

## Is psoriasis a high risk factor for tumors?

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### Abstract

Psoriasis is a chronic, autoimmune cause of the inflammatory disease, affecting about 2% to 3% of the world's population [1]. The disorder is characterized by abnormally infiltration and activation of T cells and various other immune cells, which cause hyper proliferation of keratinocytes and inflammatory processes. Common comorbidities of psoriasis include psoriatic arthritis, inflammatory bowel disease, cardiovascular disease and metabolic syndrome [2]. There is accumulating evidence suggesting a positive association between psoriasis and cancer. Although conflicting data on the risk of specific cancers in patients with psoriasis, the increased risk of some cancers in psoriasis patients has been shown. Why there's a link between psoriasis and cancers. Here are the possible explanations, the co-risk factors psoriasis and tumors, the chronic inflammatory nature of the disease, and the immune modulatory treatments.

**Keywords:** Inflammatory, Chronic inflammation, Skin cancer

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### The co-risk factors for tumors in psoriasis

Obesity and smoking are risk factors for incident psoriasis, aggravates existing psoriasis [3-5]. Obesity is defined as the expansion of white adipose tissue, which secrete various soluble mediators including cytokines (IL-1, IL-6, IL-10, TNF- $\alpha$ ), leptin, adiponectin, and resistin. The adipocytes-secreted mediators possess pro-inflammatory capabilities and cause the long-term inflammatory state in obese individuals. Obesity predisposes to the onset of psoriasis and aggravates existing psoriasis through pro-inflammatory pathways. Obesity has long been recognized as the largest avoidable cause of cancer in nonsmokers [6-7]. The adipocytes-secreted mediators also regulate the tumor microenvironment and tumor behavior. After entrance to the cancer microenvironment, cancer-associated adipocytes and adipose-derived stem cells heighten protumoral effects. Insulin resistance, hyperglycemia, and dyslipidemia stemmed from obesity can further enhance tumor growth and development.

Smoking is recognized as a strong risk factor for several cancers, especially for lung cancer [8]. Several studies have shown that patients with psoriasis are more likely to be active smokers. Tobacco smokers are exposed to a mixture of more than 7,000 chemicals including serious of dangerous free radicals, which can cause oxidative stress and interfere with psoriasis related signal pathways, such as mitogen-activated protein kinase, nuclear factor kappa B (NF- $\kappa$ B), and JAK-STAT pathways. Nicotine also induces the secretion of psoriasis causing factors including IL-2, TNF- $\alpha$ , IL-12, and granulocyte-monocyte colony-stimulating factor [5]. Moreover, smoking can also reduce the effect of anti-inflammatory drugs by promoting systemic inflammation.

### The nature of chronic inflammatory on psoriasis

Chronic inflammation can directly damage DNA and make cells more susceptible to mutagens. Through inflammatory

mediators, such as cytokines (TNF- $\alpha$ , IL-12, IL-6), chemokines, growth factors and proteases produced by tumor-associated lymphocytes and macrophages, inflammation can act as a tumor promoter by enhancing the ability of tumor cells to survive, proliferate and invade, and stimulation tumor angiogenesis and lymphatic angiogenesis [9]. Furthermore, the inflammatory mediators also can directly suppress immune responses [10]. The association between chronic inflammation and higher risk of cancer were demonstrated by the increased tumorigenesis seen in various medical conditions. Psoriasis can begin at any age and last a lifetime with inflammatory status. Patients with severe psoriasis sustained with the long-lasting chronic inflammation, which may play a role in the development of cancer, as chronic inflammation promotes initiation and progression of neoplastic growth [11]. Furthermore, skin lesions of psoriasis patients showed epidermal dysfunction and decreased filaggrin expression, which may contribute to the moderate increase of skin cancer risk by decreased UV protection. A study involving more than 32,000 women found a significant association between colon cancer and psoriasis [12]. This observed association may reflect the role of inflammation in cancer development since colon cancer has been consistently shown to be associated with inflammation. Other studies also suggest an increased risk for cancer of the NMSC, lymphoma, lung cancer, urinary bladder, oropharynx/larynx, liver/gallbladder [13-15]. Like psoriasis, lupus erythematoses and rheumatoid arthritis, another chronic inflammatory diseases, have also been associated with certain types of cancer [16,17].

### The immune modulatory treatments

The immune modulatory treatment is an effective and widely used therapy for psoriasis, which can significantly improve the disease burden and quality of life of patients with psoriasis. In general, topical therapies and narrowband ultraviolet B (UVB) phototherapy is effective in mild cases, systemic treatments

such as methotrexate (MTX), cyclosporine (CsA), retinoids, psoralen plus ultraviolet A (PUVA) phototherapy and biological agents: tumor necrosis factor alpha (TNF- $\alpha$ ) inhibitors, ustekinumab and newer biologics, are widely used in the treatment of moderate-to-severe psoriasis [18]. There is ongoing concern about whether immunomodulatory therapy for psoriasis will increase the burden of certain cancer.

Excessive UV irradiation is a well-established carcinogen for skin cancer. The association between PUVA and a substantial increase in the risk of nonmelanoma skin cancer, in a dose dependent fashion, is well documented [19]. After receiving >100 PUVA treatments, skin cancer risk is increased. The carcinogenic effect of PUVA may relate to direct DNA photoadduct formation and DNA base changes induced by reactive oxygen species [20]. Although UVB from sunlight is a well-established carcinogen, cumulative data suggest that broadband or narrowband-UVB therapy does not increase the risk of skin cancer [21,22].

As calcineurin inhibitor, CsA inhibits inflammation through blocking IL-2 production by activated CD4+ T cells. The higher risk of lymphoma, internal malignancies, and skin cancers induced by CsA are well noted in organ transplant patients [23]. When CsA is used continuously for less than 6 months or intermittently for less than 2 years, no skin cancers has been found in psoriasis, which has been confirmed by a review of 60 studies, including over 1700 psoriasis patients treated with ciclosporin [24]. However, when used for more than 2 years and previous therapies (PUVA and MTX), the incidence of cutaneous malignancies, mainly SCC, increased 6 folds [25].

As a folic acid analog, MTX suppresses cell proliferation by inhibiting DNA synthesis. The higher risk of melanoma and EBV-positive lymphomas in psoriasis patients using methotrexate have been reported [26]. More than 36 months treatment with MTX resulted in an elevated risk of lymphoma in psoriasis patients, compare to general population [27]. However, low-dose MTX treatment ( $\leq 30$  mg/week oral or 17.5-22.5 mg/week subcutaneously) monotherapy has no increased malignancy risk [28,29].

TNF- $\alpha$  is a key mediator of the dysregulated immune and inflammatory function in psoriasis. TNF- $\alpha$  inhibitors are the most widely used biologics for patients with moderate-to-severe psoriasis. Given the immunomodulatory mechanism of biologic therapies for psoriasis, there are concerns that long-term exposure to biologics may increase the risk of developing cancer. Although several studies have confirmed an increase in SCC risk in patients with psoriasis on biological therapies [30], the data for melanoma risk is contradictory. Numerous recent meta-analyses, observational and cohort studies found no significantly increased risk of systemic malignancies [31,32].

In recent years, a series of new biologics that targets of interest in psoriasis including IL-12, IL-23, IL-17, Janus kinase and phosphodiesterase-4, has greatly expanded the spectrum of therapeutic options. The malignancy incidence rates for these newer biologics remains to be determined [33,34].

## Conclusion

In summary, a variety of aggravating and inducing factors on psoriasis such as obesity, smoking, so many harmful items associated with psoriasis itself on the body's immune system, such as anxiety, depression, long-term chronic inflammatory reaction and a lot of psoriasis therapy and medications such as PUVA, immunosuppressants, biological agents, to varying degrees increase the potential risks for psoriasis patients to develop tumors. Particularly, with a large number of biological agents have widely been used in psoriasis, the mechanism on development and occurrence of tumor induction has aroused widespread concern. How the psoriasis does increases the risk for some cancers? The cancer risks are higher in patients with severe psoriasis than mild type? Is rarely the risk might be associated with the effect of systemic immunosuppressants, biological agents treatment? So many questions on cancer associated with psoriasis are worth to be explored in the future. Overall, the exactly mechanism on cancer development and incidence in psoriasis with different risk should be a long-term concern.

## References

1. Nestle FO, Kaplan DH, Barker J. Psoriasis. *N Engl J Med*. 2009;361:496-509.
2. Gulliver W. Long-term prognosis in patients with psoriasis. *Br J Dermatol*. 2008;159:2-9.
3. Jensen P, Skov L. Psoriasis and Obesity. *Dermatology*. 2016;232:633-9.
4. Budu-Aggrey A, Brumpton B, Tyrrell J, et al. Evidence of a causal relationship between body mass index and psoriasis: A mendelian randomization study. *PLoS Med*16. 2019:e1002739.
5. Naldi L. Psoriasis and smoking: links and risks. *Psoriasis (Auckl)*. 2016;6:65-71.
6. Calle EE, Thun MJ. Obesity and cancer. *Oncogene*. 2004;23:6365-6378.
7. Deng T, Lyon CJ, Bergin S, et al. Obesity, Inflammation, and Cancer. *Annu Rev Pathol*. 2016;11:421-49.
8. Sasco ZJ, Secretan MB, Straif K. Tobacco smoking and cancer: a brief review of recent epidemiological evidence. *Lung Cancer*. 2004;45:S3-9.
9. Beyaert R, Beaugerie L, Assche GV, et al. Cancer risk in immune-mediated inflammatory diseases (IMID). *Mol Cancer*. 2013;12:98.
10. Zumsteg A, Christofori G. Corrupt policemen: inflammatory cells promote tumor angiogenesis. *Curr Opin Onco*. 2009;121:60-70.
11. Krishnamoorthy S, Honn KV. Inflammation and disease progression. *Cancer Metastasis Rev*. 2006;25:481-91.
12. Prizment AE, Parisi R, Kontopantelis E, et al. Association between psoriasis and incident cancer: the Iowa's Women's Health Study. *Cancer Causes Contro*. 2011;122:1003-10.
13. Chen YJ, Wu CY, Chen TJ, et al. The risk of cancer in patients with psoriasis: a population-based cohort study in Taiwan. *J Am Acad Dermatol*. 2011;165:84-91.

14. Egeberg A, Thyssen JP, Gislason GH, et al. Skin cancer in patients with psoriasis. *J Eur Acad Dermatol Venereol.* 2016;30:1349-53.
15. Chiesa Fuxench ZC, Shin DB, Ogdie Beatty A, et al. The risk of cancer in patients with psoriasis: a population-based cohort study in the health improvement network. *JAMA Dermatol.* 2016;152:282-90.
16. Parikh-Patel A, White RH, Allen M, et al. Cancer risk in a cohort of patients with systemic lupus erythematosus (SLE) in California. *Cancer Causes Control.* 2008;19:887-94.
17. Smitten AL, Simon TA, Hochberg MC, et al. A meta-analysis of the incidence of malignancy in adult patients with rheumatoid arthritis. *Arthritis Res Ther.* 2008;10:R45.
18. Boehncke WH, Schon MP. Psoriasis. *Lancet.* 2015;386:983-994.
19. 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.
20. Peritz AE, Gasparro FP. Psoriasis, PUVA, and skin cancer--molecular epidemiology: the curious question of T->A transversions. *J Invest Dermatol Symp Proc.* 1999;4:11-16.
21. Lee E, Koo J, Berger T. UVB phototherapy and skin cancer risk: a review of the literature. *Int J Dermatol.* 2005;44:355-60.
22. Lin TL, Wu CY, Chang YT, et al. Risk of skin cancer in psoriasis patients receiving long-term narrowband ultraviolet phototherapy: Results from a Taiwanese population-based cohort study. *Photodermatol Photoimmunol Photomed.* 2015;35:164-71.
23. Patel RV, Clark LN, Lebwohl M, et al. Treatments for psoriasis and the risk of malignancy. *J Am Acad Dermatol.* 2009;60:1001-17.
24. Muellenhoff MW, Koo JY. Cyclosporine and skin cancer: an international dermatologic perspective over 25 years of experience. A comprehensive review and pursuit to define safe use of cyclosporine in dermatology. *J Dermatolog Treat.* 2012;23: 290-304.
25. Paul CF, Ho VC, McGeown C, et al. Risk of malignancies in psoriasis patients treated with cyclosporine: a 5 y cohort study. *J Invest Dermatol.* 2003;120:211-6.
26. Buchbinder R, Barber M, Heuzenroeder , et al. Incidence of melanoma and other malignancies among rheumatoid arthritis patients treated with methotrexate. *Arthritis Rheum.* 2008;59:794-9.
27. Stern RS. Lymphoma risk in psoriasis: results of the PUVA follow-up study. *Arch Dermatol.* 2006;142:1132-5.
28. Mazaud C, Fardet L. Relative risk of and determinants for adverse events of methotrexate prescribed at a low dose: a systematic review and meta-analysis of randomized placebo-controlled trials. *Br J Dermatol.* 2017;177:978-86.
29. Warre RB, Mrowietz U, Kiedrowski RV, et al. An intensified dosing schedule of subcutaneous methotrexate in patients with moderate to severe plaque-type psoriasis (METOP): a 52 week, multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.* 2017;389:528-37.
30. Peleva E, Exton LS, Kelley K, et al. Risk of cancer in patients with psoriasis on biological therapies: a systematic review. *Br J Dermatol.* 2018;178:103-13.
31. Asgari MM, Ray GT, Geier JL. et al. Malignancy rates in a large cohort of patients with systemically treated psoriasis in a managed care population. *J Am Acad Dermatol.* 2017;76:632-8.
32. Garcia-Doval I, Descalzo MA, Mason KJ, et al. Cumulative exposure to biological therapy and risk of cancer in patients with psoriasis: a meta-analysis of Psonet studies from Israel, Italy, Spain, the U.K. and Republic of Ireland. *Br J Dermatol.* 2018;179:863-71.
33. Geller S, Xu H, Lebwohl M, et al. Malignancy Risk and Recurrence with Psoriasis and its Treatments: A Concise Update. *Am J Clin Dermatol.* 2018;19:363-75.
34. Rademaker M, Rubel MD, Agnew K, et al. Psoriasis and cancer. An Australian/New Zealand narrative. *Australas J Dermatol.* 2019;60:12-8.

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