Melanoma Risk is Increased in Patients with Mycosis Fungoides Compared with Patients with Psoriasis and the General Population*

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Patients with mycosis fungoides (MF) are thought to be at increased risk of melanoma. However, studies addressing surveillance-bias and treatments as a possible confounder are lacking. This retrospective study compared the prevalence and risk of melanoma between 982 patients with MF, and 3,165 patients with psoriasis attending tertiary cutaneous-lymphoma/psoriasis clinics during 2009 to 2018. Melanoma was diagnosed in 47 patients with MF (4.8%; 43 early-stage) and in 23 patients with psoriasis (0.7%) (odds ratio 6.6, $p<0.0001$). In 60% of patients, MF/psoriasis preceded melanoma diagnosis. Hazard ratio (HR) for a subsequent melanoma in MF vs psoriasis was 6.3 (95% confidence interval (95% CI) 3.4–11.7, $p<0.0001$). Compared with the general population, melanoma standardized incidence ratios were 17.5 in patients with MF (95% CI 11.0–23.9, $p<0.0001$), and 2.2 (95% CI 0.6–3.8, $p=0.148$) in patients with psoriasis. Narrow-band ultraviolet B was not a contributory factor (HR 1.15, 95% CI 0.62–2.14, $p=0.66$). These findings add evidence that patients with MF have a significantly higher risk of melanoma, not only compared with the general population, but also compared with patients with psoriasis. This comorbidity may be inherent to MF.

Key words: mycosis fungoides; melanoma; psoriasis; phototherapy; hazard ratio; standardized incidence ratio.

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SIGNIFICANCE

Data on the comorbidity of mycosis fungoides with melanoma lack considerations of surveillance bias and treatment as a possible confounder. In this institutional-based series, Israeli patients with mycosis fungoides were found to have a significantly higher risk of melanoma, not only compared with the general population, as reported previously, but also compared with patients with psoriasis followed-up at the same tertiary clinic. Narrow-band ultraviolet B treatment was not a contributory factor. Repeated meticulous skin examination with a focus on melanoma detection is therefore paramount in patients with mycosis fungoides.

Epidemiological studies of mycosis fungoides (MF), the most prevalent cutaneous T-cell lymphoma (CTCL) (1), have consistently shown an increased comorbidity of MF with other malignancies, especially lymphomas, but also with solid colon and lung cancers (2–5). As for the association with melanoma, following early case reports and case series (6–10), reporting the association between MF and melanoma, large comparative institution- and population-based studies (2–4, 11–13) have investigated the prevalence of melanoma in MF, the association between the diseases odds ratio (OR), and the risk of secondary melanoma relative to the expected incidence in the general population according to the standardized incidence ratio (SIR). However, the results are contradictory; a study based on a SEER-9 registry ($n=1,789$ patients with MF) yielded a high SIR for melanoma of 2.60 (95% confidence interval (CI) 1.25–4.79), as opposed to an institution-based cohort ($n=429$ patients with MF), which showed a non-increased incidence compared with the general population (2). Subsequently, a study using a SEER-18 registry ($n=6,742$ patients with MF) reported a high SIR of 9.0 for melanoma (13). A recent systematic review and meta-analysis of the literature, indicated that lung cancer, bladder cancer and melanoma (5) are significantly increased in patients with MF, with a SIR of 4.10 (95% CI 1.77–6.43) for melanoma.

However, critical surveillance bias, due to relatively frequent follow-up visits of patients with MF at the dermatology clinic, and treatment as a possible confounder, which may affect the risk of melanoma in these cases, were barely addressed in previous studies (2–4, 6–12).

Surveillance bias is inherent in comparisons with large population/national registries due to the possible increased likelihood of earlier and more melanoma diagnoses in dermatology clinics in MF than in general community practices. In addition, large-scale studies evaluating the risk of a secondary malignancy, including melanoma, among patients with MF, are mostly limited to the USA and to a few European countries (2, 4, 11–15).

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In an attempt to counter the above-mentioned methodological limitations, an epidemiological cohort study was conducted to determine the lifetime prevalence of melanoma in patients with MF, as well as the risk of subsequent melanoma in Israeli patients with MF, by comparing the findings with those of patients with psoriasis attending a tertiary hospital-based clinic. Like MF, this chronic T-cell-mediated inflammatory dermatosis often requires frequent clinic visits and treatment with phototherapy and, similarly, the risk of developing melanoma was found to be equivocal (16–18). The rate of melanoma in MF was also compared with that in the general population. In addition, the potential of phototherapy as a risk factor for melanoma was investigated.

MATERIALS AND METHODS

Study participants and setting

The study group included patients diagnosed with MF and followed consecutively at the outpatient Cutaneous Lymphoma Clinic of the Division of Dermatology of Rabin Medical Center (RMC) from 2009 (when electronic record-keeping was initiated) through 2018. All diagnoses were based on the criteria of the World Health Organization-European Organization for Research and Treatment of Cancer (WHO-EORTC) (19). Exclusion criteria were co-existent MF and psoriasis and an inconclusive diagnosis of MF. The comparison group consisted of patients with a well-defined clinical diagnosis of psoriasis. Most were followed exclusively at the outpatient Psoriasis Clinic during the same period.

To ensure the systematic identification of all patients in both groups with a co-occurrence of melanoma, 3 parallel methods were used (**Fig. 1**): (*i*) institutional database search using internal codes of the relevant clinics ("cutaneous lymphoma"/"psoriasis"), for a diagnosis of "melanoma" in the past medical history/during follow-up; (*ii*) institutional database search using ICD-9 codes, cross-checking for "mycosis fungoides"/"psoriasis" and "melanoma"; and (*iii*) outpatient clinic physician information on patients with co-morbid MF/psoriasis and melanoma.

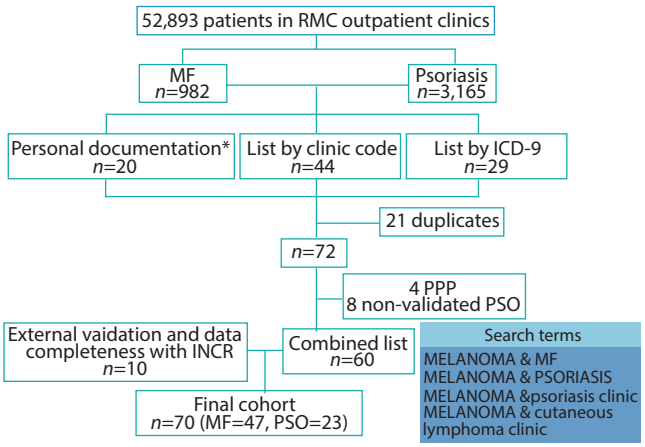

Fig. 1. Flow chart of the inclusion and exclusion process for patients with mycosis fungoides (MF) and psoriasis (PSO) attending Rabin Medical Center (RMC) outpatient clinics from 2009 to 2018 who acquired melanoma. Search methods using international diagnosis codes (International Classification of Diseases – Ninth edition; ICD-9) and internal institutional clinic codes are highlighted on the righthand side of the figure. PPP: parapsoriasis en plaque; INCR: Israel National Cancer Registry. *Among the patients with melanoma, 17 from the MF group and 3 from the psoriasis group were identified prior to initiation of the study.

Each patient identified by these methods was internally validated by review of the individual medical file. In addition, all histological diagnoses of melanoma in Israel must be reported to the Israel National Cancer Registry (INCR). Therefore, all patients who visited the RMC dermatology clinic during the study period were matched with the INCR records, using their personal identification number (Fig. 1), to assure the capture of all cases of in-hospital or community detection of melanoma.

The study protocol was approved by the Institutional Review Board.

Data collection

The following clinical data were collected: the number of visits per year at the specific outpatient clinics, age, sex, occupation (outdoor/indoor), place of residence (rural/urban), Fitzpatrick skin type, origin/ethnicity, family history of melanoma, timing of melanoma diagnosis (before/after MF/psoriasis diagnosis), latency between diagnoses, other malignancies, treatment (systemic, biologic for psoriasis, topical chemotherapy/radiation for MF), type and duration of phototherapy. In the electronic registry, treatments were coded as "narrow-band ultraviolet B (NB-UVB)" or "psoralen and ultraviolet A (PUVA)". Although data on NB-UVB were accurate and complete for the entire cohort, the type of PUVA used (systemic/bath/palmoplantar) was specified only for patients with co-morbid MF/psoriasis and melanoma.

The following clinicopathological data were collected: MF stage; psoriasis type and severity (mild/moderate-severe); melanoma subtype, location, and Breslow depth. To determine between-group differences, Breslow depth was assessed as a categorical variable, divided into either 3 ordinal categories: melanoma *in situ*, thin melanoma ($\leq$1 mm), and thick melanoma (>1 mm), or into 2 categories according to the INCR: melanoma *in situ* and invasive melanoma.

Comparison with the general population

To compare the risk of melanoma with the general population, we calculated only incidence rates of melanoma occurring after the diagnosis of MF or psoriasis. The SIR of observed cases in the study groups to the expected number of cases in the general Israeli population, matched for sex, age, race, and calendar year (based on INCR data), served as the comparative epidemiological measure. Follow-up was reported in person-years, starting from diagnosis of MF/psoriasis to development of melanoma, death, or end of the observation period, whichever occurred first. The time of diagnosis was defined as the date of histological confirmation of MF or melanoma. Cases of simultaneous (within 12 months) diagnosis of melanoma and MF/psoriasis were excluded from the SIR calculation and other statistical processing that was relevant to the timeframe. This approach was based on reports of a spike in SIR for 12 months after the initial diagnosis of a primary disease (13, 20).

Statistical analysis

Interval data are presented as mean ± standard deviation (SD) or median and were compared between groups by Student's *t*-test or Mann–Whitney *U* test, as appropriate. Categorical variables were compared between groups by Fisher's exact and χ^2 tests. Between-group differences in ordinal covariates were analysed by Mann–Whitney *U* test. Patients with missing information were excluded from the analysis.

Cox proportional hazards regression models were used to analyse the association between multiple covariates and melanoma.

To avoid overestimation of melanoma risk, mortality unrelated to melanoma was considered a competing risk (21).

A cumulative incidence curve was generated to assess differences between the MF and psoriasis groups. The contribution of phototherapy to melanoma risk was analysed in the Cox model as a time-varying covariate, in order to account for cases in which phototherapy was administered before the definitive diagnosis of MF and psoriasis was made, and for any changes in phototherapy treatment (as an "event" in the survival model) with time. Logarithmic transformation was employed to approach a symmetrical distribution.

A 2-tailed *p*-value of less than 0.05 was considered statistically significant. Statistical analysis was conducted with SAS ver 9.4 (SAS Institute Inc., Cary, NC, USA) and SPSS ver 21 (IBM Corp, Armonk, NY, USA).

RESULTS

During the study period, 52,893 patients were followed at the RMC outpatient clinics, including 982 with MF and 3,165 with psoriasis. The mean ± SD number of visits per year at the specific outpatient clinics was: 3.1 ± 1.8 in the MF patient group and 2.3 ± 1.4 in the psoriasis patient group ($p<0.0001$), median 2.8 (range 1.1–9.5), and 2 (range 1–9), respectively ($p<0.0001$).

The characteristics of patients with MF and psoriasis are shown in **Table I**.

Patients with MF were older at diagnosis than patients with psoriasis (52.5 and 42.5 years, respectively) and were followed for a shorter duration (median 7 and 9 years, respectively).

Melanoma was diagnosed in 70 patients: 47 with MF (4.8%, 33 male, **Fig. 2**) and 23 with psoriasis (0.7%, 9 male). Their clinical characteristics are shown in Table SI[1]. MF staging was as follows: 43 IA–IIA (early stage), 3 IVA_1, 1 IVA_2. In the psoriasis group, 20 patients had psoriasis vulgaris and 2 palmoplantar psoriasis; in one, the type was unknown. The disease was mild in 13 patients and moderate–severe in 10. The difference in melanoma lifetime prevalence between the MF and psoriasis groups was significant (OR 6.6, 95% CI 4.0–10.8, $p<0.0001$). There was no between-group difference in age at melanoma diagnosis (58.6 and 55.0 years, respectively) or in inherited, demographic, and exposure-related factors, (including: area of residence, and outdoor occupation).

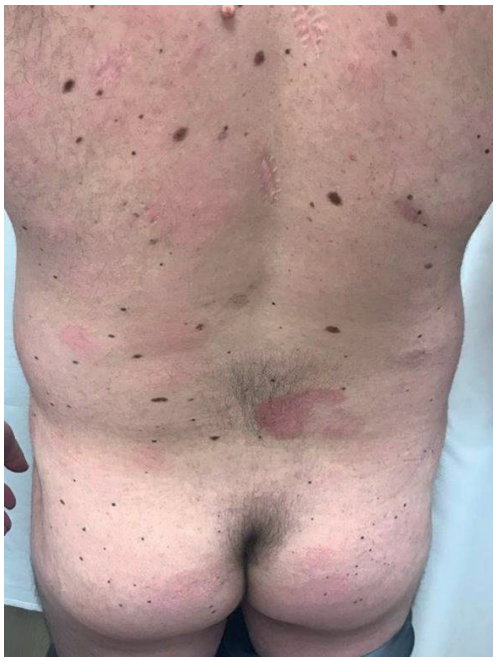

Fig. 2. A patient with classic patch-stage IB mycosis fungoides and multiple naevi. This patient was diagnosed with melanoma *in situ*.

The diagnosis of MF or psoriasis preceded the diagnosis of melanoma in approximately 60% of patients in each group (28 MF, 14 psoriasis; $p=1.0$; Table SI[1]). The duration of follow-up was 7,327 person-years in the MF group and 35,476 person-years in the psoriasis group, with median time to diagnosis of melanoma of 5.5 years (1–30) and 7 years (1–50), respectively (Table SI[1]). On univariate Cox proportional hazards analysis adjusted for competing risk, the contributory effect of MF vs psoriasis was the most significant determinant in melanoma incidence, with a hazard ratio (HR) of 6.3 (95% CI 3.4–11.7, $p<0.0001$; **Table II**). The cumulative incidence curve comparing the 2 cohorts is shown in **Fig. 3**. On multivariate analysis, the HR for MF vs psoriasis remained high (4.8) and significant (95% CI 2.5–9.2, $p<0.0001$; Table II). To attenuate further possible surveillance bias between patients with MF or psoriasis, analysis of OR conducted for cases with melanoma preceding the diagnosis of MF/psoriasis, yielded an OR of 7.1 (95% CI 3.2–15.7, $p<0.0001$).

Characteristics of melanoma ($n=70$) are shown in Table SII[1]. Twenty-one patients had superficial spreading melanoma. Missing data precluded comparison of the clinicopathological

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Table I. Demographic and clinical details of patients with mycosis fungoides (MF) and psoriasis

Characteristics	MF $n=982$	Psoriasis $n=3,165$	*p*-value
Age at diagnosis (years), mean (SD)	52.5 (17.5)	42.5 (17.7)	<0.0001
Sex, *n* (%)			<0.0001
Male	638 (65)	1,653 (52.2)	
Female	344 (35)	1,512 (47.8)	
Age at study end (years), mean (SD)	60.9 (18.3)	53.9 (18.1)	<0.0001
Phototherapy, *n* (%)			0.224
Yes	445 (46.3)	1,531 (48.6)	
No	517 (53.7)	1,622 (51.4)	
Total cumulative duration of phototherapy (months), median (range)	24.4 (1–404)	5.3 (1–344)	<0.0001
Total cumulative duration of NB-UVB (months), median (range)	18.0 (1–194)	5.0 (1–191)	<0.0001
Follow-up period (years), median(range)	7 (1–43)	9 (1–68)	<0.0001

NB-UVB: narrow-band ultraviolet B.

Table II. Adjusted Cox proportional hazards analysis for risk of subsequent melanoma

Analysis	HR	95% CI	*p*-value
Background factors			
Univariate[a]			
MF vs psoriasis	6.28	3.37–11.70	<0.0001
Sex (male vs female)	0.87	0.62–2.14	0.64
Age at diagnosis of MF/psoriasis	1.04	1.02–1.05	<0.0001
Multivariate[a]			
MF vs psoriasis	4.77	2.48–9.15	<0.0001
Sex (male vs. female)	0.89	0.49–1.64	0.72
Age at diagnosis of MF/psoriasis	1.03	1.01–1.04	0.0007
Phototherapy			
Univariate[b]			
Phototherapy – all types (2 groups)	1.39	0.75–2.60	0.30
Phototherapy – all types (MF)	1.57	0.75–3.30	0.23
Phototherapy – all types (psoriasis)	1.14	0.37–3.51	0.82
NB-UVB (2 groups)	1.15	0.62–2.14	0.66
NB-UVB (MF)	1.35	0.65–2.82	0.43
NB-UVB (psoriasis)	0.94	0.31–2.83	0.91
Univariate[c]			
Phototherapy – all types, months (2 groups)	1.19	0.85–1.65	0.32
Phototherapy – all types, months (MF)	1.05	0.72–1.55	0.79
Phototherapy – all types, months (psoriasis)	1.03	0.63–1.67	0.92
NB-UVB, months (2 groups)	1.29	0.94–1.76	0.11
NB-UVB, months (MF)	1.14	0.77–1.70	0.51
NB-UVB, months (psoriasis)	1.20	0.76–1.89	0.43

[a]Baseline – diagnosis of MF/psoriasis. [b]With time – dependent covariate (baseline–birth). [c]Baseline – end of phototherapy.
MF: mycosis fungoides; NB-UVB: narrow-band ultraviolet B; HR: hazard ratio; CI: confidence interval.

types between the groups. Twenty-eight patients with MF (63.6%) had melanoma *in situ* compared with 6 with psoriasis (30.0%). Analysis of melanoma by ordinal categories (*in situ*, thin, thick) yielded a significantly higher rate of thick melanoma (≥1 mm) in the psoriasis group ($p=0.005$, Mann–Whitney *U* test). Division into 2 groups (*in situ*, invasive), as reported by the INCR, yielded 16 cases of invasive melanoma in the MF group (36.4%) and 14 in the psoriasis group (70%). The OR of having invasive melanoma in the psoriasis group was 4.1 (95% CI 1.3–12.7, $p=0.016$). The overall mean Breslow depth was significantly greater in the psoriasis than the MF group ($p=0.001$).

Of the 982 patients with MF, 445 (46.3%) received phototherapy, the vast majority NB-UVB ($n=413$), for a median cumulative duration of 18.0 months (IQR 5.8–60.3). Similarly, of the 3,165 patients with psoriasis, 1,531 (48.6%) received phototherapy, also mainly NB-UVB ($n=1,325$), for a median cumulative duration of 5.0 months (IQR 2.5–43.3).

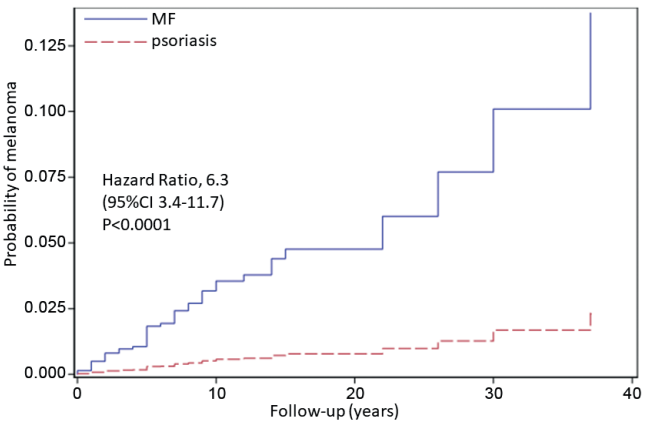

Fig. 3. Cumulative incidence curve for melanoma in mycosis fungoides (MF) and psoriasis groups after adjusting for competing risk (death unrelated to melanoma).

As expected, none of the 19 patients with MF with a prior history of melanoma received phototherapy. Of the 28 patients with MF who were subsequently diagnosed with melanoma, 18 received phototherapy, the majority of whom received NB-UVB. The distribution of phototherapy types is shown in Table SI[1]. NB-UVB was administered for a median of 13 months (IQR 8.0–26.9), and systemic PUVA for 9 months (IQR 5.3–15.3). Other treatments with carcinogenic potential were administered to only a small minority of patients in both groups (Table SI[1]).

No association was found between phototherapy-all types or NB-UVB specifically, with subsequent melanoma in MF or psoriasis. There was no effect of treatment duration of all types of phototherapy and of NB-UVB specifically on melanoma risk (Table II).

The SIR was significantly increased in the MF group compared with the matched general population (17.5, 95% CI 11.0–23.9, $p<0.0001$) (**Table III**). SIRs were significantly elevated for *in situ* melanoma (19, 95% CI 10.5–27.6, $p<0.0001$) as well as for invasive melanoma, although, to a lesser degree, in the latter (SIR 4.5, 95% CI 1.6–7.5, $p<0.0001$, Table III). In contrast, the SIR for melanoma in the psoriasis group was not increased (2.2, 95% CI 0.6–3.8, $p=0.148$).

DISCUSSION

Although the risk of subsequent melanoma in MF has been studied previously (2, 4, 5, 11–13), this is the largest institutional-based study and the first on the association between these 2 malignancies, while addressing surveillance bias and NB-UVB treatment as a possible confounder. This study found that the prevalence of melanoma is higher in patients with MF compared with the general population. Furthermore, the prevalence of melanoma was significantly higher in patients with MF than in patients with psoriasis, who were treated at our psoriasis clinic (almost 5.0% vs 0.7%, OR 6.6,

Table III. Standardized incidence ratio (SIR) of subsequent melanoma in patients with mycosis fungoides/psoriasis compared with the general Israeli population

Group	SIR	95% CI	*p*-value
Mycosis fungoides			
Melanoma, all types	17.5	11.0–23.9	<0.0001
Melanoma *in situ*	19	10.5–27.6	<0.0001
Melanoma – invasive	4.5	1.6–7.5	0.019
Psoriasis			
Melanoma, all types	2.2	0.6–3.8	0.148
Melanoma *in situ*	1.4	0–2.9	0.631
Melanoma – invasive	1	0–1.9	0.0928

SIR: standardized incidence ratio: CI: confidence interval.

$p<0.0001$). There was no between-group difference in patient age at melanoma diagnosis, Fitzpatrick skin type, or other relevant risk factors (e.g. outdoor occupation). The risk of subsequent melanoma was higher in the MF than in the psoriasis group (HR 6.3, $p<0.0001$) and the general population (SIR 17.5, $p<0.0001$). Moreover, there was no association of NB-UVB with subsequent melanoma in MF or psoriasis.

There are several possible reasons for the difference in melanoma incidence in MF and psoriasis. Cases of MF succeeding melanoma may represent an *a priori* susceptibility due to a genetic component, predisposing to the development of both malignancies (4, 22–26). This may include a common genetic basis, as suggested by the reports on the associations of the histocompatibility locus antigen (HLA) alleles, HLA-DR5 and DQB1*03 with CTCL as well as melanoma (22, 23) and the detection of mutations in the *CDKN2A* gene, encoding tumour suppressor protein p16 in both (4, 24, 25).

In contrast, cases of MF preceding melanoma may also involve exposures and immunological factors related to MF and its treatment.

Induction of systemic immunosuppression may explain the development of melanoma in advanced-stage MF, which occurred in 4 patients in our cohort. Pielop et al. (4) described the decreased levels of normal circulating CD4 in erythrodermic MF as an immunological state parallel to acquired immunodeficiency syndrome, a well-recognized risk factor for melanoma (4, 27). They summarized that, in advanced-stage MF, the immunological milieu was skewed to the pro-tumorigenic Th2 pole and decreased interferon-ɣ levels (4). Others described the regression of both MF and advanced melanoma following melanoma treatment with ipilimumab, suggesting that a similar immunological CTLA-4-mediated pathway underlies both malignancies (28).

By contrast, early MF may be characterized by local immunosuppression, as indicated by the report of 4 patients in whom multiple naevi developed on longstanding MF patches (29). The authors hypothesized that the loss of immune senescent surveillance may explain the decreased ability of the immune system to eliminate local proliferative processes, either benign (naevi) or malignant (melanoma). Local immunosuppression may be partially relevant to our cohort, although 10 patients acquired melanoma on the face/scalp, which was devoid of MF lesions.

Phototherapy is a central treatment modality in early-stage MF. UV light is a well-established carcinogen, and there are cases of melanoma appearing in patients treated with PUVA (30, 31). Early findings showed a 5-fold increase in melanoma after longstanding PUVA treatment and a long latency period (32). However, a more recent study of 3,867 patients (the majority with psoriasis) treated with NB-UVB, did not find an increase in melanoma (33). Therefore, in recent years, PUVA has largely been replaced by NB-UVB for most phototherapy-responsive dermatoses. Of note, the 2016 Consensus Statement on phototherapy in MF stresses that a review of the literature is reassuring regarding the photo-carcinogenicity of NB-UVB (34).

In the current study cohort, only 5 patients with MF and melanoma received PUVA, for a median duration of 9 months. The time-varying Cox proportional hazards model revealed no association between phototherapy-all types and specifically NB-UVB and melanoma in either MF or psoriasis (Table II).

Five of our 47 patients with MF had multiple primary melanomas, and 4 were diagnosed with melanoma before the age of 40 years. These findings support the suggestion of a genetic susceptibility as the common denominator for both malignancies (4, 22–26). It is also possible that both melanoma and MF are related to a genetic alteration induced by a shared carcinogen, such as ambient UV radiation (35–37).

The relatively high rate of melanoma *in situ* in the MF group is in accordance with the trends in melanoma diagnosis between 1990 and 2016, indicating an increase in the diagnosis of melanoma and a disproportional relative increase in the diagnosis of melanoma *in situ* (38). A similar trend was reported in the SEER database study (39).

The difference in melanoma *in situ* rates between the MF (63.6%) and psoriasis (30%) groups might be attributable to the more thorough full-skin examination conducted at the tertiary lymphoma clinic, and to the relatively fewer visits per year at the psoriasis vs the MF specific clinics (mean number of visits per year 2.3, and 3.1, $p<0.0001$, respectively). Likewise, under-diagnosis of melanoma *in situ* in the general population could be attributed to surveillance bias. To attenuate this possible surveillance bias, analysis of OR conducted for cases with melanoma preceding the diagnosis of MF/psoriasis, still yielded a significantly higher OR of 7.1 (95% CI, $p<0.0001$) of melanoma in MF compared with psoriasis, and SIR analysis only for cases of invasive melanoma, still showed an increased risk of this malignancy in MF compared with the general population (SIR 4.5, $p<0.0001$).

The current study was limited by its retrospective design and insufficient documentation of patient demographics and environmental exposures in the medical files. Moreover, as delineated above, the surveillance bias was diminished, but not eliminated. Finally, the MF group had a shorter median follow-up than the psoriasis group ($p<0.0001$); nevertheless, they also had an elevated melanoma risk. Although, it is important to consider whether melanoma preceded or followed the appearance of MF, in some cases it was not possible to reach a definitive conclusion based on the relative sequence of events in the 2 groups, because the diagnosis of MF is difficult in the early stages and therefore often delayed (40).

In summary, this study provides support to the growing body of evidence suggesting that MF patients have an increased risk of melanoma compared with the general population. Furthermore, this study found, for the first time, that patients with MF have a higher rate of co-morbid melanoma, and a higher risk of development of melanoma relative to patients with psoriasis. The development of melanoma in MF is probably multifactorial, but an inherent biological factor seems to play a role, as prior NB-UVB therapy did not impact on this risk. Thus, patients with MF require repeated meticulous full-body skin examinations, with a special focus on melanoma detection. Further prospective studies in larger cohorts are needed to corroborate these findings.

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The authors have no conflicts of interest to declare.

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