Original Article

Psoriasis and malignancy, is there a link? Data from the Malaysian Psoriasis Registry

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Abstract

Background: The risk of malignancy in psoriasis patients may be attributed to the chronic inflammatory course of the disease, the associated comorbidities and the treatment modalities employed. However, the association between psoriasis and malignancy has not been explored among Asians in depth. Our aim is to determine the frequency of malignancy and to identify the risk factors associated with malignancy among psoriasis patients in Malaysia. **Materials and Methods:** A retrospective cross-sectional study utilising the database of the Malaysian Psoriasis Registry was conducted. All psoriasis patients registered from 1 January 2007 to 31 December 2018 who were diagnosed with malignancy during their lifetime were included. **Results:** There were 123 (0.57%) psoriasis patients who reported a malignancy from a total of 21,735 patients. The male-to-female ratio was 1:1.41. The rate of malignancy was highest among inverse psoriasis (4.81%) patients followed by localised pustular psoriasis (1.79%), guttate psoriasis (0.81%), plaque psoriasis (0.57%) and erythrodermic psoriasis (0.26%). The ethnic Chinese had the highest rate of malignancy (32.5%) followed by Malays (31.7%) and Indians (14.6%). The top five cancers reported among our psoriasis patients were breast cancer, haematological cancers, colorectal cancer, female genital cancers and brain cancers. Only 1 paediatric patient (16 years old) had malignancy which was a brain tumour. **Conclusions:** The frequency of malignancy was 0.57% among psoriasis patients in our registry. Being older than 40 years and female were significantly associated with malignancy in psoriasis patients. The rate of malignancy was highest among inverse psoriasis patients.

Keywords: Biologic therapies, cyclosporine, lymphoma, malignancy, methotrexate, psoriasis, skin cancer, ultraviolet therapy

Introduction

Psoriasis is a common chronic relapsing immune-mediated disease with predominant skin and joint involvement. Its prevalence worldwide varies among different countries, ranging from 1.83% to 1.92% among European countries with a relatively lower prevalence (0.14%) in the Asia-Pacific populations.[1] Various reports have demonstrated that psoriasis is linked to multiple comorbidities including malignancy.[2-5]

The correlation between malignancy and psoriasis is conflicting.[6,7] The increased risk of malignancy in psoriasis patients has been hypothesised to be attributed to the chronic inflammatory state of the disease, systemic immunosuppressants employed and other associated comorbidities.[8,9] Several studies have considered previous exposure to oral immunosuppressive drugs and ultraviolet (UV) radiation in psoriasis patients as potential cancer risk factors.[6,8,10] In addition, the growing usage of biological agents has also raised concerns regarding the risk of malignancy.[11]

The top 10 cancers among Malaysians were breast, colorectal, lung, lymphoma, nasopharynx, leukaemia, prostate, liver, cervix uteri and ovarian.[12] The occurrence of malignancy in psoriasis patients has not been explored among Asians although there are numerous epidemiological studies in Western countries. Our aim is to determine the frequency of malignancy among patients with psoriasis in Malaysia.

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Materials and Methods

This was a retrospective multicentre cross-sectional study conducted on psoriasis patients who had been diagnosed with malignancy at any time. We included patients notified to the Malaysian Psoriasis Registry (MPR) from January 2007 till December 2018. The MPR receives notifications mainly from state public hospitals and a small number from private dermatology clinics via a standardised notification form [Figure 1]. All subjects were divided into two groups by age of psoriasis onset: type I psoriasis (<40 years) and type II psoriasis (≥40 years).[13] The severity of psoriasis was determined by percentage of body surface area (BSA) involvement and Dermatology Life Quality Index (DLQI) scores for patients aged 17 years and above.[14] Erythrodermic psoriasis is defined as extensive psoriasis affecting more than 80% BSA.

The DLQI is a validated patient-reported questionnaire that is used to evaluate the quality of life affected by a dermatological disease. Patients with more than 10% BSA involvement or a DLQI score of more than 10 were classified as moderate to severe psoriasis. All treatments received in the past 6 months were recorded.

Body mass index (kg/m^2) of the patients was categorised according to the Asia-Pacific classification.[15] The cancer diagnosis was self-reported when patients had been diagnosed by a physician based on histopathology. These cancers were categorised according to the organ involved.

Descriptive analyses were used for socio-demographic data, clinical characteristics and systemic treatments received by the patients. Results were expressed as numbers and percentages for categorical variables. Continuous variables were expressed as means and standard deviations. Categorical variables were compared using Chi-square analysis with a significance level defined as $P < 0.05$. A comparison of means was performed using the independent sample *t*-test. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software for Windows version 22.0 (IBM Corp, Armonk, NY, USA). This study was approved by the Medical Research Ethics Committee of the Ministry of Health, Malaysia, on 3 February 2020 (NMRR-19-1683-49302).

Results

Baseline characteristics

Among the 21,735 patients notified to the MPR within the study period, 123 psoriasis patients (0.57%) had reported a malignancy. The socio-demographic characteristics are shown in Table 1. Our psoriasis patients with malignancy were older, with a significantly higher mean age at notification to the registry (54.4 vs. 41.7 years, $P < 0.001$), and had a later age of psoriasis onset (43.2 vs. 33.2 years, $P < 0.001$) compared to those in the non-cancer group. There was a slight female preponderance with a male-to-female ratio of 1:1.4 in the cancer group. Ethnic Chinese patients with psoriasis had the highest rate of malignancy (32.5%) in our study followed closely by Malays (31.7%).

In our malignancy cohort, chronic plaque psoriasis was the most common type observed (89.1%) followed by guttate psoriasis (5%) and inverse psoriasis (4.2%). Of note, there were a significantly higher proportion of inverse psoriasis patients with malignancy compared to those without malignancy (4.2% vs. 0.5%, $P < 0.001$). Pustular type was seen only in one psoriasis patient (0.8%) with cancer. A significantly higher rate of diabetes mellitus ($P = 0.003$), hypertension ($P < 0.001$) and dyslipidaemia ($P = 0.008$) was demonstrated among the psoriasis patients with malignancy in comparison to those without cancer.

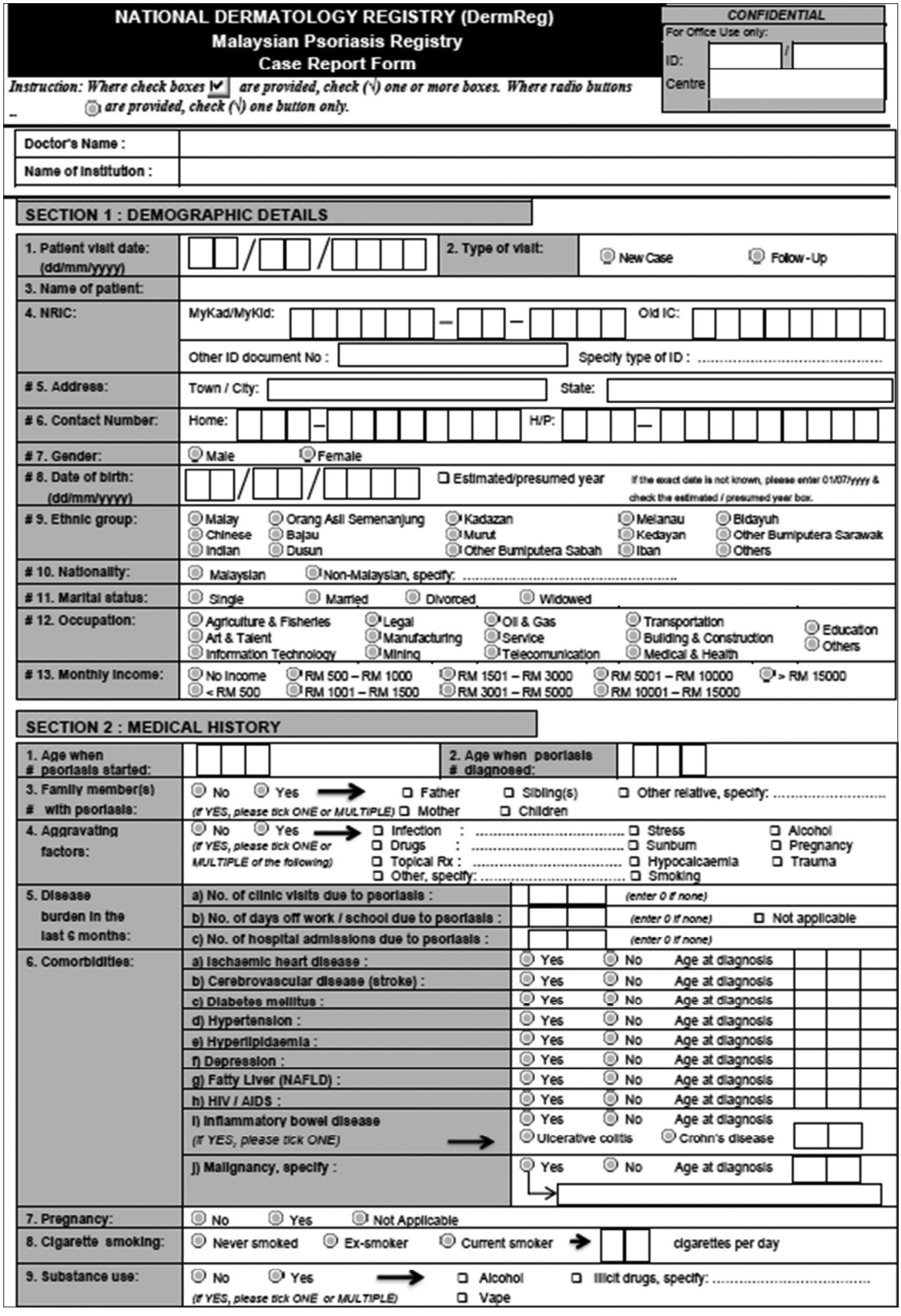
History of smoking and disease severity were similar in both groups. Of the 13 psoriasis patients with a history of cancer who received systemic therapy for their psoriasis, 7 (53.8%) were prescribed acitretin, 5 (38.5%) received methotrexate and 1 (7.7%) was treated with hydroxyurea. Only one psoriasis patient (0.8%) underwent narrow-band UV B (NBUVB) phototherapy treatment from the cancer cohort. Of note, none of the psoriatic patients with cancer were given ciclosporin or biological agents.

Types of malignancies

Majority of the psoriasis patients had solid organ cancers which were cancers of the breast (34.1%), colon (11.4%), genital tract (8.1%), brain (4.9%), thyroid (4.9%), urinary tract (4.1%), skin (2.4%), respiratory tract (2.4%) and upper aerodigestive tract (0.8%) [Table 2]. Haematological malignancies made up 11.4%, with leukaemia being the most common malignancy in the male cohort affecting seven patients. Whereas, for women, it was breast cancer (58.3%) followed by female genital tract cancers (predominantly ovarian and uterine cancers) affecting seven patients. Only one paediatric patient (16 years old) was diagnosed with brain cancer.

Discussion

To the best of our knowledge, this is the first study that evaluates the rate of malignancy among Malaysian psoriasis patients with a study duration of 12 years. Based on the data from the International Agency for Research on Cancer in Malaysia, the incidence and prevalence rates for overall cancer in the general population were 1.5 per 1000 and 4.0 per 1000 persons, respectively.[16] The prevalence rate of cancer among our psoriasis population was higher at 5.7 per 1000 persons. In a recent systematic review and meta-analysis, the overall prevalence of cancer in patients with psoriasis was stated as 4.78%. The author also found the risk of overall cancer risk for psoriasis patients was 1.21 with an incidence rate of 11.75 per 1 million population.[17] In Taiwan, the incidence of cancer for 7 years among psoriasis patients was 4.8%.[18] In a population study conducted in Korea by Lee *et al*., the incidence of overall cancer was significantly elevated in the psoriasis cohort, especially in those with severe psoriasis.[19] Similarly, our



NATIONAL DERMATOLOGY REGISTRY (DermReg)
Malaysian Psoriasis Registry
Case Report Form

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For Office Use only:
ID: /
Centre

Instruction: Where check boxes ☑ are provided, check (√) one or more boxes. Where radio buttons ◎ are provided, check (√) one button only.

Doctor's Name :	
Name of Institution :	

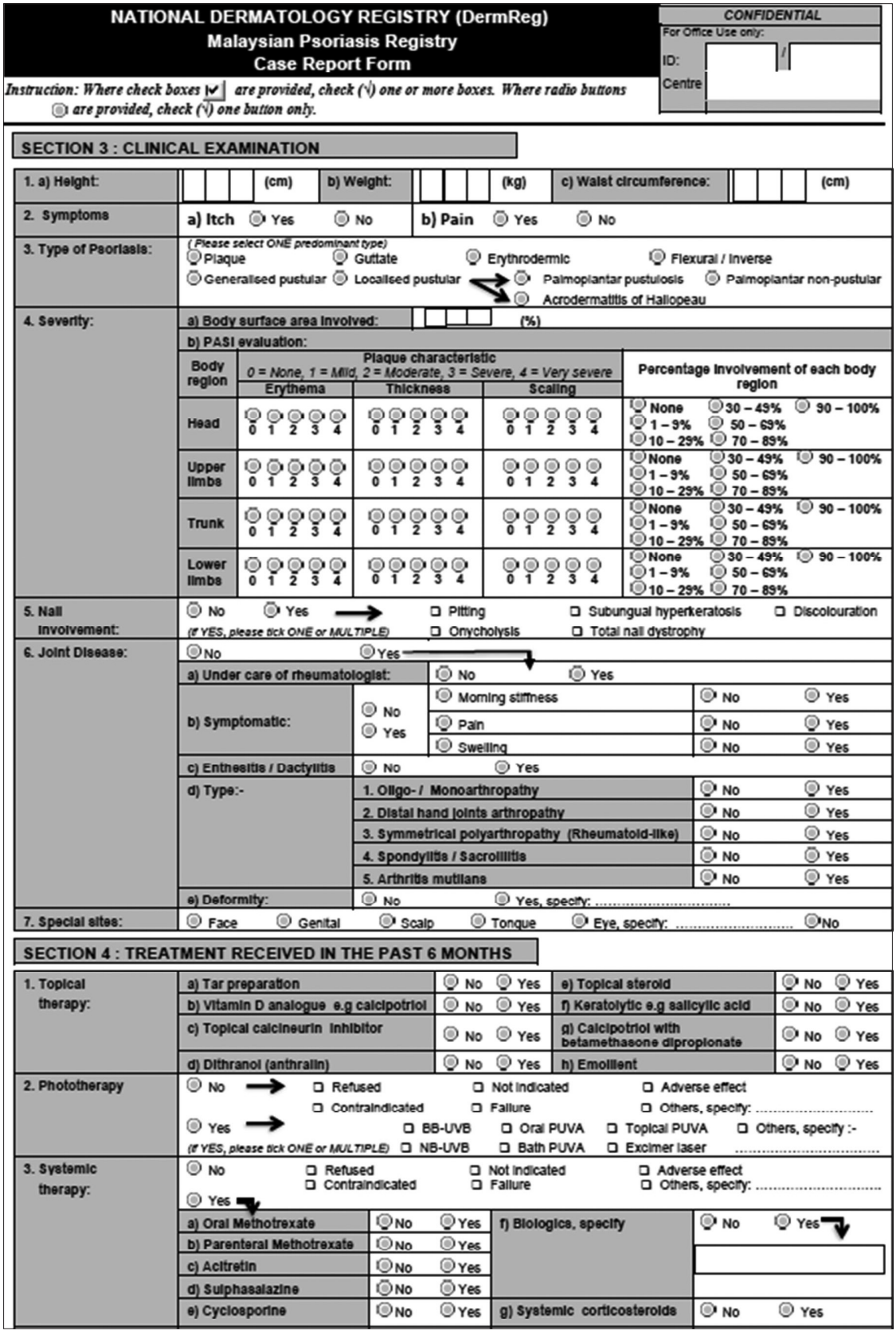
SECTION 1 : DEMOGRAPHIC DETAILS

1. Patient visit date: (dd/mm/yyyy)	☐☐/☐☐/☐☐☐☐ 2. Type of visit: ◎ New Case ◎ Follow-Up
3. Name of patient:	
4. NRIC:	MyKad/MyKid: ☐☐☐☐☐☐–☐☐–☐☐☐☐ Old IC: ☐☐☐☐☐☐☐☐
	Other ID document No : ☐☐☐☐☐☐☐☐☐☐ Specify type of ID : .....
# 5. Address:	Town / City: ☐☐☐☐☐☐☐☐☐☐ State: ☐☐☐☐☐☐☐☐☐☐
# 6. Contact Number:	Home: ☐☐☐–☐☐☐☐☐☐☐ H/P: ☐☐☐–☐☐☐☐☐☐☐
# 7. Gender:	◎ Male ◎ Female
# 8. Date of birth: (dd/mm/yyyy)	☐☐/☐☐/☐☐☐☐ ☐ Estimated/presumed year *If the exact date is not known, please enter 01/07/yyyy & check the estimated / presumed year box.*
# 9. Ethnic group:	◎ Malay ◎ Orang Asli Semenanjung ◎ Kadazan ◎ Melanau ◎ Bidayuh ◎ Chinese ◎ Bajau ◎ Murut ◎ Kedayan ◎ Other Bumiputera Sarawak ◎ Indian ◎ Dusun ◎ Other Bumiputera Sabah ◎ Iban ◎ Others
# 10. Nationality:	◎ Malaysian ◎ Non-Malaysian, specify: .....
# 11. Marital status:	◎ Single ◎ Married ◎ Divorced ◎ Widowed
# 12. Occupation:	◎ Agriculture & Fisheries ◎ Legal ◎ Oil & Gas ◎ Transportation ◎ Education ◎ Art & Talent ◎ Manufacturing ◎ Service ◎ Building & Construction ◎ Others ◎ Information Technology ◎ Mining ◎ Telecomunication ◎ Medical & Health
# 13. Monthly income:	◎ No income ◎ RM 500 – RM 1000 ◎ RM 1501 – RM 3000 ◎ RM 5001 – RM 10000 ◎ > RM 15000 ◎ < RM 500 ◎ RM 1001 – RM 1500 ◎ RM 3001 – RM 5000 ◎ RM 10001 – RM 15000

SECTION 2 : MEDICAL HISTORY

1. Age when # psoriasis started:	☐☐☐	2. Age when psoriasis # diagnosed:	☐☐☐
3. Family member(s) # with psoriasis:	◎ No ◎ Yes → *(If YES, please tick ONE or MULTIPLE)* ☐ Father ☐ Sibling(s) ☐ Other relative, specify: ..... ☐ Mother ☐ Children		
4. Aggravating factors:	◎ No ◎ Yes → *(If YES, please tick ONE or MULTIPLE of the following)* ☐ Infection : ..... ☐ Stress ☐ Alcohol ☐ Drugs : ..... ☐ Sunburn ☐ Pregnancy ☐ Topical Rx : ..... ☐ Hypocalcaemia ☐ Trauma ☐ Other, specify: ..... ☐ Smoking		
5. Disease burden in the last 6 months:	a) No. of clinic visits due to psoriasis : ☐☐☐ *(enter 0 if none)*		
	b) No. of days off work / school due to psoriasis : ☐☐☐ *(enter 0 if none)* ☐ Not applicable		
	c) No. of hospital admissions due to psoriasis : ☐☐☐ *(enter 0 if none)*		
6. Comorbidities:	a) Ischaemic heart disease :	◎ Yes ◎ No	Age at diagnosis ☐☐☐
	b) Cerebrovascular disease (stroke) :	◎ Yes ◎ No	Age at diagnosis ☐☐☐
	c) Diabetes mellitus :	◎ Yes ◎ No	Age at diagnosis ☐☐☐
	d) Hypertension :	◎ Yes ◎ No	Age at diagnosis ☐☐☐
	e) Hyperlipidaemia :	◎ Yes ◎ No	Age at diagnosis ☐☐☐
	f) Depression :	◎ Yes ◎ No	Age at diagnosis ☐☐☐
	g) Fatty Liver (NAFLD) :	◎ Yes ◎ No	Age at diagnosis ☐☐☐
	h) HIV / AIDS :	◎ Yes ◎ No	Age at diagnosis ☐☐☐
	i) Inflammatory bowel disease *(If YES, please tick ONE)* →	◎ Yes ◎ No ◎ Ulcerative colitis ◎ Crohn's disease	Age at diagnosis ☐☐
	j) Malignancy, specify :	◎ Yes ◎ No →	Age at diagnosis ☐☐
7. Pregnancy:	◎ No ◎ Yes ◎ Not Applicable		
8. Cigarette smoking:	◎ Never smoked ◎ Ex-smoker ◎ Current smoker → ☐☐ cigarettes per day		
9. Substance use:	◎ No ◎ Yes → *(If YES, please tick ONE or MULTIPLE)* ☐ Alcohol ☐ Illicit drugs, specify: ..... ☐ Vape		

Figure 1: Contd...



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Instruction: Where check boxes ☑ are provided, check (√) one or more boxes. Where radio buttons ◎ are provided, check (√) one button only.

SECTION 3 : CLINICAL EXAMINATION

1. a) Height: (cm) b) Weight: (kg) c) Waist circumference: (cm)

2. Symptoms: a) Itch ◎ Yes ◎ No b) Pain ◎ Yes ◎ No

3. Type of Psoriasis: *(Please select ONE predominant type)*
◎ Plaque ◎ Guttate ◎ Erythrodermic ◎ Flexural / Inverse
◎ Generalised pustular ◎ Localised pustular → ◎ Palmoplantar pustulosis ◎ Palmoplantar non-pustular
◎ Acrodermatitis of Hallopeau

4. Severity:
a) Body surface area involved: (%)
b) PASI evaluation:

Body region	Plaque characteristic (0 = None, 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Very severe) Erythema	Thickness	Scaling	Percentage involvement of each body region
Head	◎ 0 ◎ 1 ◎ 2 ◎ 3 ◎ 4	◎ 0 ◎ 1 ◎ 2 ◎ 3 ◎ 4	◎ 0 ◎ 1 ◎ 2 ◎ 3 ◎ 4	◎ None ◎ 1 – 9% ◎ 10 – 29% ◎ 30 – 49% ◎ 50 – 69% ◎ 70 – 89% ◎ 90 – 100%
Upper limbs	◎ 0 ◎ 1 ◎ 2 ◎ 3 ◎ 4	◎ 0 ◎ 1 ◎ 2 ◎ 3 ◎ 4	◎ 0 ◎ 1 ◎ 2 ◎ 3 ◎ 4	◎ None ◎ 1 – 9% ◎ 10 – 29% ◎ 30 – 49% ◎ 50 – 69% ◎ 70 – 89% ◎ 90 – 100%
Trunk	◎ 0 ◎ 1 ◎ 2 ◎ 3 ◎ 4	◎ 0 ◎ 1 ◎ 2 ◎ 3 ◎ 4	◎ 0 ◎ 1 ◎ 2 ◎ 3 ◎ 4	◎ None ◎ 1 – 9% ◎ 10 – 29% ◎ 30 – 49% ◎ 50 – 69% ◎ 70 – 89% ◎ 90 – 100%
Lower limbs	◎ 0 ◎ 1 ◎ 2 ◎ 3 ◎ 4	◎ 0 ◎ 1 ◎ 2 ◎ 3 ◎ 4	◎ 0 ◎ 1 ◎ 2 ◎ 3 ◎ 4	◎ None ◎ 1 – 9% ◎ 10 – 29% ◎ 30 – 49% ◎ 50 – 69% ◎ 70 – 89% ◎ 90 – 100%

5. Nail involvement: ◎ No ◎ Yes → *(If YES, please tick ONE or MULTIPLE)* ☐ Pitting ☐ Onycholysis ☐ Subungual hyperkeratosis ☐ Total nail dystrophy ☐ Discolouration

6. Joint Disease: ◎ No ◎ Yes
a) Under care of rheumatologist: ◎ No ◎ Yes
b) Symptomatic: ◎ No ◎ Yes — Morning stiffness ◎ No ◎ Yes; Pain ◎ No ◎ Yes; Swelling ◎ No ◎ Yes
c) Enthesitis / Dactylitis ◎ No ◎ Yes
d) Type:-
1. Oligo- / Monoarthropathy ◎ No ◎ Yes
2. Distal hand joints arthropathy ◎ No ◎ Yes
3. Symmetrical polyarthropathy (Rheumatoid-like) ◎ No ◎ Yes
4. Spondylitis / Sacroiliitis ◎ No ◎ Yes
5. Arthritis mutilans ◎ No ◎ Yes
e) Deformity: ◎ No ◎ Yes, specify: .....

7. Special sites: ◎ Face ◎ Genital ◎ Scalp ◎ Tongue ◎ Eye, specify: ..... ◎ No

SECTION 4 : TREATMENT RECEIVED IN THE PAST 6 MONTHS

1. Topical therapy:
a) Tar preparation ◎ No ◎ Yes
b) Vitamin D analogue e.g calcipotriol ◎ No ◎ Yes
c) Topical calcineurin inhibitor ◎ No ◎ Yes
d) Dithranol (anthralin) ◎ No ◎ Yes
e) Topical steroid ◎ No ◎ Yes
f) Keratolytic e.g salicylic acid ◎ No ◎ Yes
g) Calcipotriol with betamethasone dipropionate ◎ No ◎ Yes
h) Emollient ◎ No ◎ Yes

2. Phototherapy: ◎ No → ☐ Refused ☐ Not indicated ☐ Adverse effect ☐ Contraindicated ☐ Failure ☐ Others, specify: .....
◎ Yes → *(If YES, please tick ONE or MULTIPLE)* ☐ BB-UVB ☐ NB-UVB ☐ Oral PUVA ☐ Bath PUVA ☐ Topical PUVA ☐ Excimer laser ☐ Others, specify :- .....

3. Systemic therapy: ◎ No ☐ Refused ☐ Contraindicated ☐ Not indicated ☐ Failure ☐ Adverse effect ☐ Others, specify: .....
◎ Yes →
a) Oral Methotrexate ◎ No ◎ Yes
b) Parenteral Methotrexate ◎ No ◎ Yes
c) Acitretin ◎ No ◎ Yes
d) Sulphasalazine ◎ No ◎ Yes
e) Cyclosporine ◎ No ◎ Yes
f) Biologics, specify ◎ No ◎ Yes →
g) Systemic corticosteroids ◎ No ◎ Yes

Figure 1: Malaysian Psoriasis Registry (MPR) notification form

Table 1: Demographic and clinical characteristics of psoriasis patients with and without malignancy

Demographic and baseline characteristics	Malignancy (n=123), n (%)	No malignancy (n=21,612), n (%)	P
Age (years)			
Mean (SD)	54.4 (13.1)	41.7 (17.4)	<0.001
Minimum–maximum	16–82	20–92	
Age group (years)			
>40	104 (84.6)	11,197 (51.8)	<0.001
≤40	19 (15.4)	10,415 (48.2)	
Age of psoriasis onset, mean (SD)	43.21 (16.24)	33.24 (16.93)	<0.001
Gender			
Male	52 (42.3)	12,007 (55.6)	0.002
Female	71 (57.7)	9605 (44.4)	
Ethnicity			
Malay	44 (35.8)	11,752 (54.3)	
Chinese	38 (30.9)	4108 (19)	
Indian	15 (12.2)	3562 (16.5)	
Others	26 (21.1)	2190 (10.1)	
History of smoking	18 (23.1)	3966 (31)	0.13
Comorbidity			
Dyslipidaemia	30 (25.4)	3382 (16.4)	0.008
CVD	3 (2.5)	304 (1.5)	0.35
DM	31 (25.6)	3298 (15.8)	0.003
IHD	5 (4.1)	1006 (4.8)	0.72
Hypertension	51 (42.9)	4935 (23.7)	<0.001
BMI (kg/m^2)			
<23	36 (34.6)	5510 (29.3)	0.23
≥23	68 (65.4)	13,324 (70.7)	
Type of psoriasis			
Plaque	106 (89.1)	18,889 (99.4)	
Guttate	6 (5)	732 (3.6)	
Inverse	5 (4.2)	99 (0.5)	
Erythrodermic	1 (0.8)	389 (1.9)	
Localised pustular	1 (0.8)	55 (0.3)	
Generalised pustular	0	92 (0.5)	
Nail	0	8 (0.1)	
Palmoplantar psoriasis	0	87 (0.4)	
BSA			
≤10	75 (78.1)	12,540 (76.1)	0.65
>10	21 (21.9)	3934 (23.9)	
DLQI			
≤10	80 (66.7)	11,722 (59.7)	0.12
>10	40 (33.3)	7925 (40.3)	
Psoriatic arthritis	10 (8.2)	2746 (13.1)	0.11
Treatment			
Phototherapy	1 (0.8)	551 (2.7)	0.21
Acitretin	7 (5.8)	574 (2.8)	0.05
Methotrexate	5 (4.1)	2288 (11.1)	0.02
Ciclosporin	0	144 (0.7)	0.36
Hydroxyurea	1 (0.8)	22 (0.1)	0.02
Biologics	0	78 (0.4)	0.5

SD: Standard deviation, BMI: Body mass index, CVD: Cerebrovascular disease, DM: Diabetes mellitus, IHD: Ischaemic heart disease, BSA: Body surface area, DLQI: Dermatology Life Quality Index

study highlights the link between malignancy and psoriasis in the Asian population. Specific types of cancers, particularly cutaneous malignancies, lymphoma and solid organ cancers, were demonstrated to have variable risk in psoriasis patients.[20]

Non-melanoma skin cancer

Literature review showed that the overall prevalence of skin cancer in psoriasis patients was 2.55%.[17] Our study demonstrated a lower rate of squamous cell carcinoma in

Table 2: Types of cancers in the study population according to gender, age and ethnicity

	All (*n*=123)		Male (*n*=52)		Female (*n*=71)	
	≤40 years, *n* (%)	>40 years (*n*=108), *n* (%)	≤40 years (*n*=5), *n* (%)	>40 years (*n*=47), *n* (%)	≤40 years (*n*=10), *n* (%)	>40 years (*n*=61), *n* (%)
Ethnicity						
Malays	6 (40)	38 (35.2)	2 (40)	15 (31.9)	4 (40)	23 (37.7)
Chinese	2 (13.3)	36 (33.3)	0	16 (34.0)	2 (20)	20 (32.8)
Indians	2 (13.3)	13 (12.0)	0	7 (14.9)	2 (20)	6 (9.8)
Others	5 (33.3)	21 (19.4)	3 (60)	9 (19.1)	2 (20)	12 (19.7)
Type of cancer						
Breast	42 (34.1)		0		42 (58.3)	
Leukaemia/lymphoma	15 (12.2)		11 (21.5)		4 (5.6)	
Colorectal	14 (11.4)		10 (19.6)		Colon - 4 (5.6)	
Female genital cancer	10 (8.1)		0		10 (13.9)	
Brain	6 (4.9)		3 (5.9)		3 (4.2)	
Thyroid	6 (4.9)		2 (3.9)		4 (5.6)	
Urinary tract cancer	5 (4.1)		5 (9.8)		0	
Cutaneous squamous cell carcinoma	3 (2.4)		3 (5.9)		0	
Respiratory tract	3 (2.4)		3 (5.9)		0	
Upper aerodigestive tract	1 (0.8)		0		1 (1.4)	

psoriasis patients in Malaysia in comparison to those in the Western population. This finding could be explained by the relatively low incidence of keratinocyte cancers in Malaysia.[12] On the other hand, several reports have explored the association between psoriasis and elevated risk of non-melanoma skin cancer (NMSC), particularly in patients receiving phototherapy.[6,8,17,20,21] Patients with psoriasis have a higher propensity for developing cutaneous squamous cell carcinomas (SCC) in comparison to basal cell carcinomas (BCC), particularly in patients who had received psoralen with UV A (PUVA). The risk of cancer remained even after 15 years of discontinuing PUVA treatment.[10,22,23]

To date, there is no strong evidence to suggest an increased risk of developing cutaneous malignancies in patients who were treated with NBUVB. Previous studies have demonstrated that the risk of skin cancer did not increase in their psoriasis cohort treated with NBUVB.[18,24] None of the NMSC patients in our study had been treated with prior phototherapy.

None of our psoriasis patients were diagnosed with melanoma. Therefore, the risk of developing melanoma in our cohort does not appear to be significantly increased which corresponds with previous studies.[6,21] Oral ciclosporin has been shown to increase the risk of NMSC (primarily SCC) in psoriasis patients.[6,25] The risk of BCC was found to be higher in patients receiving methotrexate in the PSOLAR study, but this finding was not reflected in other studies.[20] Furthermore, retinoids such as acitretin have not been proven to increase cancer risk. In fact, acitretin can be protective against several malignancies, especially NMSC and cutaneous lymphomas.[20,21]

Haematological malignancy

Our study showed that haematological cancers (mainly leukaemia and lymphoma) were the second most common malignancies in psoriasis patients. Specifically for the male cohort, leukaemia was the most common malignancy observed among them. This contrasted with the overall Malaysian population in which lymphoma and leukaemia ranked fourth and seventh, respectively, in the top 10 common cancer sites seen in the MNCR.[12] Previous studies showed that patients with psoriasis have an increased risk of developing both Hodgkin and non-Hodgkin lymphomas.[17,20] Furthermore, the risk of developing cutaneous T-cell lymphoma (CTCL) is shown to be elevated, particularly in those with severe psoriasis. Two previous meta-analyses found a correlation between psoriasis and CTCL, but this relationship is thought to be partially attributed to the misdiagnosis which can occur between these two diagnoses.[6,17] Despite misclassification in some cases, there were a small number of patients who had been diagnosed with concurrent psoriasis and CTCL with confirmation from skin biopsies.[20]

The use of systemic immunomodulating agents, specifically ciclosporin in psoriasis, might increase the risk for lymphoproliferative disorders.[6,9,10,17,23,25-28] None of the patients with malignancy received ciclosporin in our study. However, it is worth noting that a relatively smaller percentage of patients received ciclosporin (<5%) compared to methotrexate (70%–80%) and acitretin (18%–19%) in our cohort. In addition, we found no correlation between the usage of methotrexate and cancer in our psoriasis patients. The risk of developing cancer in psoriasis following methotrexate treatment remains controversial.[20] The association of acitretin and cancer risk was difficult to determine in our cohort due to the lack of data on the temporal relationship between the diagnosis of malignancy and the initiation of the immunosuppressant.

Solid organ cancer

Systemic reviews and meta-analyses elucidated an elevated risk of multiple solid organ malignancies, especially respiratory tract, gastrointestinal tract and urinary tract

carcinomas in psoriasis patients.[6,17] Apart from NMSC and lymphoma, lung cancer was considered among the most common type of specific-organ cancer linked to psoriasis.[20] An Asian population-based study conducted in South Korea demonstrated an increased cancer risk of several solid organs, mainly for malignancies of the prostate, thyroid, liver, ovary, lung and testes.[19] In our Malaysian cohort, the increased rate of breast cancer among female psoriasis patients corresponded to the pattern reported in the MNCR for the general population. In terms of ethnicity, the overall cumulative breast cancer risk in Malaysia was greatest among the ethnic Chinese (4.5) and comparatively lower among Malay patients (3.4).[12] A Swedish study had reported a similar finding of increased risk of breast cancer in psoriasis patients.[26] In contrast, a population-based study conducted in Philadelphia illustrated no increased risk of breast cancer in psoriasis patients.[8] Other solid cancers seen with high incidence in the Malaysian population such as lung, nasopharyngeal and liver cancers[12] were relatively uncommon in our psoriasis cohort. Experts have affirmed the importance of not to overemphasise the association between solid organ cancers and psoriasis as they are comparatively rare.[20]

Factors contributing to increased cancer risk

The possible mechanism explaining the link between psoriasis and malignancy is still unclear. The risk of developing lymphomas is higher in chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel diseases compared to the general population. Similarly, the dysregulation of inflammatory cytokines seen in psoriasis, especially T-helper (Th17) and T regulatory cells, may contribute to the risk of having cutaneous lymphoma.[20] One of the hypotheses postulated that prolonged immune system activation and impaired immune surveillance may promote the development of malignancies.[6,29] Previous reports have highlighted that the risk of developing CTCL is increased in severe psoriasis patients possibly due to continuous immune stimulation resulting in the development of a dominant clonal expansion.[6,21]

Several predictors have been identified that may potentiate the risk of malignancy. Gender was demonstrated to have an influence on malignancy risk with male psoriatic patients found to have a higher risk of developing liver, lung, thyroid, lymphoma, prostate and testicular cancers.[19] Another study found that male patients with psoriasis have an elevated malignancy risk, particularly for lymphoma.[9,27] A population-based cohort study in Taiwan revealed elevated risks for cancer, particularly in men and younger age groups with psoriasis.[18] In contrast, our study found that malignancy was significantly associated with female patients as well as those with late-onset psoriasis. This could be explained by the persistently higher cancer incidence in females than males reported by the MNCR in the last decade. The age-standardised incidence rates of cancer patients were 86.1 and 101.6 per 100,000 for males and females, respectively.[12] This high incidence of breast cancer may also be reflective of the barrier to health-seeking behaviours among Malaysian women.[30]

Our study found a significantly greater rate of malignancy among patients with inverse psoriasis compared to other subtypes. This is a novel finding as we could not find any previous report or study to support the association between inverse psoriasis and developing cancer. Further research is required to investigate this correlation.

Several lifestyle risk factors such as obesity, cigarette smoking and alcohol intake have been linked with psoriasis[17] which incidentally are also risk factors for developing cancers.[20] Past reports have showed that psoriasis patients who were smokers and consumed alcohol excessively were at risk of developing various solid organ malignancies such as colon, colorectal, liver, pancreatic and bladder cancers.[6,20,21] In addition, smoking has been recognised as a single risk factor for lung cancer.[20] However, in our cohort, smokers did not have an increased rate of malignancy compared to non-smokers. We postulate that the higher rate of metabolic comorbidities including diabetes mellitus, hypertension and dyslipidaemia in our cohort may be indirectly linked to the cancer treatment regimen that frequently includes systemic corticosteroids. Furthermore, the cohort with malignancy was much older and more likely to develop cardiovascular comorbidities in comparison to the younger age group. More studies accounting for these confounding factors are required to assess these possible associations.

In our study, none of the psoriasis patients with malignancy had received biologics. We are not able to draw any conclusion whether biologics conferred a cancer protective effect as only a small number of patients (1%) without malignancy were prescribed biologics during the study period. The association between malignancy risk and biologic treatment remains debatable. A few studies have suggested an increased risk for NMSC in psoriasis patients receiving tumour necrosis factor (TNF)-α inhibitors.[10,31-34] To date, there is no elevated cancer risk other than NMSC in patients with TNF inhibitors.[20,33] With regards to psoriasis patients who received interleukin (IL)-12/23 inhibitors (ustekinumab), there were several reports on post-marketing safety data observing an elevated risk for NMSC, melanoma and solid organs malignancies (prostate, colorectal and breast cancers).[35] On the contrary, the PSOLAR registry revealed no increased risk of cutaneous malignancies for ustekinumab.[20] Data derived from clinical trials so far have not alerted any safety concerns for cancer risk with IL-17A inhibitors (secukinumab and ixekizumab) and IL-23 inhibitors (guselkumab) treatment.[2,20] Interesting laboratory research done in the United States showed that the inflammatory process mediated by IL-17 cytokines might play a role in promoting tumour growth. Therefore, blocking the IL-17 mechanism is thought to inhibit tumoral development.[36] Nevertheless, the existing evidence for these newer biologics are still limited and mainly derived from clinical trials. Further long-term prospective studies and registries should be conducted to evaluate the cancer risk of these biologic therapies.

Limitations

The low malignancy rate in our cohort could be due to self-reporting bias. Data on the timing of cancer diagnosis, staging and treatment were not captured in the MPR. The diagnosis of malignancy is solely on patient's history. The information on malignancy might be missed if it occurred later after the MPR was submitted.

Obesity, cigarette smoking and alcohol intake are important confounding factors which might directly contribute to the risk of developing cancers. Furthermore, the information on alcohol consumption and family history of cancer as important risk factors were also not captured in the MPR. In addition, the MPR only acquired data on systemic treatments given for psoriasis in the last 6 months and hence the earlier treatments for psoriasis or other diseases were not captured.

Recommendations

Clinicians are encouraged to be more vigilant in performing periodic cancer screening, especially in psoriasis patients with severe disease, comorbidities and ciclosporin and PUVA treatment recipients. Advocating a healthy lifestyle such as smoking cessation, limiting alcohol intake and weight reduction in overweight or obese patients should be recommended. Large population-based cohort studies may be required to investigate the true incidence of various malignancies over a longer period among our psoriasis patients. Data on family history of cancer and histopathological diagnosis should be included in the analyses. Multivariate analysis can be considered to account for confounding risk factors.

Conclusion

The frequency of malignancy was 0.57% among the psoriasis patients in our registry. Being older than 40 years and female were significantly associated with malignancy in psoriasis patients. The rate of malignancy was the highest in inverse psoriasis patients.

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Conflicts of interest

There are no conflicts of interest.

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