level in addition to information on emigration were obtained. Moreover, the cohort included healthcare data from the following available databases: inpatient register (from 2001), outpatient register (from 1958), cause of death register (from 1962), cancer register (from 1958) and the prescribed drug register (from July 2005). This last register includes only filled prescriptions from pharmacies, excluding inpatient administrations. The register is virtually complete (patient identity data are missing for less than 0-3% of all items). Relevant comorbidity categories were retrieved from the inpatient and outpatient register for the time period from 2001 to 2016. For selected comorbidities, relevant Anatomical Therapeutic Chemical (ATC) codes were used. Charlson Comorbidity Index (CCI) was calculated from the inpatient and outpatient registers and was sampled by the National Board of Health and Welfare. The number of outpatient visits and visits at a dermatology clinic were obtained. Subsequently, the number of visits that included a diagnosis of psoriasis was retrieved. The corresponding data regarding the number of hospitalizations were also collected for both groups. Data on all specific psoriasis codes for all visits from 2001 through to the date on which the first CMM
was diagnosed, or the corresponding date among the controls, were acquired from the outpatient register (ICD-10 codes) for all patients.

Covariates

The original psoriasis cohort consisted of 81,738 patients (Figure 1). To allow adequate observation time from the drug prescription registry (initiated in July 2005), patients with a first CMM diagnosis (including in situ melanoma) during the time period from 1 January 2010 to 31 December 2016 were selected (cases). Prior to the registered CMM diagnosis, the cases had to be cancer-free with the exception of basal cell carcinoma. Moreover, the first outpatient diagnosis of psoriasis had to come before the first CMM diagnosis date. In order to obtain the same precedent observation period, the date of the CMM diagnosis was used as the matching date for the controls (both of these dates will hereafter be referred to as the index date). Cases and controls were required to reside in Sweden from the start of the drug prescription registry to the index date. Eligible controls were also required to be alive and cancer-free (with the exception of basal cell carcinoma) on the index date. The matching criteria were age (same birth year) and sex. Similar to cases, the controls were required to have a first psoriasis diagnosis prior to the index date. For every case, 10 controls were drawn using risk-set sampling. Therefore the odds ratios (ORs) are unbiased estimates of the incidence rate ratios that would have emerged from a cohort investigation based on the source population. The last available CCI that preceded the index date was used in the analysis. Comorbidities relating to alcohol-associated conditions, diabetes, liver diseases, renal diseases, peptic ulcers (including gastric and duodenal ulcers), Crohn disease, RA and PsoA were obtained. A description of how the respective comorbidity classes were defined is presented in Table S1 (see Supporting Information).

Primary analysis

Ever exposure to MTX was analysed in the respective two groups and the crude OR was calculated for MTX (ATC codes L04AX03 and/or L01BA01).

Secondary analyses

The accumulated MTX doses (g) prior to the index date were calculated. As MTX can be administered orally and subcutaneously, the accumulated doses through both routes were calculated separately. Time from first to last filled MTX prescription (exposure period) prior to index date was obtained for both groups.

CMM stages (stage 0, in situ melanoma; stage I–II, invasive melanoma; stage III–IV, metastasized disease) at diagnosis were compared between the MTX-exposed and MTX-unexposed cases.

Mortality and melanoma-specific mortality were compared between the groups and within the case group.

Exposure to immunosuppressive drugs (ATC code starting with L04A) other than MTX was analysed. Ciclosporin (ATC code L04AD01) and acitretin (ATC code D05BB02) were also analysed separately. Finally, data for ever exposure to tumour necrosis factor-α inhibitors (TNFis) (ATC code starting with

Figure 1  Study flowchart.

MTX, methotrexate; CMM, cutaneous malignant melanoma including invasive and in situ melanomas. aPatients aged ≥18 years with at least two outpatient diagnoses of psoriasis with at least one of these diagnoses made by a dermatologist during the time period from 2001 to 2016. Cases and controls were required to reside in Sweden from the start of the Swedish drug prescription registry (i.e. July 2005) to the index dates. The index date was in the time period from 1 January 2010 to 31 December 2016. bPatients with a first CMM during the time period from 1 January 2010 to 31 December 2016. Prior to the CMM diagnosis, the cases we required to be cancer-free with the exception of basal cell carcinoma. The controls were required to be alive and cancer-free (with the exception of basal cell carcinoma) on the index date. The matching criteria were age (same birth year) and sex. The controls were drawn from the group of eligible patients using a risk-set sampling strategy.
Sensitivity and confounding analysis

In a sensitivity analysis, the effect of introducing different lag periods (the time period prior to index date that is disregarded in the assessment of MTX exposure) was investigated. A confounding analysis was performed on several covariates, exposures to other drugs and demographic factors.

Post hoc analysis

In a post hoc analysis (using an updated risk-set sampling), the inclusion criteria for cases and controls were altered and, in this separate analysis, any prevalent cancers (other than CMM) were allowed before the index date.

Statistical analysis

All data were analysed using R version 3.5.3 (https://www.r-project.org/). A power calculation assuming 10 controls per case, a power of 90%, an OR of 2.0 and 20% MTX-exposed controls required inclusion of at least 121 cases. Conditional logistic regression models were used with CMM as the dependent variable and MTX exposure as the independent variable. MTX using accumulated MTX dose (g), dose intervals, ever/never exposure or doses divided into two variables by route of administration (oral or subcutaneous). For the confounding analysis, the 10% rule was applied (i.e. we investigated whether any of the prespecified covariates affected the unadjusted coefficient by more than 10%). Cox proportional hazards regression models adjusted for age group (< 40 years, 40 to 50 years, 50 to 60 years, > 60 to 70 years and > 70 years) and sex, and Kaplan–Meier survival plots were used to perform mortality analyses. We tested the proportional hazards assumption, and found it not to be violated, by using a goodness-of-fit test. Fisher’s exact test was used when comparing proportions. All tests were two-sided and P < 0.05 was considered statistically significant.

Results

Overall, 395 previously cancer-free patients (202 men and 193 women) with a first CMM (including in situ) were identified (cases). A total of 3950 controls (2020 men and 1930 women) were selected. The majority of the patients were born in the Nordic countries (94%). An overview of the demographic details, comorbidities including CCI score and number of dermatology visits is available in Table 1. The proportion of patients with selected comorbidities did not differ between cases and controls. However, the level of comorbidities calculated by the CCI index was higher among the cases than the controls when adjusting for MTX ever exposure (P = 0.037). For cases and controls, the median time [interquartile range (IQR)] from the first recorded psoriasis diagnosis to the index date was 6.4 years (2.9–10.2) and 7.1 years (3.7–10.4), respectively (P = 0.029). Detailed data regarding the number of outpatient visits and hospitalizations among the cases and controls with and without MTX exposure are presented in Table S2 (see Supporting Information). There were no significant differences in number of visits within each of these two groups for any of the visit types.

Primary analysis

Of 395 cases, 97 patients (25%) had filled a prescription of MTX, as did 954 of 3950 controls (24%). A univariate conditional logistic regression model using ever exposure of MTX yielded an OR of 1.0 [95% confidence interval (CI) 0.8–1.3, P = 0.86] between the groups.

Table 1 Demographics for cases and controls

|                      | Cases (n = 395) | Controls (n = 3950) |
|----------------------|----------------|--------------------|
| **Sex**              |                |                    |
| Men                  | 202 (51)       | 2020 (51)          |
| Women                | 193 (49)       | 1930 (49)          |
| **Age median (IQR), years** |          |                    |
| < 40                 | 64 (52–73)     | 64 (52–73)         |
| 40–49                | 52 (13)        | 520 (13)           |
| 50–59                | 72 (18)        | 720 (18)           |
| 60–69                | 106 (27)       | 1060 (27)          |
| 70–79                | 96 (24)        | 960 (24)           |
| ≥ 80                 | 36 (9)         | 360 (9)            |
| **Diagnoses**        |                |                    |
| Alcohol-associated conditions | 18 (5) | 209 (5)            |
| Diabetes             | 68 (17)        | 647 (16)           |
| Liver disease        | 48 (12)        | 434 (11)           |
| Renal disease        | 10 (3)         | 100 (3)            |
| Peptic ulcer         | 9 (2)          | 84 (2)             |
| Crohn disease        | 5 (1)          | 46 (1)             |
| Rheumatoid arthritis | 18 (5)         | 148 (4)            |
| Psoriatic arthritis  | 89 (23)        | 893 (23)           |
| **CCI index**        |                |                    |
| CCI 0                | 223 (56)       | 2470 (63)          |
| CCI 1                | 106 (27)       | 888 (22)           |
| CCI 2+               | 66 (17)        | 592 (15)           |
| **Educational level**|                |                    |
| Low                  | 72 (18)        | 925 (23)           |
| Middle               | 168 (43)       | 1744 (44)          |
| High                 | 122 (31)       | 1014 (26)          |
| Missing data         | 33 (8)         | 267 (7)            |
| Number of dermatology visits, median (IQR) | 5 (2–9) | 4 (2–8) |

CCI, Charlson comorbidity index; IQR, interquartile range; MTX, methotrexate. °CCI 0 indicates no comorbidity; CCI 1, mild comorbidity; CCI 2+, moderate-to-severe comorbidity. Educational levels: low, compulsory school (< 10 years); middle, upper secondary school (10–12 years); high, higher education (> 12 years). Number of outpatient visits at a dermatological clinic prior to index date during the period from 2001 to 2016. Data are presented as a (%) unless otherwise stated.
Secondary analyses

When dividing the MTX-exposed participants into different groups relating to accumulated MTX doses, no dose–response association was observed (Table 2). The distribution of the accumulated MTX dose among the MTX-exposed participants is presented in Figure S1 (see Supporting Information). When analysing all filled MTX prescriptions, 40%, 37%, 12%, 3% and 7% were prescribed by dermatologists, rheumatologists, internists, general practitioners and other physicians, respectively. The MTX-exposure period (time from first to last filled prescription) did not differ between the groups (median 2.7 years for both groups combined). The median time (IQR) from a first prescription of MTX to CMM was 4–7 years (2–1–7–2). The corresponding time for the MTX-exposed controls was 5–3 years (2–5–7–6) (P = 0.22).

There were no differences in melanoma stages at diagnosis between the MTX-exposed and MTX-unexposed cases (Table 3).

The survival rates did not differ between cases and controls (adjusted hazard ratio 1.4, 95% CI 1.0–2.1; P = 0.058) and no statistically significant differences were seen between MTX-exposed and MTX-unexposed cases. The adjusted hazard ratios for mortality and melanoma-specific mortality within the case group were 0.7 (95% CI 0.2–1.9, P = 0.44) and 0.8 (95% CI 0.2–3.6, P = 0.76), respectively. Kaplan–Meier survival plots for the three analyses above are available in Figure S2 (see Supporting Information).

Among the cases, 40 patients (10%) had filled an immunosuppressive prescription other than MTX. The corresponding number among controls was 319 (8%) (crude OR 1.3, 95% CI 0.9–1.8; P = 0.16). Ever exposure to ciclosporin and acitretin did not differ significantly between the groups (data not shown). Overall, 29 cases (7%) and 230 controls (6%) had filled a prescription of any TNFi and/or IlI (P = 0.22), respectively.

Sensitivity and confounding analysis

The introduction of different lag periods did not influence the OR between the groups (Table S3; see Supporting Information). In the confounding analysis none of the covariates added affected the coefficient in the crude model by more than 10% (Table S4; see Supporting Information).

| Table 2 | Accumulated methotrexate (MTX) doses among cases and controls and dose–response analysis |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| MTX exposure    | Cases (N = 395), n (%) | Controls (N = 3950), n (%) | OR (95% CI)     | P-values        |
| Never           | 298 (75)         | 2996 (76)       | 1 (Reference)   |                 |
| Ever            | 97 (25)          | 954 (24)        | 1·0 (0·8–1·3)   | 0·86            |
| MTX dose intervals (g) | | | | |
| None            | 298 (75)         | 2996 (76)       | 1 (Reference)   |                 |
| 0–2·5           | 65 (16)          | 586 (15)        | 1·1 (0·8–1·5)   | 0·46            |
| 2·5–5           | 23 (6)           | 237 (6)         | 1·0 (0·6–1·5)   | 0·91            |
| 5–7·5           | 6 (2)            | 100 (3)         | 0·6 (0·3–1·4)   | 0·24            |
| > 7·5           | 3 (1)            | 31 (1)          | 1·0 (0·3–3·2)   | 0·95            |
| Median dose among exposed (range) | | | | |
| Peroral MTX dose (g) | 1·25 (0·08–7·68), n = 90 | 1·50 (0·08–14·30), n = 912 | 1·0 (0·9–1·0) | 0·35 |
| Subcutaneous MTX dose (g) | 1·22 (0·06–7·45), n = 25 | 0·64 (0·02–11·21), n = 204 | 1·1 (0·9–1·3) | 0·19 |
| Total MTX dose (g) | 1·75 (0·06–8·70), n = 97 | 1·73 (0·02–14·30), n = 954 | 1·0 (0·9–1·1) | 0·75 |

CI, confidence interval; OR, odds ratio. The accumulated doses of MTX ranged from July 2005 to index date. The index date was in the time period from 1 January 2010 to 31 December 2016. The oral MTX doses are the accumulated doses of oral MTX among cases and controls. For this specific OR, conditional logistic regression controlling for the subcutaneous dose was used. The subcutaneous MTX doses are the accumulated doses of subcutaneous MTX among cases and controls. For this specific OR, conditional logistic regression controlling for the subcutaneous dose was used. Conditional logistic regression was used with only the total dose as the independent variable.

| Table 3 | Distribution of melanoma stages among MTX-exposed and MTX-unexposed cases |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Pathological staging | MTX exposed (n = 97)* | MTX unexposed (n = 298) | All cases (n = 395) |
| 0               | 50 (52)         | 141 (47)        | 191 (48)        |
| IX              | 0 (0)           | 8 (3)           | 8 (2)           |
| IA              | 24 (25)         | 74 (25)         | 98 (25)         |
| IB              | 11 (11)         | 39 (13)         | 50 (13)         |
| II              | 6 (6)           | 27 (9)          | 33 (8)          |
| III–IV          | 1 (1)           | 2 (1)           | 3 (1)           |
| Unknown         | 5 (5)           | 7 (2)           | 12 (3)          |

MTX, methotrexate. *Pathological stage was defined as: 0, melanoma in situ; IA, ≤ 1·0 mm without ulceration and a mitotic rate of < 1 mm−2; IB, ≤ 1·0 mm with ulceration or a mitotic rate of ≥ 1 mm−2, or 1·01–2·0 mm without ulceration; IX, ≤ 1·0 mm with unknown ulceration status or mitotic rate; II, 1·01–2·0 mm with ulceration or > 2·0 mm; III–IV, N1 or M1. 1Defined as ever exposure, implying one or more filled prescription(s) of MTX in the time period from July 2005 to index date. The index date was during the period from 1 January 2010 to 31 December 2016. Data are provided as n (%).
Post hoc analysis

The post hoc analysis, where prevalent cancers (other than CMM) were allowed before the index date, yielded 525 cases (265 men and 260 women) and 5250 controls (2650 men and 2600 women). Using this updated definition, an OR of 1.1 (95% CI 0.9–1.4) was observed for the primary analysis (ever vs. never exposure to MTX). Moreover, the results from the supplementary dose–response analysis and confounding analysis were consistent with the primary analysis (Tables S5, S6; see Supporting Information).

Discussion

In this nested case–control investigation, no association between MTX treatment and CMM was observed in patients with psoriasis. This finding was consistent in all analyses performed and no indication of a dose–response association was found. Moreover, the results are in line with our subanalysis in a previous comparative retrospective cohort study where patients who were exclusively prescribed MTX by a dermatologist (n = 10 399) did not have an enhanced risk for CMM compared with MTX-unexposed age- and sex-matched individuals (n = 51 400).2

In a previous Swedish investigation, Loeb et al. conducted a similar nested case–control investigation using an enumerated cohort of patients. The authors demonstrated that sildenafil exposure was associated with an enhanced risk of CMM. Nevertheless, as there was no indication of a dose–response association, the association was questioned.25

Despite being lower in the hierarchy of study designs than cohort investigations, case–control reports can reduce the risk for confounding by indication, particularly in this setting, where there is controversy regarding whether psoriasis intrinsically increases the risk for CMM.3–7 The median time from the first diagnosis of psoriasis to the index date was significantly lower among cases, but the difference observed was small. However, owing to the retrospective design, the date of first appearance of psoriasis was unavailable and the outpatient register was available only from 2001. As drug exposures are time-dependent, controls and cases should ideally also have been matched for psoriasis onset. Only filled outpatient prescriptions are included in the Swedish Drug Register. Other drugs administered in an inpatient setting were precluded from the analysis. While this would have only a minimal impact on the MTX data, some TNFis and possibly ILis are administered in an inpatient setting, which must be considered when interpreting the results. Moreover, the register includes only redeemed prescriptions from July 2005. Thus, the number of filled MTX prescriptions in both groups is underestimated. Finally, although included patients had psoriasis, the exact diagnoses that prompted MTX prescription remain unknown as these data are not included in the register.

Importantly, we were unable to obtain data on common CMM risk factors such as UV radiation by sun exposure and subsequent sunburns, indoor tanning, the presence of multiple or large melanocytic naevi, family history of CMM, a phenotypic characteristic including fair hair, eye and skin colours, and the tendency to freckle. Another limitation that deserves special attention is that no data on the number of phototherapy treatments with narrowband (nb)UVB or psoralen plus UVA (PUVA) could be obtained as these are not included in Swedish healthcare registries. As all patients included in our analysis had been diagnosed with psoriasis at a hospital level (outpatient clinic), it is expected that, overall, psoriatic disease in these patients was more severe than in patients treated only at a primary healthcare level. Arguably, using this line of reasoning, a high number of patients who were not prescribed a systemic antipsoriatic drug, including MTX, may have been referred for phototherapy. Therefore, it can be speculated that a possible association between MTX and CMM could have been cancelled out owing to an increased use of phototherapy among patients who were not exposed to MTX. While PUVA has been linked to CMM in several investigations,26,27 Swedish investigations have failed to find such an association.28 Moreover, this treatment modality has been used only rarely during the past two decades. Furthermore, there is no support for the suggestion that nbUVB therapy for psoriasis enhances the risk for CMM.19–23 Finally, it is also expected that patients receiving systemic treatments had a history of phototherapy that turned out to be insufficient. Although a nested case–control investigation was selected for this particular investigation, we acknowledge that alternative study methodologies could have been chosen, including the active comparator design, which aims at more closely resembling randomized controlled trials.34

In the present investigation, only previously cancer-free individuals were included (excluding basal cell carcinoma). A history of cutaneous squamous cell carcinoma in situ is not regarded as a contraindication to MTX initiation by many dermatologists. Therefore, an alternative approach would have been to also include these patients in the analysis. Nevertheless, in a post hoc analysis, the inclusion criteria for cases and controls were altered to include all patients with a prevalent cancer other than CMM. This complementary approach had no impact on our results.

The majority of patients included in our investigation were born in a Nordic country, which means that most patients probably had white Fitzpatrick skin phototypes I–III.35 This is important when discussing the external validity of our results. While CMM is more frequent in patients with these skin phototypes, further investigations including other populations and ethnicities are encouraged. Moreover, our mortality analysis must be interpreted with care as it included only a limited number of patients and was not powered to detect a difference between the groups. Finally, we did not adjust for competing events in the melanoma-specific mortality analysis.

In order to be included in this cohort, the patients were required to have two psoriasis diagnoses, with at least one of these diagnoses made by a dermatologist. Overall, 23% of the cases and controls had a diagnosis of PsOA. This figure corresponds well to the expected comorbidity frequency of PsOA among patients with psoriasis.16
One important strength of this investigation is that cases and controls were both selected from a cohort of patients with psoriasis. This eliminated the possibility of confounding by indication. Moreover, as full-body examinations are a central part of the dermatological examinations for patients with psoriasis, the risk for examination and surveillance bias is, most likely, significantly reduced.

This nested case-control study could not demonstrate any association between MTX use and the risk of CMM in patients with psoriasis. As MTX still constitutes an important drug in the dermatological treatment armamentarium, the results are reassuring for dermatologists treating patients with psoriasis in everyday clinical practice.

References
1 Buchbinder R, Barber M, Heuzenoeder L et al. Incidence of melanoma and other malignancies among rheumatoid arthritis patients treated with methotrexate. Arthritis Rheum 2008; 59:794–9.
2 Polesie S, Gillstedt M, Sonnergren HH et al. Methotrexate treatment and risk for cutaneous malignant melanoma: a retrospective comparative registry-based cohort study. Br J Dermatol 2017; 176:1492–9.
3 Boffetta P, Gridley G, Lindeløf B. Cancer risk in a population-based cohort of patients hospitalized for psoriasis in Sweden. J Invest Dermatol 2001; 117:1531–7.
4 Chiesa Fuxench ZC, Shin DB, Ogdie Beatty A, Gelfand JM. The risk of cancer in patients with psoriasis: a population-based cohort study in the health improvement network. JAMA Dermatol 2016; 152:282–90.
5 Egeberg A, Thyssen JP, Gislason GH, Skov L. Skin cancer in patients with psoriasis. J Eur Acad Dermatol Venereol 2016; 30:1349–53.
6 Ji J, Shu X, Sundquist K et al. Cancer risk in hospitalised psoriasis patients: a follow-up study in Sweden. Br J Cancer 2009; 100:1499–502.
7 Pouplard C, Brenaut E, Horreau C et al. Risk of cancer in psoriasis: a systematic review and meta-analysis of epidemiological studies. J Eur Acad Dermatol Venereol 2013; 27 (Suppl. 3):36–46.
8 Lange E, Blizzard L, Venn A et al. Disease-modifying anti-rheumatic drugs and non-melanoma skin cancer in inflammatory arthritis patients: a retrospective cohort study. Rheumatology (Oxford) 2016; 55:1594–600.
9 Scott FI, Mamtani R, Brensinger CM et al. Risk of nonmelanoma skin cancer associated with the use of immunosuppressant and biologic agents in patients with a history of autoimmune disease and nonmelanoma skin cancer. JAMA Dermatol 2016; 152:164–72.
10 Bailin PL, Tindall JP, Roenigk HH Jr, Hogan MD. Is methotrexate therapy for psoriasis carcinogenic? A modified retrospective-prospective analysis. JAMA 1975; 232:359–62.
11 Stern RS, Zierler S, Parrish JA. Methotrexate used for psoriasis and the risk of noncutaneous or cutaneous malignancy. Cancer 1982; 50:869–72.
12 Nyfors A, Jensen H. Frequency of malignant neoplasms in 248 long-term methotrexate-treated psoriasis. A preliminary study. Dermatologica 1983; 167:260–1.
13 Ridker PM, Everett BM, Pradhan A et al. Low-dose methotrexate for the prevention of atherosclerotic events. N Engl J Med 2019; 380:752–62.
14 Pedersen SA, Gaist D, Schmidt SAJ et al. Hydrochlorothiazide use and risk of nonmelanoma skin cancer: a nationwide case-control study from Denmark. J Am Acad Dermatol 2018; 78:673–81.e9.
15 Pottegard A, Halls J, Olesen M et al. Hydrochlorothiazide use is strongly associated with risk of lip cancer. J Intern Med 2017; 282:322–31.
16 Pottegard A, Pedersen SA, Schmidt SAJ et al. Association of hydrochlorothiazide use and risk of malignant melanoma. JAMA Intern Medicine 2018; 178:1120–2.
17 Kunisada M, Masaki T, Ono R et al. Hydrochlorothiazide enhances UVA-induced DNA damage. Photochem Photobiol 2013; 89:649–54.
18 Chahidi C, Morriere P, Aubally M et al. Photosensitization by methotrexate photoproducst. Photochem Photobiol 1983; 38:317–22.
19 Morison W, Montaz K, Parrish JA, Fitzpatrick TB. Combined methotrexate-PVUA therapy in the treatment of psoriasis. J Am Acad Dermatol 1982; 6:46–51.
20 Kubica AW, Brewer JD. Melanoma in immunosuppressed patients. Mayo Clin Proc 2012; 87:991–1003.
21 Wettermark B, Hammar N, Fored CM et al. The new Swedish Prescribed Drug Register Opportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiol Drug Saf 2007; 16:726–35.
22 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40:373–83.
23 Brusselaers N, Lagergren J. The Charlson Comorbidity Index in registry-based research. Methods Inf Med 2017; 56:901–6.
24 Rothman KJ, Greenland S, Lash TL. Modern Epidemiology. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2008.
25 Loeb S, Folkvaljon Y, Lambe M et al. Use of phosphodiesterase type 5 inhibitors for erectile dysfunction and risk of malignant melanoma. JAMA 2015; 313:2449–55.
26 Stern RS. The risk of melanoma in association with long-term exposure to PUVA. J Am Acad Dermatol 2001; 44:755–61.
27 Stern RS, Nichols KT, Vikevå LH. Malignant melanoma in patients treated for psoriasis with methoxsalen (psoralen) and ultraviolet A radiation (PUVA). The PUVA Follow-Up Study. N Engl J Med 1997; 336:1041–5.
28 Lindeløf B, Sigurgeirsson B, Tegner E et al. PUVA and cancer risk: the Swedish follow-up study. Br J Dermatol 1999; 141:108–12.
29 Hearn RM, Kerr AC, Rahim KF et al. Incidence of skin cancers in 3867 patients treated with narrow-band ultraviolet B phototherapy. Br J Dermatol 2008; 159:931–5.
30 Man L, Crombie IK, Dawe RS et al. The photocarcinogenic risk of narrowband UVB (TL-01) phototherapy: early follow-up data. Br J Dermatol 2005; 152:755–7.
31 Weischer M, Blum A, Eberhard F et al. No evidence for increased skin cancer risk in psoriasis patients treated with broadband or narrowband UVB phototherapy: a first retrospective study. Acta Derm Venereol 2004; 84:370–4.
32 Osumanovic A, Gillstedt M, Wennberg AM, Larkö O. The risk of skin cancer in psoriasis patients treated with UVB therapy. Acta Derm Venereol 2014; 94:425–30.
33 Archier E, Devaux S, Castela E et al. Carcinogenic risks of psoralen UV-A therapy and narrowband UV-B therapy in chronic plaque psoriasis: a systematic literature review. J Eur Acad Dermatol Venereol 2012; 26 (Suppl. 3):22–31.
34 Yoshida K, Solomon DH, Kim SC. Active-comparator design and new-user design in observational studies. Nat Rev Rheumatol 2015; 11:437–41.
35 Fitzpatrick TB. The validity and practicality of sun-reactive skin types I through VI. Arch Dermatol 1988; 124:869–71.
36 Ritchlin CT, Colbert RA, Gladman DD. Psoriatic arthritis. N Engl J Med 2017; 376:957–70.
Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher’s website:

- **Figure S1** Histogram of methotrexate doses among cases and controls.
- **Figure S2** Survival analyses.
- **Table S1** Definition of comorbidities.
- **Table S2** Data on number of outpatient visits and hospitalizations.
- **Table S3** Odds ratios when using different lag periods.
- **Table S4** Confounding analysis.
- **Table S5** Dose–response analysis for the supplementary risk-set sampling allowing for prevalent cancer other than cutaneous melanoma before index date.
- **Table S6** Confounding analysis for the supplementary risk-set sampling allowing for prevalent cancer other than cutaneous melanoma before index date.
- **Powerpoint S1** Journal Club Slide Set.
- **Video S1** Author video.