H.10 Phototherapy, systemic therapy, tar and risk of cancer

H.10.1 Prospective cohorts

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>R. S. Stern, L. A. Thibodeau, R. A. Kleinerman, J. A. Parrish, and T. B. Fitzpatrick. Risk of cutaneous carcinoma in patients treated with oral methoxsalen photochemotherapy for psoriasis. New Engl.J.Med. 300 (15):809-813, 1979.

Ref ID: STERN1979</td>
<td>Observational:
Prospective cohort

1976-1979

Representative population sample: unclear (recruited from 16 university centres) – 94% of those eligible enrolled in the follow-up study (and the other 7%were similar for age, sex, severity and exposure to ionising radiation)

Prognostic factor adequately measured: yes

Confounders adjusted for: age, sex and region</td>
<td>N: 1380</td>
<td>Inclusion criteria:
PUVA treated

Exclusion criteria: Not stated

<table>
<tr><th>Parameter</th><th>All (n=1380)</th></tr>
<tr><td>Mean age – years</td><td>44</td></tr>
<tr><td>Male (%)</td><td>65%</td></tr>
<tr><td>Mean BSA (%)</td><td>33</td></tr>
<tr><td>History of cutaneous carcinoma before PUVA</td><td>3%</td></tr>
<tr><td colspan="2">Psoriasis subtypes</td></tr>
</table>
</td>
<td>Oral 8-MOP PUVA</td>
<td>2.1 years</td>
<td>Incidence of SCC and BCC

Tumour counting

Person counts: if tumour of a given type developed that patient was removed from the at-risk set (effectively analysing time-to-first tumour; each patient only counted once for each tumour type even if multiple tumours – this would give a lower value than the federal survey data)</td>
<td>NIH and National Center for Health Services Research</td>
</tr>
</table>

	(plus interactions of prior cancer, skin type and ionising radiation exposure) **Attrition bias:** 2% died **Outcomes adequately measured:** Yes (histological examination – diagnosis confirmed by one dermatopathologist across all centres) **Appropriate statistical analysis:** yes		Plaque 84% Guttate 12% Erythrodermic 4% **Skin type** I 5.4% II 22.1% III 56.3% IV 12.7% V 1.4% VI 2.0% **Prior therapy** Topical steroids 86% Coal tar 84% UV 61% MTX 45% Goekerman 38% x-ray 18% Grenz ray 12%				

			Most patients had severe psoriasis				

Effect Size

Outcomes

Observed vs expected incidence

- **Expected based on specific incidence rate for age-, sex- and geographic location-matched rate from federal survey**
- 30 patients had one or more cutaneous carcinomas (11.4 expected); **RR: 2.63 (1.91-3.90)**
- Total observed: 29 SCC in 18 patients; 19 BCC in 15 patients
- NOTE: 39 patients had a history of cutaneous carcinoma before PUVA (17% SCC and 83% BCC)

Risk group incidence

- Risk of cutaneous carcinoma is related to skin type, ionising radiation exposure, previous cutaneous carcinoma; but not to conventional sunlamp use, tar or immunosuppressive drugs

Risk factor (total N=1182)	**RR (observed/expected; age-sex-region adjusted)**	**95% CI**
Skin type		
I-II	4.73	2.12-9.16
III-IV	1.89	1.00-3.67
Ionising radiation exposure		
Yes	3.68	2.42-8.69
No	1.49	0.74-3.34

Previous cutaneous carcinoma		
Yes	10.22	4.78-37.1
No	1.99	1.13-3.51

Interactions (RR: observed/expected; age-sex-region adjusted):

Previous skin cancer	**Skin type I and II**		**Skin type III and IV**	
	Exposure to radiation		Exposure to radiation	
	Yes	No	Yes	No
Yes	11.13 (0.89-32.0)	22.20 (1.78-63.9)	9.47 (0.24-31.2)	5.13 (0.05-28.7)
No	5.95 (2.30-20.7)	1.64 (0.55-7.14)	2.74 (1.19-7.68)	0.95 (0.36-3.03)

Author's conclusion

- Patients with psoriasis and a previous history of cutaneous carcinoma or ionising radiation use and those with skin type I or II have a higher risk of skin cancer when using PUVA

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>R. S. Stern, N. Laird, and J. Melski. Cutaneous squamous-cell carcinoma in patients treated with PUVA. New Engl.J.Med. 310 (18):1156-1161, 1984.

Ref ID: STERN1984A

AND

R. S. Stern and K. Momtaz. Skin typing for assessment of skin cancer risk and acute response to UV-B and oral</td>
<td>Observational:
Prospective cohort

1977-1982

Representative population sample: unclear (recruited from 16 university centres) – 94% of those eligible enrolled in the follow-up study

Prognostic factor adequately measured: yes

Confounders adjusted for: follow-up, tar and radiation in dose-risk analysis only

Attrition bias: 94 died (similar to expected figure); 82% of these</td>
<td>N: 1380</td>
<td>Inclusion criteria:
PUVA treated

Exclusion criteria: Not stated

<table>
<tr><th>Parameter</th><th>All (n=1380)</th></tr>
<tr><td>Mean age – years</td><td>44</td></tr>
<tr><td>Male (%)</td><td>65%</td></tr>
<tr><td>Mean BSA (%)</td><td>33</td></tr>
<tr><td colspan="2">Psoriasis subtypes</td></tr>
<tr><td>Plaque</td><td>84%</td></tr>
<tr><td>Guttate</td><td>12%</td></tr>
<tr><td>Erythrodermic</td><td>4%</td></tr>
<tr><td colspan="2">Skin type</td></tr>
<tr><td>I</td><td>5.4%</td></tr>
</table>
</td>
<td>Oral 8-MOP PUVA

Note: to separate the effect of dose from time, dose was classified as low, medium or high the limits of which depended upon follow-up time (see below; approximate divisions made at 60th and 80th percentiles)</td>
<td>5.7 years (range: 1.3-8.3 years)

Five cycles of follow-up (as well as pre-treatment examinations) – interviewed annually and examined periodically regardless of continued use of PUVA

Note: for dose risk analysis tumours had to be detected at least 22 months after first PUVA treatment

98% of all patients had a dermatologic assessment performed at least 22 months after first</td>
<td>Incidence of SCC and BCC

Tumour counting
1.Person counts: if tumour of a given type developed that patient was removed from the at-risk set (effectively analysing time-to-first tumour; each patient only counted once for each tumour type even if multiple tumours – this would give a lower value than the federal survey data)

2.Population counts: Federal survey rates are based on annual incidence so also computed observed rates by counting only the first tumour of a given type observed that year, but continuing individuals in the risk set after tumour occurrence</td>
<td>NIH and National Center for Health Services Research</td>
</tr>
</table>

<table>
<tr>
<td>methoxsalen photochemotherapy. Arch.Dermatol. 120 (7):869-873, 1984. Ref ID: STERN1984</td>
<td>had at least one follow-up visit

Outcomes adequately measured: Yes (histological examination)

Appropriate statistical analysis: yes</td>
<td></td>
<td>
<table>
<tr><td>II</td><td>22.1%</td></tr>
<tr><td>III</td><td>56.3%</td></tr>
<tr><td>IV</td><td>12.7%</td></tr>
<tr><td>V</td><td>1.4%</td></tr>
<tr><td>VI</td><td>2.0%</td></tr>
<tr><td colspan="2">Prior therapy</td></tr>
<tr><td>Topical steroids</td><td>86%</td></tr>
<tr><td>Coal tar</td><td>84%</td></tr>
<tr><td>UV</td><td>61%</td></tr>
<tr><td>MTX</td><td>45%</td></tr>
<tr><td>Goekerman</td><td>38%</td></tr>
<tr><td>x-ray</td><td>18%</td></tr>
<tr><td>Grenz ray</td><td>12%</td></tr>
</table>
Most patients had severe psoriasis
</td>
<td></td>
<td>treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td colspan="7">PUVA dose classification
<table>
<tr><th rowspan="2">Time to tumour (months)</th><th rowspan="2">Time to follow-up interview (months)</th><th colspan="3">PUVA exposure (number of treatments)</th></tr>
<tr><td>Low</td><td>Medium</td><td>High</td></tr>
</table>
</td>
</tr>
</table>

22-27	24	<80	80-99	>99
28-39	35	<100	100-119	>119
40-57	47	<100	100-139	>139
58-69	60	<120	120-159	>159
>69	70	<120	120-159	>159

Effect Size

Outcomes

Observed vs expected incidence

- **Expected based on specific incidence rate for age-, sex- and geographic location-matched rate from federal survey**
- Numbers observed (at least 22 months after exposure and only counting one tumour of a given type each year): 89 SCC and 43 BCC
- Total observed: 169 SCC in 54 patients; 74 BCC in 50 patients
- In addition: SCC in situ observed in 12 patients with 24 lesions and keratoancanthoma in 18 patients with 23 lesions

PUVA dose	Person years	Population rates				Person counts			
		SCC		BCC		SCC		BCC	
		SMR	95% CI	SMR	95% CI	SMR	95% CI	SMR	95% CI
Low	3315	4.1	2.3-6.8	1.6	1.1-2.4	2.2	0.9-4.3	1.4	0.9-2.2
Medium	978	22.3	13.5-34.1	1.8	0.7-3.6	14.4	7.6-24.6	0.8	0.2-2.2
High	1219	56.8	42.7-74.2	4.5	2.8-6.9	31.6	21.3-45.1	3.2	1.8-5.3

Total	*5512*	*16.2*	*13.0-19.9*	*2.2*	*1.6-2.9*	*9.3*	*6.9-12.2*	*1.7*	*1.2-2.3*

SMR: ratio of observed to expected tumours

Risk group incidence: dose-risk relationship (person counts; adjusted for duration of follow-up, PUVA dose and prior exposure to ionising radiation and prior use of tar)

	Adjusted relative standard morbidity ratio					
	SCC			**BCC**		
	SMR	**95% CI**	**p-value**	**SMR**	**95% CI**	**p-value**
PUVA dose						
Medium:low	5.7	2.4-13.9		0.5	0.2-1.7	>0.1
High:low	12.8	5.8-28.5	<0.0001 (SS even after adjustment for tar and ionising radiation; $\chi^2 = 52.2$)	2.0	1.0-4.1	<0.5
High: medium and low	-	-		2.2	1.2-4.4	<0.05
Tar dose						
High:low	1.8	1.0-3.3	<0.05 ($\chi^2 = 5.5$)	1.3	0.6-2.6	>0.1
Ionising radiation						
Some:none	-	-		1.3	0.7-2.4	>0.5

Some:none (high tar)	0.7	0.3-1.6		-	-	-
Some:none (low tar)	2.3	1.1-4.8		-	-	-

Interactions:

- SCC: Ionising radiation interacted with dose of tar (χ^2 = 4.72; p<0.05)
- SCC: No interactions between PUVA and tar or ionising radiation

Note: 402 skin type I and II had SMR = 12 for SCC for high PUVA dose compared with low PUVA dose (SMR NS different from skin types III-VI; p>0.2)

Note: if first SCC was detected after high PUVA dose, patients had a significantly higher mean number of tumours than those who developed SCC at low PUVA dose (3.4 vs 1.5; p,0.05)

Risk group incidence: skin-type-risk relationship (STERN1984)

Skin type	N at risk	RR vs ref strata	p-value
I	90	3.2	<0.05
II	312	2.3	<0.05
III	735	1.2	NS
IV	178	1.0	-

Author's conclusion

- Risk of SCC greater with high vs low dose PUVA – this suggests that PUVA can act as an independent carcinogen
- No substantial dose-related increase for BCC

<table>
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<tr>
<td>R. S. Stern and R. Lange. Cardiovascular disease, cancer, and cause of death in patients with psoriasis: 10 years prospective experience in a cohort of 1,380 patients. J.Invest.Dermatol. 91 (3):197-201, 1988.

STERN1988A</td>
<td>Observational:
Prospective cohort

1976-1986

Representative population sample: unclear (recruited from 16 university centres) – 94% of those eligible enrolled in the follow-up study

Prognostic factor adequately measured: yes

Confounders adjusted for: age, sex and location only (but a comparable proportion of patients in the high and low dose strata were exposed to ionising radiation and high doses of tar and UVB; and the</td>
<td>N: 1380</td>
<td>Inclusion criteria:
PUVA treated

Exclusion criteria: Not stated

<table>
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</table>
</td>
<td>Oral 8-MOP PUVA</td>
<td>Mean >10 years

Note: tumours had to be detected at least 58 months after first PUVA treatment

77% of surviving patients had a dermatologic assessment performed at least 9 years after first treatment; >90% had a dermatologic assessment performed at least 6 years after first treatment</td>
<td>Incidence of SCC and BCC

Tumour counting
1.Person counts: if tumour of a given type developed that patient was removed from the at-risk set (effectively analysing time-to-first tumour; each patient only counted once for each tumour type even if multiple tumours – this would give a lower value than the federal survey data)

Note: all patients with incident tumours occurring after 58 months are considered separately to those patients among whom the first incident tumour occurred at least 58 months after first exposure to PUVA</td>
<td>NIH</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td>magnitude of increased risk for SCC associated with greater exposure to PUVA was comparable for both skin type groupings

Attrition bias: Unclear

Outcomes adequately measured: Yes (histological examination)

Appropriate statistical analysis: not regression</td>
<td></td>
<td>
<table>
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Most patients had severe psoriasis
</td>
<td></td>
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<tr>
<td colspan="8">Effect Size

Outcomes</td>
</tr>
</table>

Observed numbers

Treatments	All pts with tumours (number of tumours)		All pts with first tumour ≥58 months after first treatment (number of tumours)	
	SCC	**BCC**	**SCC**	**BCC**
<160	30 (124)	37 (94)	21 (49)	26 (45)
160-199	13 (47)	8 (14)	10 (29)	7 (11)
200-259	22 (60)	14 (23)	17 (52)	13 (22)
260+	15 (61)	10 (30)	11 (28)	9 (19)
Total	**80 (292)**	**69 (161)**	**59 (158)**	**55 (97)**

Observed vs expected incidence

- **Expected based on specific incidence rate for age-, sex- and geographic location-matched rate from federal survey**

PUVA dose	All pts with tumours (number of tumours)				All pts with first tumour ≥58 months after first treatment (number of tumours)			
	SCC		BCC		SCC		BCC	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
<160	5.3	3.6-7.6	1.6	1.1-2.2	4.2	2.6-6.4	1.3	0.8-1.9
160-199	25.5	13.6-43.6	3.1	1.3-6.1	22.2	10.6-40.9	3.0	1.2-6.3
200-259	37.5	23.5-56.7	5.3	2.9-9.0	32.1	18.7-51.4	4.8	3.5-6.5

260+	62.5	35.0-103.1	7.0	4.1-11.2	50.1	24.9-89.5	6.9	3.2-13.1
Total	***11.4***	***9.1-14.2***	***2.3***	***1.8-2.9***	***9.5***	***7.2-12.3***	***2.1***	***1.6-2.7***

Risk group incidence: dose-risk relationship (not adjusted)

PUVA dose	**All pts with tumours (number of tumours)**				**All pts with first tumour ≥58 months after first treatment (number of tumours)**			
	SCC		**BCC**		**SCC**		**BCC**	
	RR	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**
<160	1.0		1.0		1.0		1.0	
160-199	4.8	2.6-8.2	1.9	0.8-3.8	4.3	2.5-9.7	2.3	0.9-4.8
200-259	7.0	4.4-10.7	3.4	1.8-5.6	7.6	4.4-12.2	3.1	2.0-6.4
260+	11.8	8.1-16.7	3.7	2.1-8.0	11.9	5.9-21.3	5.3	2.4-10.1

Risk factors:

- A comparable proportion of patients in the high and low dose strata were exposed to ionising radiation and high doses of tar and UVB (p>0.2)
- Although the risk of SCC was higher than the expected rate for skin types I and II vs III and IV, the magnitude of increased risk for SCC associated with greater exposure to PUVA was comparable for both skin type groupings:

Risk group incidence: skin-type-risk relationship

PUVA dose	**RR of SCC**	**RR of BCC**

	Skin type I-II	Skin type III-VI	Skin type I-II	Skin type III-VI
<160	1.0	1.0	1.0	1.0
160-199	6.1	4.4		
200-259	7.7	4.7		
260+	11.2	13.2	Nearly identical risk vs low dose	

NOTE: increase in RR for BCC vs that expected in general population is ~2.5-fold higher for skin type I-II vs types III and IV with comparable PUVA exposure

Author's conclusion

- Long-term exposure to PUVA substantially increases risk of SCC
- Risk of SCC greater with high vs low dose PUVA – this suggests that PUVA can act as an independent carcinogen
- Modest, but significant dose-related increase for BCC

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>R. S. Stern, E. Abel, B. Wintroub, J. H. Epstein, J. Tschen, J. Wolf, T. P. Nigra, J. Voorhees, T. F. Anderson, R. Armstrong, L. Harber, S. Muller, J. R. Taylor, P. Frost, S. Horwitz, F. Urbach, K. A. Arndt, R. D. Baughman, and I. M. Braverman. Genital tumours among men with psoriasis exposed to psoralens and</td>
<td>Observational:
Prospective cohort

1977-1989

and

1989-1998

Representative population sample: unclear (recruited from 16 university centres) – 94% of those eligible enrolled in the follow-up study

Prognostic factor adequately measured: yes

Confounders adjusted for: STERN1990: no; but also performed a nested case-control analysis (1 case:4 controls)</td>
<td>N: 892</td>
<td>Inclusion criteria: PUVA treated

Exclusion criteria: Not stated

<table>
<tr><th>Parameter</th><th>All (n=892)</th></tr>
<tr><td>Mean age – years</td><td>46±15</td></tr>
<tr><td>Male (%)</td><td>100%</td></tr>
<tr><td>White (%)</td><td>97%</td></tr>
<tr><td>BSA (%)</td><td>35±23</td></tr>
</table>
</td>
<td>Oral 8-MOP PUVA and UVB

Note: to separate the effect of dose from time, dose was classified as low, medium or high the limits of which depended upon follow-up time (see below; approximate divisions made at 60th and 80th percentiles)</td>
<td>12.3 years (1990)

>20 years (2002)

Interviewed annually and examined periodically regardless of continued use of PUVA

1990: 89% of surviving patients had a dermatologic assessment performed at least 6 years after first treatment</td>
<td>Incidence of genital tumours (SCC)

Tumour counting
1.Person counts (1990 and 2002 data): if tumour of a given type developed that patient was removed from the at-risk set (effectively analysing time-to-first tumour; each patient only counted once for each tumour type even if multiple tumours – this would give a lower value than the federal</td>
<td>NIH</td>
</tr>
</table>

ultraviolet A radiation (PUVA) and ultraviolet B radiation. New Engl.J.Med. 322 (16):1093-1097, 1990. Ref ID: STERN1990 R. S. Stern, S. Bagheri, K. Nichols, and Up Study PUVA Follow. The persistent risk of genital tumors among men treated with psoralen plus ultraviolet A (PUVA) for psoriasis. J.Am.Acad. Dermatol. 47 (1):33-39, 2002.	matched for age, site and time of enrolment – control for age, race and ethnicity, circumcision and variations between centres in genital shielding and in PUVA use and therapies before PUVA **STERN2002:** MVA adjusted for age, tumour site, tumour type, PUVA dose, combined PUVA/tar/UVB dose **Attrition bias:** **STERN1990** 160 (18%) died Of the remaining 732 men, 86% were interviewed at least 11 years after first treatment with PUVA **STERN2002** 336 (38%) died Of the remaining 556 men, 82% were interviewed at last					survey data) 2.*Population counts (2002 data)*: Federal survey rates are based on annual incidence so also computed observed rates by counting only the first tumour of a given type observed that year, but continuing individuals in the risk set after tumour occurrence	

Ref ID: STERN2002	follow-up interview **Outcomes adequately measured:** Yes (histological examination by pathologists blinded to levels of exposure to PUVA) **Appropriate statistical analysis:** yes						

PUVA dose classification

Time to tumour (months)	**Time to follow-up interview (months)**	**PUVA exposure (number of treatments)**		
		Low	Medium	High
0-27	24	<80	80-99	>99
28-39	35	<100	100-119	>119
40-57	47	<100	100-139	>139
58-69	60	<120	120-159	>159
70-96	70	<120	120-159	>159
>96	121	<140	140-239	>239

Note: in the matched case-control analysis (1990) time to development of tumours varied among cases so annual number of treatments before development of first genital tumour was used as a measure of level of PUVA exposure:

- Low: <20 treatments per year

- Medium: 20-39 treatments per year
- High: ≥40 treatments per year

Other dose classifications

- High tar: topical tar for >90 months in STERN1990 and >44 months in STERN2002
- High UVB: >300 treatments

Effect Size

Outcomes

Observed vs expected incidence (1990)

- **Expected based on specific incidence rate for age- and sex-matched incidence rate from 3 population-based cancer registries**
- Numbers observed: 30 genital tumours in 14 patients

PUVA dose	Tumour					
	Invasive SCC of penis and scrotum		Invasive and in situ penile tumours		Invasive SCC of scrotum	
	SMR	95% CI	SMR	95% CI	SMR	95% CI
Low	17.5	0.4-97.7	23.0	2.8-83.0	No cases	
Medium	125.0	15.1-451.5	34.5	0.9-192.1	147.1	3.7-819.4
High	285.7	104.9-621.9	162.2	59.5-353.0	449.4	122.5-1150.7
Total	*95.7*	*43.8-181.8*	*58.8*	*26.9-111.7*	*131.6*	42.7-307.1

Number of tumours	*21*	*19*	9

SMR: ratio of observed to expected tumours

Observed vs expected incidence (2002)

- **Expected based on specific incidence rate for age- and sex-matched incidence rate from SEER registry**
- Numbers observed: 51 genital tumours in 24 patients (42 incident events and 28 person counts – including one BCC)

PUVA dose	**Tumour**					
	Invasive SCC of penis and scrotum			**All genital SCCs (including all sites and types)**		
	N	**SMR**	**95% CI**	**N**	**SMR**	**95% CI**
After 5/1/89						
Population counts						
Low	2	44.4	5.4-160.5	2	28.8	3.5-103.2
Medium	1	36.1	0.9-201.1	4	90.9	24.8-232.8
High	7	168.7	67.8-347-5	10	151.5	72.2-145.2
Total	*10*	*87.7*	*42.1-161.3*	*16*	*89.4*	*51.1-145.2*

Person counts						
Low	2	44.4	5.4-160.5	2	28.8	3.5-103.2
Medium	1	36.1	0.9-201.1	3	68.2	14.1-199.3
High	3	72.3	14.9-211.3	6	90.9	33.4-197.9
Total	*6*	*52.6*	*19.3-114.6*	*11*	*61.5*	*30.7-110.0*
Both periods						
Population counts						
Low	4	39.2	10.7-100.4	5	-	-
Medium	3	68.2	14.1-199.3	7	-	-
High	21	283.8	175.7-433.8	29	-	-
Total	*28*	*134.6*	*89.5-194.6*	41	-	-
Person counts						
Low	3	29.4	6.1-86.0	4	-	-
Medium	3	68.2	14.1-199.3	6	-	-
High	11	148.	74.2-	17	-	-

		6	266.0			
Total	*17*	*81.7*	*52.1-122.6*	27	-	-

SMR: ratio of observed to expected tumours

Risk group incidence: dose-risk relationship 1990 (not adjusted)

PUVA dose	**Tumour**					
	Invasive SCC of penis and scrotum		**Invasive and in situ penile tumours**		**Invasive SCC of scrotum**	
	SMR	**95% CI**	**SMR**	**95% CI**	**SMR**	**95% CI**
High:low	16.3	9.4-26.4	7.1	2.8-14.5	No cases in low dose group	
High:medium and low	-	-	-	-	13	24.1-48.3

Case-control analysis (controlling for confounders)

Characteristic	**Cases (N=14)**	**Age-matched controls (N=56)**	**p-value**
Age (years)	52±15	52±14	>0.2

BSA at enrolment (%)	41±22	35±20	>0.2
Number of PUVA treatments*	210±124	113±86	<0.02
PUVA treatments per year	41±22	23±17	<0.01
UVB treatments	712±640	202±343	<0.01
Exposure to x-ray therapy (%)	29	45	>0.2
Months of tar therapy	114±218	55±130	>0.2
PUVA dose			
Low	2	28	<0.002
Medium	4	20	
High	8	8	
Tar exposure			
Low	9	46	>0.2
High	5	10	

*In the period before development of first genital tumour, or during a similar period in the matched controls

Risk group incidence: dose-risk and site-risk relationship 2002

	Genital SCC	
	IRR (age-adjusted)	**95% CI**
Both periods		
Low PUVA	1	
Medium PUVA	1.8	0.7-4.5
High PUVA	8.8	4.5-17.2
All penile	1	
Invasive scrotal SCC	3.1	1.9-5.0

Multivariate (adjusted for age, tumour site, tumour type, PUVA dose, combined PUVA/tar/UVB dose); data only for after 1/5/1989 (to 1998)

NOTE: the distribution of skin type did not differ among those with and without genital SCCs

	Genital SCC	
	IRR	**95% CI**
Exposure		
Low PUVA	1	
High PUVA	2.8	0.5-15.5
Low PUVA, not high tar/UVB	1	
Medium	8.8	0.9-85.1

PUVA/high tar/UVB		
High PUVA, high tar/UVB	4.5	1.3-16.1
Site		
All penile	1	
Invasive scrotal SCC	4.7	1.4-15.2
In situ scrotal SCC	23.8	6.4-87.9

Author's conclusion

- The apparent high susceptibility of male genitalia to carcinogenic effects of UV light (PUVA and UVB) suggests that genital protection is prudent when people are exposed to therapeutic UV
- Although use of PUVA decreased and genital shielding in our cohort increased between the first and second reports, the dose-dependent increase in the risk of genital tumours in men treated with PUVA has persisted.
- Particularly high risks occur among those with high-dose exposures to both PUVA and topical tar/ultraviolet B.

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>R. S. Stern and N. Laird. The carcinogenic risk of treatments for severe psoriasis. Photochemotherapy Follow-up Study. Cancer 73 (11):2759-2764, 1994.

Ref ID: STERN1994</td>
<td>Observational:
Prospective cohort

1977-1989

Representative population sample: unclear (recruited from 16 university centres) – 94% of those eligible enrolled in the follow-up study

Prognostic factor adequately measured: yes

Confounders adjusted for: yes – age, sex, ionising radiation, dosage of tar and UVB, dosage of MTX, duration of treatment

Attrition bias: 227 (16%)</td>
<td>N: 1380</td>
<td>Inclusion criteria: PUVA treated

Exclusion criteria: Not stated

<table>
<tr><th>Parameter</th><th>All (n=1380)</th></tr>
<tr><td>Mean age – years</td><td>44</td></tr>
<tr><td>Male (%)</td><td>65%</td></tr>
<tr><td>Mean BSA (%)</td><td>33</td></tr>
<tr><td colspan="2">Psoriasis subtypes</td></tr>
<tr><td>Plaque</td><td>84%</td></tr>
<tr><td>Guttate</td><td>12%</td></tr>
<tr><td>Erythrodermic</td><td>4%</td></tr>
<tr><td colspan="2">Skin type</td></tr>
<tr><td>I</td><td>5.4%</td></tr>
</table>
</td>
<td>Oral 8-MOP PUVA

Note: to separate the effect of dose from time, dose was classified as low, medium or high the limits of which depended upon follow-up time (see below; approximate divisions made at 60th and 80th percentiles)</td>
<td>13.2 years

Interviewed annually and examined periodically regardless of continued use of PUVA

This includes data to the end of 12th cycle of follow-up interviews and 7th cycle of physical examinations</td>
<td>Incidence of BCC and invasive SCC (SCC in situ excluded)

Tumour counting
1.Person counts: if tumour of a given type developed that patient was removed from the at-risk set (effectively analysing time-to-first tumour)

2.Population counts: Federal survey rates are based on annual incidence so also computed observed rates by counting only the first tumour of a given type observed that year as an incidence, but continuing individuals in the</td>
<td>NIH</td>
</tr>
</table>

	died Of the remaining 1153, 93% were interviewed at final follow-up cycle and 83% had physical exam at least 10 years after first exposure **Note:** tumours occurring in patients who died are also counted **Outcomes adequately measured:** Yes (histological examination by pathologists) **Appropriate statistical analysis:** yes		II 22.1% III 56.3% IV 12.7% V 1.4% VI 2.0% **Prior therapy** Topical steroids 86% Coal tar 84% UV 61% MTX 45% Goekerman 38% x-ray 18% Grenz ray 12% Most patients had severe psoriasis			risk set after tumour occurrence	

PUVA dose classification

Time to tumour (months)	Time to follow-up interview (years)	Number of surviving patients	PUVA exposure (number of treatments)		
			Low	Medium	High

0-27	2	1358	<80	80-99	>99
28-39	3	1341	<100	100-119	>119
40-57	4	1321	<100	100-139	>139
58-69	5	1302	<120	120-159	>159
70-96	6	1286	<120	120-159	>159
94-136	10	1210	<140	140-239	>239
>136	13	1153	<160	160-299	>299

Other dose classifications (based on historical data collection)

- High tar: topical tar for >45 months
- High UVB: >300 treatments
- High MTX: ≥4 years use (approximately 3 g)

Effect Size

Outcomes

Observed vs expected incidence

- **Expected based on specific incidence rate for age-, sex- and geographic region-matched incidence rate from a federal survey**
- Numbers observed: 618 SCCs in 144 patients; 341 BCCs in 130 patients (41 patients had both BCC and SCC)
- Population counts: 326 incident cases of SCC and 217 incidence cases of BCC

PUVA dose	SCC			BCC		
	N	SMR	95% CI	N	SMR	95% CI

Population counts (occurrence of one or more tumours of a given type in a given year = an incident event)						
Low	80	10.6	8.5-13.2	114	3.6	3.0-4.3
Medium	51	23.6	18.0-31.1	28	2.9	2.0-4.2
High	195	83.0	72.1-95.5	75	6.0	4.8-7.5
Total	*326*	*27.0*	*24.2-30.1*	*217*	*4.1*	*3.5-4.7*
Person counts (only the first tumour of a given type is counted)						
Low	38	5.0	3.6-6.9	66	2.1	1.6-2.7
Medium	29	13.4	9.3-19.3	19	1.9	1.2-3.0
High	77	32.8	26.2-41.0	45	3.8	2.8-5.1
Total	*144*	*11.9*	*10.1-14.0*	*130*	*2.5*	*2.1-3.0*

Risk group incidence: (person counts: adjusted for duration of follow-up, and prior exposure to ionising radiation, dosage of tar and UVB and dosage of MTX)

	Adjusted RR					
	SCC			**BCC**		
	RR	**95% CI**	**p-value**	**RR**	**95% CI**	**p-value**
PUVA dose						
Medium:low	2.6	2.0-3.3	-	0.9	-	>0.1
High:low	5.9	4.0-8.7	-	1.7	1.1-2.5	-

Skin type						
I-II:III-IV	~2-fold			~2-fold		

Note - interactions: none of the other risk factors (MTX, UVB or ionising radiation) modified the effect of PUVA.

Variable	**Adjusted RR** (adjusted for age, sex, residence, level of PUVA exposure)					
	SCC			**BCC**		
	RR	**95% CI**	**p-value**	**RR**	**95% CI**	**p-value**
High MTX	2.0	1.4-2.8	SS	-	-	NS
High UVB/tar	-	-	NS	-	-	NS
Exposure to ionising radiation	-	-	NS	-	-	NS

Note: no evidence that the association between prior MTX and SCC was **modified** by other exposures, including level of PUVA exposure

Note: the lack of independent carcinogenic effect of UVB, topical tar or ionising radiation conflicts with earlier findings in this cohort – this may be because PUVA is the main carcinogen and as more is received it outweighs the impact of other factors

Author's conclusion

- Long term exposure to PUVA and methotrexate significantly increases the risk of SCC in patients with psoriasis.
- The ultimate morbidity of these tumours is undetermined

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>R. S. Stern, E. J. Liebman, and L. Vakeva. Oral psoralen and ultraviolet-A light (PUVA) treatment of psoriasis and persistent risk of nonmelanoma skin cancer. J.Natl.Cancer Inst. 90 (17):1278-1284, 1998.

Ref ID: STERN1998A</td>
<td>Observational:
Prospective cohort

1977-1996

Representative population sample: unclear (recruited from 16 university centres) – 94% of those eligible enrolled in the follow-up study

Prognostic factor adequately measured: yes

Confounders adjusted for: yes – age, sex, and all exposures that were significant predictors of risk in the univariate analysis

Attrition bias: 299</td>
<td>N: 1380</td>
<td>Inclusion criteria: PUVA treated

Exclusion criteria: Not stated

<table>
<tr><th>Parameter</th><th>All (n=1380)</th></tr>
<tr><td>Mean age – years</td><td>44</td></tr>
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<tr><td>Mean BSA (%)</td><td>33</td></tr>
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<tr><td colspan="2">Skin type</td></tr>
<tr><td>I</td><td>5.4%</td></tr>
</table>
</td>
<td>Oral 8-MOP PUVA

0.4-0.6 mg/kg psoralen orally, followed in 1.5-2.0 h by UVA (standing in an UV irradiation unit; fluorescent bulbs with emissions in the range of 320-400 nm).

Initial UVA dose 1.5-5 J/cm^2 depending on photosensitivity. During the clearing phase, patients undergo two or three light treatments per week and UVA dose is gradually increased according to the degree of erythema or pigmentation.</td>
<td>20 years

Interviewed annually and examined periodically regardless of continued use of PUVA

This includes data to the end of 18th cycle of follow-up interviews and 8th cycle of physical examinations

Separately assessed those with tumour development during the first decade and those surviving without tumour occurrence by the end of the first decade</td>
<td>Incidence of BCC and invasive SCC

Tumour counting
1.Person counts: if tumour of a given type developed that patient was removed from the at-risk set (effectively analysing time-to-first tumour)

2.Population counts: Federal survey rates are based on annual incidence so also computed observed rates by counting only the first tumour of a given type observed that year as an incidence, but continuing individuals in the risk set after tumour</td>
<td>NIH</td>
</tr>
</table>

	(21.7%) died **Outcomes adequately measured:** Yes (histological examination by pathologists) **Appropriate statistical analysis:** yes		II 22.1% III 56.3% IV 12.7% V 1.4% VI 2.0% **Prior therapy** Topical steroids 86% Coal tar 84% UV 61% MTX 45% Goekerman 38% x-ray 18% Grenz ray 12% Most patients had severe psoriasis	Average max UVA dose = 8-15 J/cm^2. With disease improvement therapy slowly tapered off. If disease flared, patients treated again with PUVA or other therapies for psoriasis as determined by their physician. Note: for dose stratification the highest dose group was defined as the number of treatments received by the top decile who survived to 1986 without SCC		occurrence	

PUVA dose stratification and number of patients followed after 1985 with SCC or BCC

Exposure	Number (%) of patients with cancers developing after 1985		
	Total	**SCC**	**BCC**
PUVA treatments up to 1986			
<100	435 (37%)	18 (13%)	29 (19%)
100-159	243 (21%)	15 (11%)	30 (20%)
160-336	373 (32%)	68 (50%)	58 (38%)
≥337	132 (11%)	34 (25%)	34 (23%)
Total	1183	135	151
PUVA treatments after 1985			
<50	877 (74%)	66 (49%)	99 (66%)
≥50	306 (26%)	69 (51%)	52 (34%)
Total	1183	135	151

Other dose classifications (based on historical data collection)

- High tar: topical tar for ≥45 months
- High UVB: >300 treatments
- High MTX: ≥4 years use (approximately 3 g)

Effect Size

Outcomes

Numbers observed: 1422 SCCs in 237 patients (17.2%); 1042 BCCs in 247 patients (17.9%)

Tumour type	**Total number of tumours by date of detection**		**Total**
	Before 1986	**Beginning 1986**	
SCC	**375**	**1047**	**1422**
BCC	**221**	**821**	**1042**

Tumour type	**Total number of patients with skin cancer by date of first detection and total number of cancers developed in these patients at any time**		**Total**
	Before 1986 (n=1380)	**Beginning 1986 (n=1081)**	
SCC			
• Number of patients	102	135	237
• Number of tumours	829	593	1422
BCC			
• Number of patients	96	151	247
• Number of tumours	NA	NA	1042

Observed vs expected incidence

- **Expected based on specific incidence rate for age-, sex- and geographic region-matched incidence rate from a federal survey**

Figures for 1st cancer after 1985

Total PUVA treatments to 1986	**SCC**		**BCC**	
	RR	**95% CI**	**RR**	**95% CI**
Population counts (occurrence of one or more tumours of a given type in a given year = an incident event)				
<100	5.1	3.5-7.2	1.7	1.2-2.3
100-159	8.4	5.6-12.1	3.9	3.0-5.0
160-336	26.5	22.2-31.4	4.5	3.5-5.7
≥337	68.5	54.9-84.5	11.7	9.3-14.5
All dosages	*17.6*	*15.6-19.8*	*4.1*	*3.7-4.6*

RR for all observed tumours after 1985 (including those who had experienced a first tumour before 1986) vs expected incidence

Total PUVA treatments to 1986	**SCC**	
	RR	**95% CI**
≥337	104	88.3-121.9

Risk group incidence: (person counts)

Univariate analysis showed the following regarding relation of potentially carcinogenic treatments to the risk of SCC and BCC (so the multivariate analysis was adjusted for those found to be SS predictors of risk, as well as age, sex, residence, and anatomic site)

Variable	**SCC**	**BCC**
PUVA exposure up to 1985	SS	SS
PUVA exposure after 1985	SS	*NS*
UVB/tar exposure	SS	SS
MTX exposure	SS	SS
Grenz ray/x-ray exposure	*NS*	SS

Exposure	**Multivariate adjusted OR for 1st cancer after 1985**			
	SCC		**BCC**	
	OR	**95% CI**	**OR**	**95% CI**
<100	1	-	1	-
100-159	1.6	0.9-3.1	2.0	1.3-3.1
160-336	4.5	2.7-7.4	2.1	1.4-3.1

≥337	8.6	4.9-15.2	4.7	3.1-7.3
≥50 vs <50	1.4	1.0-2.0	NA	-
UVB/tar (high vs low)	1.4	1.0-2.0	1.5	1.1-2.0
MTX (high vs low)	1.3	0.9-1.9	1.1	0.7-1.5
Grenz ray/x-ray (exposed vs not exposed)	NA	-	1.5	1.1-2.0

Author's conclusion

- High dose exposure to PUVA is associated with a persistent, dose-related increase in the risk of SCC, even among patients lacking substantial exposure to other carcinogens and among patients without substantial recent exposure to PUVA.
- The carcinogenic effects of PUVA are unlikely to solely reflect immunosuppressive effects on the skin (which diminish after treatment is stopped)
- Exposure to PUVA has far less effect on the risk of basal cell cancer.
- The use of PUVA for psoriasis should be weighed against the increased cancer risk.

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>I. Marcil and R. S. Stern. Squamous-cell cancer of the skin in patients given PUVA and ciclosporin: Nested cohort crossover study. Lancet 358 (9287):1042-1045, 2001.

Ref ID: MARCIL2001</td>
<td>Observational: Prospective cohort study

1977-1998

Representative population sample: unclear (recruited from 16 university centres) – 94% of those eligible enrolled in the follow-up study

Prognostic factor adequately measured: yes

Confounders adjusted for: follow-up time, PUVA and MTX exposure

Attrition bias: 396 died (29%); 55 (4%)</td>
<td>N: 1380 (844 analysed)</td>
<td>Inclusion criteria: PUVA treated

Exclusion criteria: Not stated

<table>
<tr><th>Parameter</th><th>CSA users (n=28)</th><th>Others (n=816)</th></tr>
<tr><td>Mean age – years</td><td>53±11</td><td>55±14</td></tr>
<tr><td>Male (%)</td><td>71%</td><td>61%</td></tr>
<tr><td colspan="3">PUVA treatments to 1992</td></tr>
<tr><td><200</td><td>39%</td><td>63%</td></tr>
<tr><td>≥200</td><td>61%</td><td>37%</td></tr>
<tr><td colspan="3">UVB or tar</td></tr>
<tr><td>Less use</td><td>39%</td><td>63%</td></tr>
<tr><td>>300 UVB or 45 months</td><td>61%</td><td>37%</td></tr>
<tr><td colspan="3">MTX use</td></tr>
<tr><td><36</td><td>61%</td><td>85%</td></tr>
</table>
</td>
<td>Oral 8-MOP PUVA and ciclosporin</td>
<td>Average of 6 years for ciclosporin

Note: 6/28 CSA users had <3 months of use

Mean time for remaining 22 = 35±34 months (median = 20 months [IQR:12-53])</td>
<td>Incidence of SCC/keratoacanthoma and BCC</td>
<td>NIH</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td>withdrawn

91% of remaining participants were followed up

Outcomes adequately measured: Yes (histological examination)

Appropriate statistical analysis: yes</td>
<td></td>
<td>
<table>
<tr><td>months</td><td></td><td></td></tr>
<tr><td>≥36 months</td><td>39%</td><td>15%</td></tr>
</table>

PUVA exposure and MTX use SS higher in those who did receive CSA
</td>
<td></td>
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</tr>
<tr>
<td colspan="8">
Effect Size

Outcomes

<u>Observed incidence</u>

14 of 28 CSA users developed BCC or SCC

<table>
<tr><th>Parameter</th><th>CSA users (n=28)</th><th>Others (n=816)</th></tr>
<tr><td colspan="3">SCC</td></tr>
<tr><td>Patients (n)</td><td>-</td><td>212</td></tr>
</table>
</td>
</tr>
</table>

Tumours (n)	212	1736
BCC		
Patients (n)	-	-
Tumours (n)	55	

Incidence for patients who used CSA (nested cohort, N=28)

Treatment	Patients	Patients with SCC	Total SCC	Patient years	IRR	
					Univariate	Multivariate
Time						
5 years before CSA	28	6	20	140	1.0	1.0
After first CSA	28	13	169	172	6.9 (4.3-10.9)	6.9 (4.3-11.0)
PUVA treatments to 1992						
<200	11	4	15	123	1.0	1.0
≥200	17	9	174	187	7.8 (4.5-13.2)	5.1 (3.0-8.9)
MTX use						
<36 months	17	7	50	190	1.0	1.0

≥36 months	11	6	139	121	4.3 (3.1-6.0)	2.7 (2.0-3.8)

Incidence for full cohort (N=844)

Treatment	Patients	Total SCC	Patient years	IRR	
				Univariate	Multivariate
Time					
5 years before CSA	844	417	4220	1.0	1.0
After first CSA	844	1178	4853	2.5 (2.2-2.7)	2.1 (2.0-2.5)
CSA use					
No	816	1426	8901	1.0	1.0
Yes	28	169	172	6.1 (5.2-7.2)	3.1 (2.6-3.7)
PUVA treatments to 1992					
<200	525	514	5571	1.0	1.0
≥200	319	1081	3502	3.3 (3.0-3.7)	2.8 (2.6-3.2)
MTX use					

<36 months	710	1107	7653	1.0	1.0
≥36 months	134	488	1419	2.4 (2.1-2.6)	1.7 (1.5-1.9)

Note: the risk associated with long-term MTX was SS lower than that associated with any CSA use or high-dose PUVA (p<0.0001)

Incidence stratified by PUVA dose (adjusted by extent of MTX use)

Variable	**IRR**	
	Nested cohort (n=28)	**Full cohort (n=844)**
≥200 PUVA treatments		
Pre-use/non-user	1.0	1.0
CSA user	8.1 (4.8-13.5)	3.5 (2.9-4.2)
≤200 PUVA treatments		
Pre-use/non-user	1.0	1.0
CSA user	2.4 (0.9-7.8)	1.2 (0.7-2.2)

Note: SS increased risk of SCC for those using CSA only for those also having received high-dose PUVA

Author's conclusion

- The risk of SCC of the skin is increased by ciclosporin in patients with psoriasis who have been exposed to PUVA.
- Such risks should be balanced against the effectiveness of the drug and possible newer immunosuppressive agents.

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>T. E. C. Nijsten and R. S. Stern. The increased risk of skin cancer is persistent after discontinuation of psoralen + ultraviolet A: A cohort study. J.Invest.Dermatol. 121 (2):252-258, 2003.

Ref ID: NIJSTEN2003A</td>
<td>Observational: Prospective cohort study

1975-2001

Representative population sample: unclear (recruited from 16 university centres) – 94% of those eligible enrolled in the follow-up study

Prognostic factor adequately measured: yes

Confounders adjusted for: yes – IRR: calendar year plus all exposures that were significant predictors of risk in the univariate analysis; HR: age, sex and PUVA dose</td>
<td>N: 1380</td>
<td>Inclusion criteria: PUVA treated

Exclusion criteria: Not stated

<table>
<tr><th></th><th>No. of persons at last follow-up (%) (n=1380)</th></tr>
<tr><td>Age (y)</td><td></td></tr>
<tr><td><45</td><td>129 (9.3%)</td></tr>
<tr><td>45–64</td><td>565 (40.9%)</td></tr>
<tr><td>>64</td><td>686 (49.7%)</td></tr>
<tr><td>Men</td><td>892 (64.6%)</td></tr>
<tr><td colspan="2">Skin type</td></tr>
<tr><td>I–II</td><td>402 (29.1%)</td></tr>
<tr><td>III–VI</td><td>978 (70.9%)</td></tr>
<tr><td>Region</td><td></td></tr>
<tr><td>North</td><td>781 (56.6%)</td></tr>
</table>
</td>
<td>Oral 8-MOP PUVA

Note: for 85.3% of the person-years, no use of PUVA was recorded</td>
<td>>20 years

Interviewed annually and examined periodically regardless of continued use of PUVA

This includes data to the end of 19th cycle of follow-up interviews</td>
<td>Incidence of BCC and invasive SCC (ie only biopsy confirmed SCC not SCC in situ or keratacanthoma)

Tumour counting All tumours counted (different method to other analyses of this cohort)</td>
<td>NIH and Fund for Scientific Research</td>
</tr>
</table>

	Attrition bias: see table below **Outcomes adequately measured:** Yes (histological examination) **Appropriate statistical analysis:** yes (all incorporated time-dependent variables)							

Middle	233 (16.9%)
South	364 (26.4%)
Methotrexate exposure	
Low	1039 (75.3%)
High	341 (24.7%)
Tar and/or UVB exposure	
Low	877 (63.6%)
High	503 (36.5%)
X-ray therapy prior to entering study	
No	1053 (76.3%)
Yes	327 (23.7%)
No. of PUVA treatments	
<100	497 (36.0%)
100–199	371 (26.9%)
200–299	218 (15.8%)
300–399	121 (8.8%)
400–499	70 (5.1%)

≥500	103 (7.5%)
Years since stopping PUVA	
<2	85 (6.2%)
2–5	235 (17.0%)
6–10	324 (23.5%)
11–15	268 (19.4%)
>15	468 (33.9%)

Status of 1380 patients originally enrolled by end of year

	Year				
	1979	**1984**	**1989**	**1995**	**2001**
Interviewed	1293	1152	988	860	609
Dead	59	134	223	395	510
Not interviewed	28	94	169	125	261

Effect Size

Outcomes

Note: values for each patient for all variables determined for each calendar year (so were time-dependent)

Dose classifications (based on historical data collection)

- High tar: topical tar for ≥45 months
- High UVB: >300 treatments
- High MTX: ≥3 years use
- PUVA exposed year: ≥10 PUVA treatments per calendar year
- PUVA non-exposed year: ≤10 PUVA treatments per calendar year

TUMOUR RISK

SCC

- Incidence of SCC has increased over the 25 years of the study
- 2147 invasive SCC in 303 patients

BCC

- Average incidence has increased substantially over the last 10 y of the study
- 1363 BCC in 294 persons

Multivariate estimates of IRR and 95% CI for SCC and BCC adjusted for all other significant risk factors and for study year in members of the PUVA Follow-up Study (n=1380)

	SCC		BCC	
	IRR	**95% CI**	**IRR**	**95% CI**
Age (y)				
< 45	1		1	
45–64	2.08	1.63–2.65	2.19	1.64–2.92
>64	3.40	2.63–4.40	5.13	3.82–6.89
Men, compared with women	1.38	1.15–1.66	1.91	1.55–2.35
Skin type				
III–VI	1		1	
I–II	2.90	2.43–3.47	1.41	1.15–1.72
Region				
North	1		1	
Middle	0.74	0.58–0.95	1.18	0.91–1.52
South	2.19	1.79–2.68	1.79	1.43–2.25
Years since stopping PUVA				
< 2	1		1	
2–5	1.19	0.93–1.53	1.86	1.40–2.48

6–10	1.25	0.92–1.70	2.74	1.95–3.85
11–15	0.90	0.62–1.31	2.61	1.70–4.02
>15	0.94	0.58–1.52	3.18	1.86–5.44
High methotrexate exposure (36+mo) compared with low	2.18	1.79–2.66	1.46	1.17–1.81
High tar (45+mo) and/or UVB exposure (300+treatments) compared with low	1.02	0.85–1.22	1.61	1.33–1.95
X-ray therapy prior to entering study compared with none	2.87	2.40–3.44	2.13	1.75–2.60
No. of PUVA treatments				
< 100	1		1	
100–199	3.20	2.27–4.51	2.35	1.64–3.38
200–299	5.28	3.38–8.25	3.76	2.34–6.06
300–399	8.18	4.95–13.53	4.63	2.68–7.98
400–499	14.36	7.97–25.87	7.62	4.03–14.43
≥500	18.67	10.23–34.07	12.69	6.34–25.40
No. of PUVA treatments in first 5 y				
< 100	1		1	
100–199	1.10	0.83–1.46	0.86	0.63–1.17
≥200	1.39	0.95–2.03	0.75	0.49–1.14

Period (adjusted for all variables except study year)				
1975–80	1		1	
1981–85	0.99	0.71–1.39	0.84	0.57–1.25
1986–90	1.28	0.88–1.87	0.90	0.58–1.41
1991–95	2.18	1.43–3.30	1.32	0.80–2.18
1996–2000	2.76	1.71–4.48	1.12	0.64–1.97

Summary:

SCC

- Level of PUVA exposure is the single factor most strongly associated with SCC risk
- Even 15 years after stopping PUVA the risk of SCC observed was not lower than that while still using PUVA
- Early intense therapy with PUVA was not significantly related to SCC risk.
- For most other significant predictors of risk for SCC, including methotrexate, X-ray, UVB and tar, the risk estimates from the multivariate analysis were somewhat lower than the univariate estimates

BCC

- BCC risk is significantly associated with increasing PUVA use, the years since first PUVA treatment and age.
- In the multivariate analysis, BCC risk increased greatly with very high levels of PUVA exposure
- For most significant predictors of risk for BCC, including years since stopping PUVA, there was little difference in the estimates obtained in the univariate and multivariate analysis
- The risk of BCC increases significantly with the passage of time since stopping PUVA and is about three times higher 10 y after stopping PUVA than during treatment.

RISK OF FIRST TUMOUR

Multivariate estimates of HR and 95% CI for a first SCC (n=303) and a first BCC (n=294) in members of the PUVA Follow-up Study (Each variable adjusted for the other two variables)

	SCC		BCC	
	HR	**95% CI**	**HR**	**95% CI**
Age (y)				
< 45	1		1	
45–64	1.37	0.98, 1.91	0.40	0.28, 0.57
>64	1.50	1.06, 2.14	0.74	0.57, 0.95
Men, compared with women	1.75	1.35, 2.28	1.45	1.12, 1.88
No. of PUVA treatments				
<100	1		1	
100–199	2.38	1.60, 3.54	1.52	1.09, 2.12
200–399	6.03	4.09, 8.88	2.26	1.62, 3.17
≥400	10.75	6.99, 16.54	3.17	2.13, 4.72

Summary:

SCC

- Total PUVA exposure significantly associated with risk of a first SCC
- Males had a modestly, but significantly, higher risk of developing a first SCC
- Risk of a first SCC and age were not significantly associated
- In 25 y, patients with fewer than 200 PUVA treatments have about 7% risk at least one SCC (Figure 3). After 25 y, more than half of the patients with 400 or more treatments develop at least one SCC.

BCC

- More than 100 PUVA treatments was significantly associated with an increased risk of a first BCC
- Risk of developing at least one BCC was higher in males.
- Risk of a first BCC was lower among patients older than 44 than younger patients.
- Risk of developing at least one BCC did not increase as sharply with increasing PUVA dose as did the risk of SCC.
- After 25 y, almost one-third of the patients with 200 treatments develop at least one BCC

Author's conclusion

- Substantial exposure to PUVA increases the risk of SCC and BCC
- The carcinogenic effects of PUVA increase over time, are independent of the intensity of the initial therapeutic regimen and persist for many years after stopping treatment
- The stabilization of SCC incidence after about 20 y of follow-up may reflect the death and/or loss of follow-up of highly susceptible patients or a stabilization of the SCC risk associated with PUVA therapy with the additional passage of time

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>T. E. C. Nijsten and R. S. Stern. Oral retinoid use reduces cutaneous squamous cell carcinoma risk in patients with psoriasis treated with psoralen-UVA: A nested cohort study. J.Am.Acad. Dermatol. 49 (4):644-650, 2003.

Ref ID: NIJSTEN2003</td>
<td>Observational:
Prospective nested cohort study

1985-2000

Representative population sample: unclear (recruited from 16 university centres) – 94% of those eligible enrolled in the follow-up study

Prognostic factor adequately measured: yes

Confounders adjusted for: yes – all factors that were significant predictors of risk in the univariate analysis</td>
<td>N: 135 (11.3% of surviving cohort)</td>
<td>Inclusion criteria: PUVA treated

Exclusion criteria: Not stated

<table>
<tr><th></th><th>Retinoid users at 1989 (n=135)</th><th>Non-users at 1989 (n=942)</th></tr>
<tr><td>Age (y)</td><td></td><td></td></tr>
<tr><td><45</td><td>34.1%</td><td>28.6%</td></tr>
<tr><td>45–64</td><td>41.5%</td><td>43%</td></tr>
<tr><td>>64</td><td>24.4%</td><td>28.4%</td></tr>
<tr><td>Men</td><td>65.2%</td><td>62.2%</td></tr>
<tr><td>Skin type</td><td></td><td></td></tr>
<tr><td>I–II</td><td>28.9%</td><td>30.9%</td></tr>
<tr><td>III–VI</td><td>71.1%</td><td>69.1%</td></tr>
<tr><td>Region</td><td></td><td></td></tr>
</table>
</td>
<td>Retinoids 25-50 mg/day (year of use: at least 26 weeks of treatment

year of no use: < 26 weeks of treatment</td>
<td>≥1 year (mean >4 years)

Interviewed annually and examined periodically regardless of continued use of PUVA

This includes data to the end of 19th cycle of follow-up interviews (but only at each of the 1 interviews since 1985 was use of oral retinoids – isotretinoin, etretinate or acitretin –</td>
<td>Incidence of BCC and SCC (including SCC in situ and keratacanthoma)

Tumour counting
Categorised according to date of diagnosis (year of use or no use)

All tumours counted</td>
<td>NIH and Fund for Scientific Research</td>
</tr>
</table>

	Attrition bias: unclear **Outcomes adequately measured:** Yes (histological examination) **Appropriate statistical analysis:** yes		North	60%	56.8%		recorded; 95% aromatic retinoids)	
			Middle	21.5%	17.5%			
			South	18.5%	25.7%			
			No. of PUVA treatments					
			<200	44.4%	66%			
			200–499	41.5%	31.1%			
			>499	14.1%	3.4%			
			Methotrexate exposure					
			High (+3 y)	39.3%	17.4%			
			Tar and/or UVB exposure					
			High (+45 mo or +300)	29.6%	29.9%			
			X-ray therapy prior to entering study					
			Yes	31.1%	20.9%			
			History of SCC before 1985	14.1%	6.9%			

			Retinoid users had higher PUVA exposure and MTX use and more had a history of SCC between enrolment and 1985				

Effect Size

Outcomes

<u>TUMOUR RISK</u>

SCC

- Incidence MD for years of use vs no use = 106 SCCs/1000 person-years (95%CI 173, 22)

BCC

- Incidence MD for years of use vs no use = 28 BCCs/1000 person-years (95%CI 79, -22)

Multivariate analysis (adjusted for retinoid use, age, sex, PUVA dose, radiograph, MTX, tar and UVB exposure and history of SCC before retinoid use)

	SCC		**BCC**	
	IRR	**95% CI**	**IRR**	**95% CI**
Retinoid use	**0.79**	**0.65-0.95**	**0.94**	**0.67-1.32**
Age (y)				

< 45	1		1	
45–64	1.03	0.81-1.31	1.25	0.68-2.31
>64	0.69	0.51-0.93	6.25	3.58-10.92
Men, compared with women	1.42	1.16-1.74	3.75	2.31-6.07
High tar (45+mo) and/or UVB exposure (300+treatments)	2.42	2.00-2.93	3.34	2.32-4.79
X-ray therapy prior to entering study compared with none	3.17	2.06-4.89	8.42	4.51-15.73
No. of PUVA treatments				
< 200	1		1	
200–499	3.36	2.34-4.85	1.17	0.78-1.78
>499	7.26	4.91-10.75	2.65	1.62-4.36
History of SCC >3 y before first retinoid use	4.51	3.61-5.64		
History of BCC >3 y before first retinoid use			3.44	2.28-5.21

Author's conclusion

- In patients with psoriasis treated with PUVA, systemic retinoid use reduced SCC risk but did not significantly alter basal cell carcinoma incidence.
- Level of exposure to PUVA and history of SCC were the strongest predictors of SCC risk

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>J. L. Lim and R. S. Stern. High levels of ultraviolet B exposure increase the risk of non-melanoma skin cancer in psoralen and ultraviolet A-treated patients. J.Invest.Dermatol. 124 (3):505-513, 2005.

Ref ID: LIM2005</td>
<td>Observational:
Prospective cohort study

1975-2003

Representative population sample: unclear (recruited from 16 university centres) – 94% of those eligible enrolled in the follow-up study

Prognostic factor adequately measured: yes

Confounders adjusted for: yes – Univariate analyses adjusted for age and year only. Multivariate analyses: level of PUVA exposure, age, year since enrolment, gender, skin type, geographic residence, year, and use</td>
<td>N: 1380 (442 exposed to high UVB)</td>
<td>Inclusion criteria: PUVA treated

Exclusion criteria: Not stated

<table>
<tr><th>Parameter</th><th>All (n=1380)</th></tr>
<tr><td>Mean age – years</td><td>44</td></tr>
<tr><td>Male (%)</td><td>65%</td></tr>
<tr><td>Mean BSA (%)</td><td>33</td></tr>
<tr><td colspan="2">Psoriasis subtypes</td></tr>
<tr><td>Plaque</td><td>84%</td></tr>
<tr><td>Guttate</td><td>12%</td></tr>
<tr><td>Erythrodermic</td><td>4%</td></tr>
<tr><td colspan="2">Skin type</td></tr>
<tr><td>I</td><td>5.4%</td></tr>
<tr><td>II</td><td>22.1%</td></tr>
</table>
</td>
<td>Oral 8-MOP

PUVA

UVB (mostly BBUVB)

Note: UVB treatments outnumber PUVA by about 2:1</td>
<td>28 years (>15 years for UVB)

Interviewed annually and examined periodically regardless of continued use of PUVA

This includes data to the end of 21st cycle of follow-up interviews</td>
<td>Incidence of BCC and invasive SCC (excluding SCC in situ and keratacanthoma)

Tumour counting

To assess the risk of UVB, two primary endpoints used:
(1) development of at least one SCC or BCC in a given year for a given patient (i.e., incident tumours)

(2) total number of SCC or BCC in a given year for a given patient (i.e., total tumours).</td>
<td>NIH</td>
</tr>
</table>

	of methotrexate, tar, ciclosporin, and retinoids. **Attrition bias:** 609/1380 remained (521 died – consistent with number expected – and 250 lost to follow-up or withdrawn) **Outcomes adequately measured:** Yes (histological examination) **Appropriate statistical analysis:** yes RR/IRR = incidence rate among exposed divided by the incidence rate among non-exposed Attributable risk = difference between observed incidence at the highest level of exposure compared		<table><tr><td>III</td><td>56.3%</td></tr><tr><td>IV</td><td>12.7%</td></tr><tr><td>V</td><td>1.4%</td></tr><tr><td>VI</td><td>2.0%</td></tr><tr><td colspan="2">**Prior therapy**</td></tr><tr><td>Topical steroids</td><td>86%</td></tr><tr><td>Coal tar</td><td>84%</td></tr><tr><td>UV</td><td>61%</td></tr><tr><td>MTX</td><td>45%</td></tr><tr><td>Goekerman</td><td>38%</td></tr><tr><td>x-ray</td><td>18%</td></tr><tr><td>Grenz ray</td><td>12%</td></tr></table> Most patients had severe psoriasis				

	with the lowest level, and gives an estimate of the absolute effect of the exposure.						

Dose classifications

- **PUVA:**

  1. <100 treatments
  2. 100-199
  3. 200-299
  4. 300-399
  5. 400-499
  6. ≥500 treatments

- **UVB**:

  High: ≥300 treatments

  Low <300 treatments

Effect Size

Outcomes

TUMOUR RISK

SCC

- 2528 SCCs in 329 patients

BCC

- 1566 SCCs in 305 patients

Variable	Person years (%)	Number of tumours (%)	Tumour incidence per 100,000 person years	Number of incident tumours (%)	Tumour incidence per 100,000 person years, if only including incident tumours
Squamous cell carcinoma (SCC)					
UVB					
Low (<300)	20,921 (74.9)	1538 (60.8)	7351	696 (63.0)	3327
High (≥300)	7007 (25.1)	990 (39.2)	14,129	408 (37.0)	5823
PUVA					
Low (<100)	11,922 (42.7)	197 (7.8)	1652	118 (10.7)	990
Not low (≥100)	16,006 (57.3)	2331 (92.2)	14,563	986 (89.3)	6160[b]
Basal cell carcinoma (BCC)					

UVB					
Low (<300)	20,921 (74.9)	880 (56.2)	4206	511 (61.8)	2443
High (≥300)	7007 (25.1)	686 (43.8)	9790	316 (38.2)	4510
PUVA					
Low (<100)	11,922 (42.7)	256 (16.3)	2147	148 (17.9)	1241
Not low (≥100)	16,006 (57.3)	1310 (83.7)	8184	679 (82.1)	4242

Univariate and multivariate analysis of potential risk factors associated with the development of at least one SCC (in a given year) for the entire cohort[a]

	Univariate model[b]			**Multivariate model[c]**		
	IRR	**95% CI**	**p-value for trend**	**IRR**	**95% CI**	**p-value for trend[d]**
No. of lifetime UVB treatments			<0.001			<0.001
<300[e]	1			1		

≥300	1.42	1.08–1.86		1.37	1.03–1.83	
No. of lifetime PUVA treatments			<0.001			<0.001
<100[e]	1			1		
100–199	2.34	1.48–3.70		2.36	1.51–3.68	
200–299	4.15	2.59–6.66		4.14	2.64–6.50	
300–399	5.93	3.59–9.79		5.54	3.38–9.09	
400–499	10.25	6.26–16.78		11.05	6.88–17.76	
≥500	10.47	6.28–17.45		10.81	6.76–17.29	
Gender			0.007			0.005
Women[e]	1			1		
Men	1.57	1.13–2.19		1.62	1.19–2.20	
Skin type			0.010			<0.001
III–IV[e]	1			1		
I–II	1.46	1.09–1.95		1.76	1.33–2.31	
High methotrexate exposure (≥36 mo) compared with low	1.95	1.51–2.51	<0.001	1.66	1.32–2.08	<0.001
High tar exposure (≥45 mo) compared with low	1.21	0.89–1.65	0.216	1.02	0.75–1.39	0.926

High ciclosporin exposure (≥3 mo in a given year until 5 y after last use, compared with low exposure)	2.08	1.17–3.69	0.013	1.43	0.88–2.31	0.048
Year with high retinoid exposure (≥26 wk in a given year, compared with low exposure)	1.20	0.77–1.87	0.427	0.88	0.57–1.35	0.725

[a] Estimates of the incident rate ratios were obtained from univariate and multivariate negative binomial regression models.

[b] Univariate analysis adjusted for age and year.

[c] In addition to the variables listed, the multivariate model adjusted for age and year.

[d] The analysis for p for trend considered age, year, UVB, PUVA, and residence as continuous variables and gender, skin type, methotrexate, tar, ciclosporin, and retinoid use as categorical variables.

[e] This group served as the reference group.

Univariate and multivariate analysis of potential risk factors associated with the development of at least one BCC (in a given year) for the entire cohort

	Univariate model[b]			**Multivariate model[c]**		
	IRR	**95% CI**	**p-value for trend**	**IRR**	**95% CI**	**p-value for trend[d]**
No. of lifetime UVB treatments			0.024			0.025
<300[e]	1			1		
≥300	1.53	1.15–2.03		1.45	1.07–1.96	
No. of lifetime PUVA treatments			<0.001			<0.001
<100[e]	1			1		

100–199	1.87	1.23–2.82		1.80	1.21–2.70	
200–299	2.07	1.33–3.24		2.00	1.32–3.03	
300–399	3.07	1.90–4.95		2.81	1.75–4.51	
400–499	3.00	1.73–5.20		2.93	1.73–4.98	
≥500	3.73	2.21–6.30		3.65	2.21–6.03	
Gender			<0.001			<0.001
Women[e]	1			1		
Men	1.80	1.35–2.40		1.80	1.35–2.40	
Skin type			0.993			0.485
III–IV[e]	1			1		
I–II	1.00	0.74–1.36		1.15	0.85–1.55	
High methotrexate exposure (≥36 mo) compared with low	1.39	1.03–1.89	0.031	1.24	0.92–1.67	0.095
High tar exposure (≥45 mo) compared with low	1.45	1.09–1.95	0.012	1.28	0.93–1.76	0.075
High ciclosporin exposure (≥3 mo in a given year until 5 y after last use, compared with low exposure)	1.88	0.87–4.04	0.108	1.38	0.64–2.99	0.284
Year with high retinoid exposure (≥26 wk in a given year, compared with low	1.45	0.89–2.36	0.131	1.28	0.80–2.04	0.261

exposure)						

[a] Estimates of the incident rate ratios were obtained from univariate and multivariate negative binomial regression models.

[b] Univariate analysis adjusted for age and year.

[c] In addition to the variables listed, the multivariate model adjusted for age and year.

[d] The analysis for p for trend considered age, year, UVB, PUVA, and residence as continuous variables and gender, skin type, methotrexate, tar, ciclosporin, and retinoid use as categorical variables.

[e] This group served as the reference group.

Note: Based on the IRR estimated in the multivariate analysis, among those patients who were exposed to high levels of UVB therapy, about 27% of SCC and 31% of BCC were attributable to receiving high levels of UVB (300 treatments).

Author's conclusion

- High UVB exposure levels (300 treatments) confer a modest but significant increase in NMSC risk in adults.
- The modest risks associated with UVB therapy must be weighed in the context of a patient's underlying skin cancer risk and against the benefits of therapy.
- Overall, UVB therapy is substantially less carcinogenic than PUVA therapy and so should continue to be considered a primary treatment option for patients with moderate-to-severe psoriasis

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>C. F. Paul, V. C. Ho, C. McGeown, E. Christophers, B. Schmidtmann, J. C. Guillaume, V. Lamarque, and L. Dubertret. Risk of malignancies in psoriasis patients treated with cyclosporine: a 5 y cohort study. J.Invest. Dermatol. 120 (2):211-216, 2003.

Ref ID:</td>
<td>Observational: Prospective cohort study

Representative population sample: unclear (recruited from 277 centres in 11 countries)

Prognostic factor adequately measured: yes

Confounders adjusted for: yes

Attrition bias: Median duration of follow-up = 4.5 y (Range: 0-8.6 y); 48% attended final 60 month visit</td>
<td>N: 1252</td>
<td>Inclusion criteria: severe psoriasis; ciclosporin treated for at least 1 month

Exclusion criteria: Not stated

<table>
<tr><th></th><th>Total (n=1252)</th><th>≤2 y of CSA (n=781)</th><th>>2 y of CSA (n=471)</th></tr>
<tr><td>Age (mean ±SD)</td><td>43.3 ± 14.0</td><td>44.0 ± 14.3</td><td>42.3 ± 13.4</td></tr>
<tr><td>Sex (% M/F)</td><td>68/32</td><td>70/30</td><td>65/35</td></tr>
<tr><td>Weight (kg)</td><td>76.9 ± 16.6</td><td>76.7 ± 16.4</td><td>77.3 ± 16.9</td></tr>
<tr><td>Duration of psoriasis (y)</td><td>16.2 ± 11.2</td><td>15.8 ± 11.5</td><td>16.8 ± 10.7</td></tr>
<tr><td>Age at onset</td><td>27.1 ± 14.3</td><td>28.2 ± 14.6</td><td>25.3 ± 13.6</td></tr>
</table>
</td>
<td>Ciclosporin

Mean starting dose 3 mg/kg/d,

Mean daily dose decreased over time from 3.1 mg/kg/d at month 6 to 2.7 mg/kg/d at the end of month 54.

Approximately 40% of all patients received CSA intermittently

The remaining 60% received</td>
<td>5 years (assessed every 6 months by a dermatologist)

Mean duration of CSA therapy was 1.9 y</td>
<td>Incidence of skin cancers (SCC, BCC and melanoma)

Tumour counting

Unclear</td>
<td>Novartis Pharma</td>
</tr>
</table>

<table>
<tr>
<td>PAUL2003</td>
<td>Outcomes adequately measured: Yes

Appropriate statistical analysis: yes

RR/IRR = incidence rate among exposed divided by the incidence rate among non-exposed calculated separately for each year of exposure

All models included three explanatory variables: exposure to ciclosporine, previous history of malignancy, and the respective exposure to previous treatments for psoriasis (PUVA, oral retinoids, methotrexate, other immuno-suppressants, phototherapy, tar)</td>
<td></td>
<td>
<table>
<tr><td>of psoriasis (y)</td><td></td><td></td><td></td></tr>
<tr><td colspan="4">Previous systemic therapy of psoriasis (% of patients receiving therapy)</td></tr>
<tr><td>PUVA</td><td>47</td><td>45</td><td>49</td></tr>
<tr><td>Retinoids</td><td>45</td><td>41</td><td>51</td></tr>
<tr><td>MTX</td><td>28</td><td>25</td><td>33</td></tr>
<tr><td>UVB/UVA</td><td>19</td><td>21</td><td>17</td></tr>
<tr><td>Tar</td><td>8</td><td>9</td><td>8</td></tr>
<tr><td>Ciclosporine</td><td>8</td><td>8</td><td>8</td></tr>
<tr><td>Immunosup. (excluding CSA).</td><td>6</td><td>4</td><td>8</td></tr>
<tr><td>Fumaric acid</td><td>2</td><td>2</td><td>1</td></tr>
<tr><td>Arsenic</td><td>< 1</td><td>< 1</td><td>< 1</td></tr>
</table>
</td>
<td>it continuously.

Concomitant therapies during follow-up: 34% of patients received other systemic therapy for psoriasis

MTX and retinoids by 20% each; PUVA by 13% and phototherapy by 10%</td>
<td></td>
<td></td>
<td></td>
</tr>
</table>

Effect Size

Outcomes

TUMOUR INCIDENCE

Cancer	Patients		Person-Years	Incidence rate	95% CI
	N	(%)			
All skin malignancies	23	1.8	4377	5.3	3.3–7.9
BCC	5	0.4	4426	1.1	0.4–2.6
SCC	15	1.2	4401	3.4	1.9–5.6
Melanoma	2	0.2	4431	0.5	0.1–1.6

Note: all patients with BCC and/or SCC had previously received PUVA therapy

Observed vs expected incidence

- **Expected based on specific incidence rate for age-, sex- and geographic location-matched rate**

	Overall			Low exposure ≤2 y of CSA (n=781)			High exposure >2 y of CSA (n=471)		
	person-years	**SIR**	**95% CI**	**Person years**	**SIR**	**95% CI**	**Person years**	**SIR**	**95% CI**
Any skin malignancy	4330	6.1	3.8–9.1	3300	4.8	2.6–8.1	1029	10.1	4.6–19.2
BCC	4379	1.8	0.6–4.1	3338	0.9	0.1–3.3	1041	4.6	0.9–13.3
SCC	4354	24.6	13.8–40.7	3317	19.2	8.8–36.5	1037	42.7	15.7–93.2
Malignant melanoma	4384	4.7	0.6–17.0	3336	6.2	0.8–22.5	1048	0.0	

Multivariate analysis of potential risk factors associated with the development of skin cancer (SIR as outcome variable and previous history of malignancy, exposure to ciclosporine, and exposure to respective previous therapy as explanatory variables; adjusted for all other factors in the model)

	RR	**95% CI**
All skin malignancies		
Exposure to ciclosporine (high/low)	2.7	1.1–6.4
Exposure to PUVA (some/none)	5.8	2.0–25.0

Exposure to retinoids (some/none)	4.5	1.5–19.5
Exposure to methotrexate (some/none)	2.1	0.9–5.3
Exposure to immunosuppressant (some/none)	2.9	1.2–6.8
Exposure to phototherapy (some/none)	0.7	0.2–1.8
Exposure to tar (some/none)	2.4	0.7–6.6
All nonmelanoma skin malignancies		
Exposure to ciclosporine (high/low)	3.3	1.3–8.4
Exposure to PUVA (some/none)	7.3	1.3–134.5
Exposure to retinoids (some/none)	4.6	0.9–86.1
Exposure to methotrexate (some/none)	2.7	1.1–7.3
Exposure to immunosuppressant (some/none)	3.5	1.4–8.4
Exposure to phototherapy (some/none)	0.5	0.1–1.5
Exposure to tar (some/none)	1.9	0.4–5.7
All BCC		
Exposure to ciclosporine (high/low)	4.9	0.8–36.9
Exposure to PUVA (some/none)	Not estimable	
Exposure to retinoids (some/none)	Not estimable	

Exposure to methotrexate (some/none)	2.5	0.4–18.7
Exposure to immunosuppressant (some/none)	3.3	0.4–19.6
Exposure to phototherapy (some/none)	2.3	0.1–24.0
Exposure to tar (some/none)	6.5	0.9–39.4
All SCC		
Exposure to ciclosporine (high/low)	3.3	1.0–10.6[b]
Exposure to PUVA (some/none)	4.4	0.7–84.7
Exposure to retinoids (some/none)	2.6	0.4–50.7
Exposure to methotrexate (some/none)	2.5	0.8–8.6
Exposure to immunosuppressant (some/none)	4.0	1.3–11.5
Exposure to phototherapy (some/none)	0.6	0.1–2.7
Exposure to tar (some/none)	1.5	0.1–9.3

Author's conclusion

- The risk of skin cancer associated with ciclosporine treatment in psoriasis appears to be significantly increased with more than 2 y of cumulative treatment as compared with less than 2 y.
- The contributing role of previous exposure to PUVA, methotrexate, and other immunosuppressants was demonstrated.

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>R. S. Stern, K. T. Nichols, and L. H. Vakeva. Malignant melanoma in patients treated for psoriasis with methoxsalen (psoralen) and ultraviolet a radiation (PUVA). New Engl.J.Med. 336 (15):1041-1045, 1997.

Ref ID: STERN1997

AND</td>
<td>Observational: Prospective cohort study

1975-1996

Representative population sample: unclear (recruited from 16 university centres) – 94% of those eligible enrolled in the follow-up study

Prognostic factor adequately measured: yes

Confounders adjusted for: STERN1997: inadequate (not adjusted for other treatments)

STERN2001: yes (age, sex, year of follow-up and ‘all other risk</td>
<td>N: 1380</td>
<td>Inclusion criteria: PUVA treated

Exclusion criteria: Not stated

<table>
<tr><th>Parameter</th><th>All (n=1380)</th></tr>
<tr><td>Mean age – years</td><td>44</td></tr>
<tr><td>Male (%)</td><td>65%</td></tr>
<tr><td>Mean BSA (%)</td><td>33</td></tr>
<tr><td colspan="2">Psoriasis subtypes</td></tr>
<tr><td>Plaque</td><td>84%</td></tr>
<tr><td>Guttate</td><td>12%</td></tr>
<tr><td>Erythrodermic</td><td>4%</td></tr>
<tr><td colspan="2">Skin type</td></tr>
<tr><td>I</td><td>5.4%</td></tr>
<tr><td>II</td><td>22.1%</td></tr>
</table>
</td>
<td>Oral 8-MOP PUVA

0.4-0.6 mg/kg psoralen orally, followed in 1.5-2.0 h by UVA (standing in an UV irradiation unit; fluorescent bulbs with emissions in the range of 320-400 nm).

Initial UVA dose 1.5-5 J/cm^2 depending on photosensitivity. During the clearing phase, patients undergo two or three light treatments per week and UVA dose is gradually increased according to the degree of erythema or pigmentation.

Average max UVA dose = 8-15 J/cm^2. With disease improvement</td>
<td>Mean 20.2 years (+2.2 years for STERN2001)

Interviewed annually and examined periodically regardless of continued use of PUVA</td>
<td>Incidence of malignant/invasive melanoma and melanoma in situ

Tumour counting

Population counts: Federal survey rates are based on annual incidence so also computed observed rates by counting only the first tumour of a given type observed that year as an incidence, but continuing individuals in the risk</td>
<td>NIH</td>
</tr>
</table>

<table>
<tr>
<td>R. S. Stern and Up Study PUVA Follow. The risk of melanoma in association with long-term exposure to PUVA. J.Am.Acad.Dermatol. 44 (5):755-761, 2001.

Ref ID: STERN2001</td>
<td>factors')

Attrition bias: >90% interviewed in most years

To 1996: 398 died; 160 lost to follow-up or withdrawn

Outcomes adequately measured: Yes up to 1989 (but after 1991 no study-sponsored dermatological assessments and diagnosis based on patient report and medical records)

Note: study- sponsored dermatological assessments took place between 1997 and 2001

Appropriate statistical analysis: yes</td>
<td></td>
<td>
<table>
<tr><td>III</td><td>56.3%</td></tr>
<tr><td>IV</td><td>12.7%</td></tr>
<tr><td>V</td><td>1.4%</td></tr>
<tr><td>VI</td><td>2.0%</td></tr>
<tr><td colspan="2">Prior therapy</td></tr>
<tr><td>Topical steroids</td><td>86%</td></tr>
<tr><td>Coal tar</td><td>84%</td></tr>
<tr><td>UV</td><td>61%</td></tr>
<tr><td>MTX</td><td>45%</td></tr>
<tr><td>Goekerman</td><td>38%</td></tr>
<tr><td>x-ray</td><td>18%</td></tr>
<tr><td>Grenz ray</td><td>12%</td></tr>
</table>
Most patients had severe psoriasis</td>
<td>therapy slowly tapered off.

If disease flared, patients treated again with PUVA or other therapies for psoriasis as determined by their physician.</td>
<td></td>
<td>set after tumour occurrence</td>
<td></td>
</tr>
<tr><td colspan="7"></td></tr>
</table>

Effect Size

Outcomes

Dose classifications (based on historical data collection)

- PUVA high: ≥200 or 250 PUVA treatments
- PUVA low: <200 or 250 PUVA treatments

STERN1997 data

Observed vs expected incidence

- **Expected based on specific incidence rate for age-, sex- and geographic location-matched rate**

Study period	Number of invasive melanomas		RR (95% CI)
	Observed	Expected	
1975-1990			
<250 treatments	2	2.9	0.7 (0.1-2.5)
≥250 treatments	2	0.6	3.1 (0.4-11.3)
All patients	4	3.5	1.1 (0.3-2.9)
1991-1996			
<250 treatments	3	0.8	3.5 (0.7-10.3)

≥250 treatments	4	0.4	8.9 (2.4-22.8)
All patients	7	1.3	5.4 (2.2-11.1)
1975-1996			
<250 treatments	5	3.7	1.3 (0.4-3.1)
≥250 treatments	6	1.1	5.5 (2.0-12.0)
All patients	**11**	**4.8**	**2.3 (1.1-4.1)**

Adjusted RR of PUVA dose and duration as potential risk factors associated with the development of skin cancer (adjusted for age, sex and increase in melanoma over time in USA, as well as the other factor in the model ie PUVA treatments or time to first tumour)

Variable	**IRR**	**95% CI**
Number of PUVA treatments (≥250 vs <250)	3.1	0.9–10.5
Years since first treatment (≥15 vs <15)	3.8	1.1–13.3

STERN2001 data

Study period	**Number of melanomas**		
	Invasive melanoma	**In situ melanoma**	**All melanoma**

	Observed	Incidence (per 1000 person-years)	Observed	Incidence (per 1000 person-years)	Observed	Incidence (per 1000 person-years)
1975 to 1990	4	0.22	0	0	4	0.22
1991 to 29/2/96	7	1.73	3	0.74	10	2.47
29/2/96 to end	7	3.82	4	2.18	11	6.00
All years	18	0.69	7	0.35	25	1.04

Characteristics of cohort members with and without melanoma

	Melanoma (n=23)	No melanoma (n=1357)	p-value
Age	50±12	44±16	0.13
% male	78	65	0.17
Skin type (%)			
I	13	7	<0.005
II	44	23	<0.005
III	44	54	
IV or higher	0	17	

- Additionally:

- Number of patients with exposure to ionising radiation and high dose MTX was nearly identical in those who did and did not develop melanoma
- Proportion with high dose exposure to UVB and tar was NS lower among melanoma patients (p>0.2)

Adjusted RR of PUVA dose and duration as potential risk factors associated with the development of skin cancer (adjusted for age, sex and increase in melanoma over time in USA)

Study period	**Invasive melanomas**		**In situ**		**All melanoma**	
	IRR	**95% CI**	**IRR**	**95% CI**	**IRR**	**95% CI**
No. of PVUA treatments						
<200 treatments	1		1		1	
≥200 treatments	2.6	1.0-6.6	3.5	0.8-14.7	2.9	1.3-6.4
Period						
1975-1990	1		1		1	
1991-Feb 1996	4.7	1.4-16.1	8.1	0.8-77.6	5.4	1.8-15.7
March 1996-1999	7.4	2.2-25.1	16.8	1.9-150.5	9.3	3.2-26.6

Note: the 70% higher incidence of all melanoma after Feb 1996 did not reach significance (p=0.21)

Incidence of melanoma 6.9-times (95% CI 2.6-18.3) higher from 1991-1998 than from 1975-1990

Adjusted RR of PUVA dose and duration as potential risk factors associated with the development of skin cancer (adjusted for age, sex and increase in melanoma over time in USA, as well as significant predictors of risk in the univariate analysis)

Variable	Invasive melanoma		All melanomas	
	IRR	95% CI	IRR	95% CI
Number of PUVA treatments (≥200 vs <200)	1.9	0.7–4.9	2.0	0.9–9.5
Years since first treatment (≥15 vs <15)	5.0	1.6–15.5	5.9	2.2–15.9

Author's conclusion

- The increased risk of malignant melanoma that begins 15 years after the first PUVA treatment and is associated with a high level of exposure is a reason for caution in the long-term use of this therapy
- Neither the number of PUVA treatments at which the risk of melanoma begins to increase substantially, nor the relation between an increasing level of exposure and risk can be determined.
- Patients receiving substantial numbers of PUVA treatments should be followed carefully for the development of both melanoma and nonmelanoma skin cancer.

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>K. A. Papp, Y. Poulin, R. Bissonnette, M. Bourcier, D. Toth, L. Rosoph, M. Poulin-Costello, M. Setterfield, and J. Syrotuik. Assessment of the long-term safety and effectiveness of etanercept for the treatment of psoriasis in an adult population. J.Am.Acad.Dermatol. 66 (2):e33-e45, 2012.

Ref ID: PAPP2012A</td>
<td>Observational: Retrospective cohort study of prospectively studied participants

Representative population sample: yes

Prognostic factor adequately measured: yes

Confounders adjusted for: inadequate (matched for age and sex only)

Attrition bias: no (39% lost to follow-up)

Outcomes adequately</td>
<td>N: 506

(307 completed: 39% attrition)</td>
<td>Inclusion criteria: from previous RCTs and open-label extension studies of etanercept Moderate-to-severe psoriasis

Exclusion criteria: any anti-TNF other than etanercept, PUVA, UVA, UVB, systemic psoriasis therapy or corticosteroids within 14 days of first dose. Active guttate or

<table>
<tr><th>Parameter</th><th>All (n=506)</th></tr>
<tr><td>Mean age – years</td><td>46.0±11.7</td></tr>
<tr><td>Male (%)</td><td>67.4%</td></tr>
<tr><td>Mean BSA (%)</td><td>26.3±17.4</td></tr>
<tr><td>Mean DLQI</td><td>11.1±6.5</td></tr>
<tr><td>History of</td><td>71.9%</td></tr>
</table>
</td>
<td>Etanercept

50 or 25 mg once or twice weekly</td>
<td>Up to 4 years</td>
<td>Incidence of BCC and SCC

Tumour counting

Multiple tumours in one patient are counted as multiple tumours</td>
<td>Amgen and Pfizer</td>
</tr>
</table>

	measured: unclear **Appropriate statistical analysis:** not regression		**phototherapy** **Note:** any concomitant therapies necessary to provide adequate supportive care were permitted except PVUA, UVA/UVB, systemic psoriasis therapy and systemic or topical corticosteroids (except for mild facial/genital lesions)				

Effect Size

Observed vs expected incidence

- Expected based on specific incidence rate for age- and sex-matched rate based on 1305.4 years of patient exposure

Outcome	**General population registry**	**Number of NMSCs by completion**		**SIR (95% CI)**
		Observed	**Expected**	
BCC	Southeastern **Arizona** Skin Cancer Registry	8	15.3	0.52 (0.23-1.03)
SCC	Southeastern **Arizona** Skin Cancer Registry	4	3.71	1.08 (0.29-2.76)
	Rochester Epidemiology Project; **Minnesota**	4	1.49	2.68 (0.72-6.87)

Author's conclusion

- The majority of observed malignancies were NMSCs, but no significant difference in incidence was observed compared with the general population based on available registry data

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>P. P. M. van Lumig, R. J. B. Driessen, M. A. M. Berends, J. B. M. Boezeman, P. C. M. Van de Kerkhof, and E. M. G. J. De Jong. Safety of treatment with biologics for psoriasis in daily practice: 5-year data. J.Eur.Acad.Dermatol.Venereol. 26 (3):283-291, 2012.

Ref ID: VANLUMIG2012</td>
<td>Observational:
Prospective cohort study

Enrolled in registry between February 2005 and April 2010

Representative population sample: yes – consecutive sample of those starting biologic therapy

Prognostic factor adequately measured: unclear

Confounders adjusted for: inadequate (matched for gender and 10-year age group)

Attrition bias: unclear</td>
<td>N: 173

(409 patient years)</td>
<td>Inclusion criteria: all those starting biological treatment for psoriasis at a Dermatology Outpatient clinic in The Netherlands

Exclusion criteria: not stated

<table>
<tr><th>Parameter</th><th>All (n=173)</th></tr>
<tr><td>Mean age – years</td><td>50.6±12.1</td></tr>
<tr><td>Male (%)</td><td>63.0%</td></tr>
<tr><td>Duration of psoriasis, years (mean ±SD)</td><td>26.0±12.8</td></tr>
<tr><td>Psoriatic arthritis (%)</td><td>29%</td></tr>
<tr><td>Total exposure to biologics years (mean ±SD)</td><td>2.7 ± 1.6</td></tr>
</table>
</td>
<td>Biologics (etanercept, adalimumab, infliximab, ustekinumab, efalizumab, alefacept and onercept – note alefacept and onercept were only used pre-enrolment to the registry)

Dose and interval changes were according to the opinion of the dermatologist and topical or systemic therapies could be added as required</td>
<td>Registry follow-up: mean 2.3 ± 1.6 years</td>
<td>Incidence of BCC and SCC according to ICD-10

Tumour counting

Multiple tumours in one patient are counted as multiple tumours</td>
<td>Wyeth Pharmaceuticals</td>
</tr>
</table>

	Outcomes adequately measured: yes **Appropriate statistical analysis:** not regression – SMR compared with general incidence rate for Dutch general population from Dutch General Practice Registry (CMR)		Number of different biologics One: 50.9% Two: 30.6% Three: 13.9% Four: 4.0% Five: 0.6%				

Treatment characteristics

Biologic	**N**	**Treatment episode duration (years)**		**Patient-years**	**Mean weekly dose (mg)**
		Mean ±SD	**Median (range)**		
Etanercept	150	2.0±1.5	1.7 (0.01-5.2)	319.8	67.6
Adalimumab	59	0.9±0.5	0.9 (0.02-1.9)	55.4	25.5
Efalizumab	27	0.9±0.9	0.5 (0.08-3.4)	24.8	Per label
Infliximab	7	0.6±0.5	0.5 (0.04-1.6)	5.3	Per label
Ustekinumab	8	0.5±0.4	0.4 (0.14-1.1)	4.0	Per label

Effect Size

Outcome	N malignancies	Treatment	Time to event (months)	Pre-treatment	Relevant medical history
BCC					
Patient 1	5	Etanercept	2, 2, 4, 30, 33	UVB, PUVA, CSA, MTX, azathioprine	-
Patient 2	2	Etanercept	5	UVB, PUVA, MTX	SCC, multiple BCCs
Patient 3	1	Etanercept	3	CSA, PUVA, MTX	-
Patient 4	2	Adalimumab	3	CSA, MTX, UVB, PUVA, etanercept	-
SCC					
Patient 1	3	Etanercept	4	UVB, PUVA, CSA, MTX	-
Patient 2	1	Etanercept	6	UVB, PUVA, MTX	SCC, multiple BCCs
Patient 3	1	Etanercept	17	UVB, PUVA, CSA, MTX, alefacept	-
Patient 4	5	Efalizumab	27	CSA, MTX	-

Observed vs expected incidence

- Expected based on specific incidence rate for age- and sex-matched rate

Outcome	Number of malignancies		SIR (95% CI)
	Observed	Expected	
BCC	10	0.8	12.2 (5.9-22.5)
SCC	10	0.1	81.4 (39.0-149.8)

H.10.2 Retrospective cohort

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>R. M. Hearn, A. C. Kerr, K. F. Rahim, J. Ferguson, and R. S. Dawe. Incidence of skin cancers in 3867 patients treated with narrow-band ultraviolet B phototherapy. Br.J.Dermatol. 159 (4):931-935, 2008. Ref ID: HEARNE2008

I. Man, I. K. Crombie, R. S. Dawe, S. H. Ibbotson, and J. Ferguson. The photocarcinogenic risk of</td>
<td>Observational: Retrospective cohort

Representative population sample: all TL-01 treated patients from departmental database

Prognostic factor adequately measured: data from Tayside phototherapy database with linkage to the Scottish Cancer registry

Confounders adjusted for: age, sex and location (insufficient cases to do regression analysis)</td>
<td>N:3867 (2130 [55%] with psoriasis)</td>
<td>Inclusion criteria: whole body NBUVB

Exclusion criteria: Follow-up <6 months; first treated after 2002

<table>
<tr><th>Characteristic</th><th>All (3867)</th></tr>
<tr><td>Gender (M/F %)</td><td>44/56</td></tr>
<tr><td>Median age at first treatment with NBUVB (range)</td><td>34 years (2.6–93.8)</td></tr>
<tr><td>Median number of NBUVB treatments</td><td>29 (19-53)</td></tr>
<tr><td colspan="2">Skin type</td></tr>
<tr><td>I</td><td>23%</td></tr>
<tr><td>II</td><td>47%</td></tr>
<tr><td>III</td><td>27%</td></tr>
</table>
</td>
<td>TL-01</td>
<td>Median: 5.5 (3.0-9.0) years</td>
<td>Incidence of malignant melanoma, BCC and SCC (at least 6 months after first NBUVB treatment)

Tumour counting

First registered tumour per person</td>
<td>None stated</td>
</tr>
</table>

narrowband UVB (TL-01) phototherapy: early follow-up data. Br.J.Dermatol. 152 (4):755-757, 2005. Ref ID: MAN2005	**Attrition bias:** all included in analysis but missing data for many **Outcomes adequately measured**: Cancer registry and case notes **Appropriate statistical analysis:** yes		IV+ 3% **Other treatments** PUVA 24% Psoriasis + PUVA 707/2130 (33%) BBUVB 4%				

Effect Size

Outcomes

Observed vs expected incidence (compared with age- and sex-matched Tayside population rates)

- Observed in total population (55% psoriasis): 27 first BCC; 7 first SCC; 6 first MM
- 15 BCC vs 7.9 expected among those with psoriasis treated with both NBUVB and PUVA

SIR among psoriasis subgroup

Cancer	Treatments	SIR (95% CI)*	p-value
BCC	TL-01 only	156 (57-339)	NS
	TL-01 + PUVA	190 (106-313)	<0.05
SCC	TL-01 only	0 (0-465)	NS
	TL-01 + PUVA	126 (15-454)	NS

MM	TL-01 only	105 (3-586)	NS
	TL-01 + PUVA	157 (32-460)	NS

*Note: A standardised incidence ratio (SIR) of 100 = no difference between observed and expected

Author's conclusion

- No significant association between NB-UVB treatment and BCC, SCC or melanoma.
- There was a small increase in BCCs amongst those also treated with PUVA.
- The early increase in skin cancers associated with PUVA treatment is not found with NBUVB.
- However, the cohort contained relatively few patients who had a high treatment number and the slow evolution of skin cancers may result in a delayed incidence peak.