Do Psoriasis Therapies Increase the Risk of Skin Cancer?

Mark Lebwohl, MD
Sol and Clara Kest Professor
And Chairman
Department of Dermatology
The Mount Sinai School of Medicine
Mark Lebwohl is an employee of Mount Sinai which receives research funds from: Abbvie, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen / Johnson & Johnson, Kadmon, Medimmune/Astra Zeneca, Novartis, Pfizer, Valeant and ViDac.

Dr. Lebwohl is also a consultant for Allergan, Aqua Leo-pharma, and Promius.
The risk of cancer in patients with psoriasis: A population-based cohort study in the Health Improvement Network.

Chiesa Fuxench ZC, et al.

<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Severe</th>
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</thead>
<tbody>
<tr>
<td>Cancer ((\Theta)NMSC)</td>
<td>HR: 1.06 (1.02-1.09)</td>
<td>1.08 (0.96-1.22)*</td>
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<tr>
<td>Lymphoma:</td>
<td>1.31 (1.15-1.49)*</td>
<td>1.89 (1.25-2.86)*</td>
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<tr>
<td>NMSC:</td>
<td>1.09 (1.05-1.13)*</td>
<td>1.61 (1.42-1.84)*</td>
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<tr>
<td>Lung cancer:</td>
<td>1.12 (1.01-1.25)*</td>
<td>1.62 (1.16-2.28)*</td>
</tr>
</tbody>
</table>

No association with breast, colon, prostate, or leukemia

**Includes patients with systemic therapy**

Chiesa Fuxench ZC, et al.  
The risk of melanoma and hematologic cancers inpatients with psoriasis.
Reddy SP, Martires K, Wu JJ.

• Patients with psoriasis had 1.53 times the risk of melanoma and hematologic cancers
- UVB
- Narrowband UVB
- PUVA
- MTX
- Retinoids
- Cyclosporine
- Biologics
- Apremilast
UVB doses in maintenance psoriasis phototherapy versus solar UVB exposure.
Schothorst AA, et al

“The cumulative incidence among patients who received maintenance phototherapy for several decades was calculated to be a factor of 2.5 to 7.5 higher than the incidence among individuals with an outdoor occupation.”
Skin Cancer In Patients With Psoriasis Treated With Coal Tar
A 25-Year follow-up study

Pittelkow MR, Perry HO, Muller SA, Maughan WZ, O'Brien PC.
• Phototherapy is administered in a controlled manner, with slowly increasing increments.

• **Typical phototherapy burn is often only a little higher than the MED.** Blistering sunburns are often several times the MED.

• **UV spectrum** of phototherapy is not identical to that of sunlight.
The photocarcinogenic risk of narrowband (TL-01) phototherapy: early follow-up data

Man I, Crombie IK, Dawe RS et al.


- 1908 pts
- .04 – 14 years (median 4)
- 1-199 NB treatments (median 23)
- 30-284,415 mJ/cm² (median 13,337)
• No increase SCC or MM
• 10 BCC vs. 4.7 expected, 9 on face
• *Patients under regular dermatological follow-up are more likely to have skin cancers detected.*
Carcinogenic risks of psoralen UV-A therapy and narrowband UV-B therapy in chronic plaque psoriasis: a systematic literature review.

“No increased risk of skin cancer was evidenced in the four studies specifically assessing the potential carcinogenic risk of NB-UVB.”
Nonmelanoma skin tumors in long-term photochemotherapy treatment of psoriasis.

An 8-year follow-up study.
Malignant melanoma in patients treated for psoriasis with methoxsalen (psoralen) and ultraviolet A radiation (PUVA). The PUVA Follow-Up Study.

Stern RS, Nichols KT, Vakeva LH.


• relative risk 5.4, beginning 15 yrs. after 1st treatment
• ↑risk with ↑number of treatments

- RA pts started on MTX pre 1986
- State cancer registry (not NMSC)
- 4,145 person-years (avg.9.3 yrs)
MTX associated with:

- 50% ↑ risk of malignancy
- 3-fold ↑ in melanoma
- 5-fold ↑ in nonHodgkins lymphoma
- 3-fold ↑ in lung ca.

Buchbinder R et al.  


- Acitretin 30 mg/d
- 2/19 ➔ 2 SCCs vs 9/19 ➔ 18 SCCs
Chemoprevention of skin cancer in xeroderma pigmentosum.

- 121 BCCs or SCCs in 5 patients 2 years prior to Rx
- Isotretinoin 2 mg/kg/d → 25 tumors over 2 years of Rx
Incidence and prediction of nonmelanoma skin cancer post-renal transplantation: a prospective study in Queensland, Australia.

- 18.8%, <5 years
- 24.8%, 5-10 years
- 33.3%, 10-20 years
- 47.1%, >20 years
Skin Cancer in Organ Transplant Patients

Immunosuppressive Drugs
- Cyclosporine A
- Tacrolimus

Berg and Otley, JAAD 47:1-17, 2002
Risk of malignancies in psoriasis patients treated with cyclosporine: a 5 y cohort study.

- 1252 patients for up to 5 years (average 1.9)
- 6-fold ↑ skin cancer
- No ↑ nonskin cancer
**Cutaneous malignant melanoma occurring after cyclosporin A therapy.**
Arellano F, Krupp PF.

**Cutaneous malignant melanomas occurring under cyclosporin A therapy: a report of two cases.**
Mérot Y, et al.
Metastatic melanoma after solid organ transplantation: An interdisciplinary, institution-based review of management with systemic and targeted therapies.


Invasive Melanomas ↑2 fold
M:F ratio 14:1
TNF blockers

Key Cells and Mediators in Psoriasis

Adalimumab
Etanercept
Infliximab
Certlizumab

Rapid onset of cutaneous squamous cell carcinoma in patients with rheumatoid arthritis after starting tumor necrosis factor alpha receptor IgG1-Fc fusion complex therapy.

Smith KJ, Skelton HG. 
Multiple squamous cell carcinomas in the setting of psoriasis treated with etanercept: A report of four cases and review of the literature.

Brewer JD, et al.

The rapid onset of multiple squamous cell carcinomas during etanercept treatment for psoriasis.

Ly L, et al.

Rapid onset and fatal outcome of two squamous cell carcinomas of the genitalia in a patient treated with etanercept for cutaneous psoriasis.

Comte C, et al.

Multiple and fulminant cutaneous squamous cell carcinomas in a Crohn's disease patient treated with immunosuppressants and adalimumab.

Nancey S, et al.

*Inflammm Bowel Dis. 2011;17(4):1060-1.*
Kowalzick L et al.
Metastatic melanoma in a young woman treated with TNF-α inhibitor for psoriatic arthritis: a case report.

Marasini B, et al.

Eruptive latent metastatic melanomas after initiation of antitumor necrosis factor therapies.

Fulchiero GJ Jr, et al.

Cutaneous melanoma in patients in treatment with biological therapy: review of the literature and case report.

Manganoni AM, et al.

Development of two primary malignant melanomas after treatment with adalimumab: a case report and review of the possible link between biological therapy with TNF-alpha antagonists and melanocytic proliferation.

Katoulis AC, Kanelleas A, Zambacos G, Panayiotides I, Stavrianeas NG. 
Dermatology. 2010;221:9-12.
Melanoma at a dysplastic nevus excision site in a patient on etanercept.

Hacard F, et al.

*Ann Dermatol Venereol.*

Primary cutaneous melanoma: a complication of infliximab treatment?

Khan I, et al.

Multiple basal cell carcinomas after etanercept treatment for psoriasis.

Maire C, et al.

Merkel cell carcinoma in a patient treated with adalimumab: case report.

Krishna SM, et al.

Malignancy rates in a large cohort of patients with systemically treated psoriasis in a managed care population.
Maryam M. Asgari, et al.
JAAD. Available online 3 February 2017 (In press).

age, gender, race & comorbidity adjusted HR

• Any cancer (except NMSC) 0.86 (0.66-1.13)
• cSCC 1.81 (1.23-2.67)
• BCC 1.23 (0.91-1.66)
• MM 1.57 (0.61-4.09)
• Lymphoma 1.01 (0.38-2.70)
### Cumulative Rates of NMSC Through 5 Years of Follow-up

- 47 patients reported NMSCs (3 patients reported both SCC and BCC)
  - 40 had BCC (21 on 45 mg and 19 on 90 mg)
  - 10 had SCC (5 on 45 mg and 5 on 90 mg)

<table>
<thead>
<tr>
<th>Controlled Period</th>
<th>2010 Analyses</th>
<th>2011 Analyses</th>
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<tbody>
<tr>
<td><strong>BCC:SCC = 3:1</strong></td>
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<tr>
<td>Rate per 100 PY (95% CI)</td>
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<tr>
<td>1.13 (0.14, 4.09)</td>
<td>0.70 (0.43, 1.09)</td>
<td>0.64 (0.41, 0.95)</td>
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<tr>
<td>0.49 (0.01, 2.75)</td>
<td>0.53 (0.33, 0.82)</td>
<td>0.44 (0.28, 0.66)</td>
</tr>
<tr>
<td>0.98 (0.12, 3.55)</td>
<td>0.61 (0.43, 0.82)</td>
<td>0.52 (0.39, 0.70)</td>
</tr>
<tr>
<td><strong>BCC:SCC = 4:1</strong></td>
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</table>

- 47 patients reported NMSCs (3 patients reported both SCC and BCC)
  - 40 had BCC (21 on 45 mg and 19 on 90 mg)
  - 10 had SCC (5 on 45 mg and 5 on 90 mg)

ACCEPT data were not included in the Controlled Period rates since it did not include a placebo comparator.

For PHOENIX 2, patients who were dose adjusted from 45 mg to 90 mg were switched to the corresponding column following dose adjustment.
Rates of NMSC by Year Through 5 Years of Follow-up

PHOENIX 2 patients who were dose adjusted from 45 mg to 90 mg were switched to the corresponding column following dose adjustment.
Results: Unadjusted Cumulative Rates of Malignancies (excluding NMSC) per 100 Patient-Years (PY) for Any Exposure to Therapy (Figure 1)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Unadjusted Rates (n=No. of Events)</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>Ustekinumab (N=8870 PY)</td>
<td>0.51 (0.37, 0.68)</td>
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<tr>
<td>Infliximab/Golimumab* (N=4205 PY)</td>
<td>0.64 (0.42, 0.93)</td>
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<tr>
<td>ADA/ETN** (N=13167 PY)</td>
<td>0.74 (0.60, 0.91)</td>
<td>0.81 (0.59, 1.08)</td>
</tr>
<tr>
<td>No Biologic (N=5576 PY)</td>
<td></td>
<td></td>
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<tr>
<td>All (N=31818 PY)</td>
<td>0.68 (0.59, 0.77)</td>
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</table>

*Sponsor biologics, other than ustekinumab, approved for PsO &/or PsA; includes almost exclusively infliximab patients (n=1400); few patients were exposed to golimumab (n=35). **95% (n=4374) are adalimumab &/or etanercept patients, with the remainder exposed to efalizumab, alefacept, or other non-sponsor biologic.

Inborn errors of human IL-17 immunity underlie chronic mucocutaneous candidiasis.

Puel A, et al.

IL-17 Mediated Inflammation Promotes Tumor Growth and Progression in the Skin

D. He, et al

IL-23→↑IL-17→↑tumor growth

Could blocking IL-17 be protective against cancer?
Secukinumab

PUBMED search
1/10/18

NO ↑ MALIGNANCIES
Ixekizumab

Search results


2. Severe and acute complications of biologics in psoriasis.

3. Short- and long-term safety outcomes with ixekizumab from 7 clinical trials in psoriasis: Etanercept comparisons and integrated data.

PUBMED search 1/10/18
NO ↑ MALIGNANCIES
Brodalumab
PUBMED search
1/10/18
NO ↑ MALIGNANCIES

**Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis.**
PMID: 2917481
Similar articles
Guselkumab

PUBMED search

1/10/18

NO ↑ MALIGNANCIES

Search results

Items: 2


Search results

Items: 8

   PMID: 29271481
   Similar articles

2. Recurrence of Melanoma after Starting Apremilast for Psoriasis
   Salopek TG.
   PMID: 29033813
   Free PMC article
   Similar articles

3. Small molecule therapy for managing moderate to severe psoriatic arthritis.
   Review.
   PMID: 28891341
   Similar articles
apremilast mode of action

Apremilast modulates the production of cytokines through the cAMP pathway and inhibits the activity of PDE-4, leading to a reduction in TNF, IL-17, and IL-23.
Recurrence of Melanoma after Starting Apremilast for Psoriasis.

Salopek TG.


h/o 2 melanomas:
    2009 - 1.53mm Clark IV
    2012 - 0.9mm Clark IV
2015 started apremilast
>4mos. later→recurrence near first MM
Association with Skin Cancer

- Sunlight – strong association
- PUVA – strong association
- Cyclosporine – strong association
- Phototherapy UVB, narrowband UVB – No clear association
- Methotrexate – association
- Retinoids – protective
- TNF blockers – association
- Ustekinumab – no association
- IL-17 blockers – no association – too new
- IL-23 blockers – no association – too new
- Apremilast – no association – too new
Which therapies have been associated with an increase in skin cancers?

1) Methotrexate
2) Apremilast
3) Ustekinumab
4) Anti-IL-17 antibodies
5) Anti-IL-23 antibodies
Sildenafil use and increased risk of incident melanoma in US men: A prospective cohort study.

Li WQ et al.