Table 2.1. Cohort studies of treatment with methoxsalen plus UV radiation and cutaneous and extracutaneous cancers

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Squamous cell carcinoma of skin								
Forman et al. (1989) USA The PUVA-48 Cooperative Study (multicentre study)	Retrospective cohort study of 551 psoriatic patients of both sexes treated with PUVA since 1975 in seven medical centres; cancer incidence follow-up for an average of 4 years and 9 months (at least to April 1984)	Ever treated with PUVA and cumulative dosage of UV-A measured in joules per cm^2	Squamous cell carcinoma of skin as reported by dermatologists and confirmed histlogically			**SMR**	Age and sex	Reference rates from a national skin cancer survey in 1977–78. Only first squamous cell carcinoma of skin was counted. Increasing SMR by increasing UV-A dosage. Unmeasured proportion of cohort members lost to follow-up.
				PUVA treatment ever	9	[10.8 (5.0–20.6)]		
				Individuals with no previous carcinogenic treatments	6	[9.4 (3.4–20.4)]		
Stern & Laird (1994), USA The PUVA Follow-up Study (multicentre study)	Prospective cohort study of 1 380 predominantly white individuals (892 men, 488 women) first treated for psoriasis with PUVA during 1975–76 at 16 university centres; cancer incidence follow-up to August, 1989 (mean: 13.2 years)	Intensity (level) of exposure to PUVA measured by number of treatments recorded at each of seven follow-up dermatological examinations	Squamous cell carcinoma of skin as reported by patient or study dermatologist and confirmed histologically			**SMR**	Age, sex and location	Reference rates from federal survey of skin carcinoma. Only the first squamous cell carcinoma of skin was counted. Multivariate analysis
				PUVA treatment ever	144	11.9 (10.1–14.0)		
				Intensity of treatment				
				Low	38	5.0 (3.6–6.9)	Self-reported exposure to topical tar, UV-B therapy, methotrexate, and ionizing radiation	
				Medium	29	13.4 (9.3–19.3)		
				High	77	32.8 (26.2–41.0)		
						RR		
				Medium vs low	29 vs 38	2.6 (2.0–3.3)		
				High vs low	77 vs 38	5.9 (4.0–8.7)		

Table 2.1. Cohort studies of treatment with methoxsalen plus UV radiation and cutaneous and extracutaneous cancers

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Stern (1990) USA The PUVA Follow-up Study (multicentre study)	Prospective cohort study of 892 predominantly white men first treated for psoriasis with PUVA during 1975–76 at 16 university centres; cancer incidence follow-up to April, 1989 (mean: 12.3 years)	Intensity (level) of exposure to PUVA measured by number of treatments recorded at each of six follow-up dermatological examinations	Squamous cell carcinoma of penis or scrotum (genital sites) as reported by patient or dermatologist and confirmed histologically			**SMR**	Age	Reference rates from federal survey of skin carcinoma. Only the first squamous cell carcinoma of skin was counted.
				PUVA treatment ever	14	95.7 (44–182)		
				Intensity of treatment				
				Low		17.5 (0.4–97.7)		
				Medium		125.0 (15.1–452)		
				High		285.7 (105–622)		

Table 2.1. Cohort studies of treatment with methoxsalen plus UV radiation and cutaneous and extracutaneous cancers

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Stern et al. (2002) USA The PUVA Follow-Up Study (multicentre study)	Male part of the US cohort as described above; extended follow-up for incidence of male genital cancer through October 1998; shielding of genital organs introduced in May 1989	Intensity (level) of exposure to PUVA measured by number of treatments recorded at each of 18 follow-up interviews and 10 dermatological examinations	Squamous cell carcinoma of penis or scrotum (genital sites) as reported by patient or dermatologist and confirmed histologically			**SMR**	Age	Reference rates from the US SEER. Only the first squamous cell carcinoma of skin was counted.
				PUVA treatment ever	17	81.7 (52–123)		
				Intensity of treatment				
				Low	3	29.4 (6.1–86)		
				Medium	3	68.2 (14–199)		
				High	11	148.6 (74–266)	Age	
				Follow-up after introduction of genital shielding May 1989:				
				Any treatment	6	52.6 (19–115)		
				Intensity of treatment				
				Low	2	44.4 (5.4–88)		
				Medium	1	36.1 (0.9–201)		
				High	3	72.3 (14.9–123)		
				PUVA treatment ever		**RR**		
				Medium vs low	3 vs 3	1.8 (0.7–4.5)		
				High vs low	11 vs 3	8.8 (4.5–17.2)		

Table 2.1. Cohort studies of treatment with methoxsalen plus UV radiation and cutaneous and extracutaneous cancers

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Lindelöf et al. (1991) Sweden The Swedish PUVA-cancer Study (multicentre study)	Retrospective cohort study of 4 799 individuals (2 343 men, 2 456 women) treated for psoriasis or other skin disorders with PUVA during 1974–85 in 11 dermatological centres; cancer incidence follow-up through 1987 (mean: 6.9 years for men, 7.2 for women); 77% of patients were treated with oral 8-methoxypsoralen and UV-A, while the remaining patients were treated with other types of photochemotherapy (mainly trimethoxypsoralen baths and UV-A)	Ever treated with PUVA and cumulative dosage of UV-A measured in joules per cm^2	Squamous cell carcinoma of skin as notified in national cancer registry	<u>Men</u>		**SMR**	Age, sex and calendar period	Reference rates from national cancer registry. All cases of squamous cell carcinomas of skin were counted. Increasing SMR by increasing UV-A dosage. 1.5% of cohort members lost to follow-up. No adjustment for other anti-psoriatic treatment regimens. Update in Lindelöf et al., 1999
				PUVA treatment ever	21	6.3 (3.9–9.6)		
				Dose (J/cm^2)				
				0–99	6	4.2 (1.6–9.2)		
				100–199	2	3.8 (0.5–13.8)		
				200–389	1	1.9 (0.1–10.6)		
				400–1199	4	7.1 (1.9–18.1)		
				≥ 1 200	8	27.2 (11.3–53.6)		
				<u>Women</u>				
				PUVA treatment ever	7	5.7 (2.3–11.7)		
				Dose (J/cm^2)				
				0–99	2	3.7 (0.5–13.3)		
				100–199	1	4.8 (0.1–26.8)		
				200–389	2	10.3 (1.2–37.1)		
				400–1199	1	5.0 (0.1–27.6)		
				≥ 1 200	1	13.2 (0.3–73.3)		

Table 2.1. Cohort studies of treatment with methoxsalen plus UV radiation and cutaneous and extracutaneous cancers

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Lindelöf et al. (1999) Sweden The Swedish PUVA-cancer Study (multicentre study)	Swedish cohort as described above; extended follow-up for cancer incidence through 1994 (mean: 15.9 years for men, 16.2 years for women)	Ever treated with PUVA; subgroups of patients according latency and specific treatment regiment	Squamous cell carcinoma as notified in national cancer registry	<u>Men</u>		**SMR**	Age, sex and calendar period	Reference rates from national cancer registry. All cases of squamous cell carcinoma of skin were counted. Increasing SMR by increasing UV-A dosage. 1.5% of cohort members lost to follow-up. No adjustment for other anti-psoriatic treatment regimens.
				Total cohort (*n* = 2 343)	68	5.6 (4.4–7.1)		
				Subgroups	55	8.1 (6.1–10.6)		
				Followed for ≥ 15 years (*n* = 1 046)	56	8.5 (6.4–11.0)		
				Total-body treatment for psoriasis (*n* = 1 357)				
				<u>Women</u>				
				Total cohort (*n* = 2 456)	17	3.6 (2.1–5.8)		
				Subgroups		6.4 (3.3–11.2)		
				Followed for ≥ 15 years (*n* = 821)	12	5.3 (2.7–9.5)		
				Total treatment for psoriasis (*n* = 1 090)	11			

Table 2.1. Cohort studies of treatment with methoxsalen plus UV radiation and cutaneous and extracutaneous cancers

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Hannuksela-Svahn et al. (2000) Finland (countrywide study)	Register-linked cohort study of 5 687 individuals (3 132 men and 2 555 women) in Finland hospitalized for psoriasis with a nested case-case control study of the relationship between treatment with PUVA and risk of squamous cell carcinoma of skin (30 cases, 137 controls); cancer incidence follow-up in cohort to 1995 (mean: 14 years)	Information of PUVA treatment (8-methoxypsoralen and UV-A) from medical records of cases and controls	Squamous cell carcinoma as notified in national cancer registry	PUVA treatment ever vs never	12	**RR** 6.5 (1.4–31.4)	Age, sex, duration of psoriasis, and each of the other regimens used in the treatment of psoriasis	Four cases and zero controls received more than 200 PUVA treatments
Perkins et al. (1990) Glasgow, Scotland (single centre study)	Retrospective cohort study of 130 men treated with PUVA for an average of 8 years and 2 months	Ever treated with PUVA and cumulative dosage of UVA measured in joules per cm^2	Squamous cell carcinoma of nongenital skin as notified in regional cancer registry	PUVA treatment ever	5	**SMR** 31 (10–72)	Age	Reference rates from regional cancer registry for the period 1983–87. Only first squamous cell carcinoma of skin were counted. Patients exposed to topical tar, only, before the treatment with PUVA. All carcinomas observed in patients receiving more than 400 J/cm^2.

Table 2.1. Cohort studies of treatment with methoxsalen plus UV radiation and cutaneous and extracutaneous cancers

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Bruynzeel et al. (1991) The Nederlands (single centre study)	Retrospective cohort study of 260 individuals (165 men, 95 women) treated for psoriasis with PUVA during 1975–88; cancer incidence follow-up to December 1987 (mean: 8 years and 8 months)	Ever treated with PUVA, and total dosage of UV-A	Squamous cell carcinoma of skin as reported by study dermatologist and confirmed histologically	PUVA treatment ever	4	**SMR** 12 (3–28)	Age and sex	Reference rates from a regional cancer registry. Only first non-melanoma skin cancer was counted. Indication of an increasing SMR by increasing UV-A dosage. 10% of initial cohort of 334 persons were lost to follow-up
Chuang et al. (1992) Wisconsin, USA (single centre study)	Retrospective cohort study of 492 individuals treated for psoriasis with PUVA 1975–89 in one treatment centre; cancer incidence follow-up to 1989 (mean: 5.4 years)	Total dosage of UVA measured in joules per cm^2 of skin	Squamous cell carcinoma of skin reported in patients' files and confirmed histologically	Low dose (n = 389) (≤ 200 J/cm^2)	1	**SMR** [1.0 (0.0–18)]	Age and sex	Reference rates from skin cancer survey in Rochester, Minnesota. 21% of cohort members lost to follow-up. Only first squamous cell carcinoma of skin was counted.
				High dose (n = 103) (≥ 1 000 J/cm^2)	3	[6.0 (1.2–18)]		
Maier et al. (1996) Vienna, Austria (single centre study)	Retrospective cohort study of 496 individuals (273 men, 223 women) in whom PUVA treatment for psoriasis was initiated before 1987; median length of follow-up: 6 years and 8 months (range, 3 months–17 years and 2 months)	Total dosage of UVA measured in joules per cm^2 of skin	Squamous cell carcinoma of skin as reported by patient or study dermatologist	UVA exposure above median exposure level vs UVA exposure below:		**RR**	No adjustment Age, sex, skin type, exposure to arsenic, X-rays, tar, UVB, methotrexate, and retinoids	Only the first squamous cell carcinoma of skin was counted. Response rate at latest follow-up invitation was 49%
				univariate analysis	9	2.47 (P = 0.009)		
				multivariate analysis	9	2.77 (P = 0.056)		

Table 2.1. Cohort studies of treatment with methoxsalen plus UV radiation and cutaneous and extracutaneous cancers

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Basal cell carcinoma of skin								
Forman et al. (1989) USA The PUVA-48 Cooperative Study	Retrospective cohort study of 551 psoriatic patients treated with PUVA since 1975 in seven medical centres; followed-up for cancer incidence for an average of 4 years and 9 months (at least to April 1984)	Ever treated with PUVA and cumulative dosage of UV-A measured in joules per cm^2	Basal cell carcinoma of skin as reported by study dermatologist and confirmed histologically			**SMR**	Age and sex	Reference rates from a national skin cancer survey in 1977–78. Only first basal cell carcinoma of skin was counted. No increasing trend in SMR by increasing UVA dosage. Unmeasured proportion of cohort members lost to follow-up.
				PUVA treatment ever	13	[2.8 (1.5–4.8)]		
				Individuals with no previous carcinogenic treatments	8	[2.2 (0.9–4.3)]		
Stern & Laird (1994), USA The PUVA Follow-up Study	Prospective cohort study of 1 380 predominantly white individuals (892 men, 488 women) first treated for psoriasis with PUVA during 1974–76 at 16 university centres; cancer incidence follow-up to August 1989 (mean: 13.2 years)	Level and intensity of exposure to PUVA measured by number of treatments recorded at each of seven follow-up dermatological examinations	Basal cell carcinoma of skin as reported by patient or study dermatologist and confirmed histologically			**SMR**	Age, sex and location Self-reported exposure to topical tar, UV-B therapy, methotrexate, and ionizing radiation	Reference rates from federal survey of skin carcinoma. Only the first basal cell carcinoma of skin was counted. Multivariate analysis
				PUVA treatment ever	130	2.5 (2.1–3.0)		
				Intensity of treatment				
				Low	66	2.1 (1.6–2.7)		
				Medium	19	1.9 (1.2–3.0)		
				High	45	3.8 (2.8–5.1)		
						RR		
				Medium vs low	29 vs 38	0.9 ($P > 0.1$)		
				High vs low	77 vs 38	1.7 (1.1–2.5)		

Table 2.1. Cohort studies of treatment with methoxsalen plus UV radiation and cutaneous and extracutaneous cancers

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Bruynzeel et al. (1991) the Netherlands Leiden (single centre study)	Retrospective cohort study of 334 individuals (165 men, 95 woman) treated for psoriasis with PUVA during 1975–88; cancer incidence follow-up through December 1987 (mean: 8 years and 8 months)	Ever treated with PUVA, and total dosage of UVA	Basel cell carcinoma of skin as reported by study dermatologist	PUVA treatment ever	24	**SMR** 5 (3–9)	Age and sex	Reference rates from a regional cancer registry. Only first non-melanoma skin cancer was counted. Indication of an increasing SMR by increasing UV-A dosage. 10% of initial cohort of 334 persons were lost to follow-up.
Chuang et al. (1992) USA Wisconsin (single centre study)	Retrospective cohort study of 492 individuals treated for psoriasis with PUVA 1975–89 in one treatment centre; cancer incidence follow-up through 1989 (mean: 5.4 years)	Total dosage of UVA measured in joules/cm^2 skin	Basal cell carcinoma of skin reported in patients' files	Low dose (n = 389) (≤ 200 J/cm^2)	4	**SMR** [1.1 (0.3–2.7)]	Age and sex	Reference rates from skin cancer survey in Rochester, Minnesota. 21% of cohort members lost to follow-up. Only first basal cell carcinoma of skin was counted.
				High dose (n = 103) (≥ 1 000 J/cm^2)	1	[0.5 (0.0–2.8)]		

Table 2.1. Cohort studies of treatment with methoxsalen plus UV radiation and cutaneous and extracutaneous cancers

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Malignant melanoma of skin								
Lindelöf et al. (1999) Sweden The Swedish PUVA-cancer Study	Retrospective cohort study of 4 799 individuals (2 343 men, 2 456 women) treated for psoriasis or other skin disorders with PUVA during 1974–85 in 11 dermatological centres; extended cancer incidence follow-up through 1994 (mean: 15.9 years for men, 16.2 for women); 77% of patients were treated with oral 8-methoxypsoralen and UV-A, while the remaining patients were treated with other types of photochemotherapy (mainly trimethoxypsoralen and UV-A)	Ever treated with PUVA	Malignant melanoma as notified in national cancer registry	Men		**SMR**	Age, sex and calendar period	Reference rates from national cancer registry. 1.5% of cohort members lost to follow-up. No adjustment for other anti-psoriatic treatment regimens.
				Total cohort (*n* = 2 343)	8	1.1 (0.5–2.2)		
				Subgroups	4	1.0 (0.3–2.6)		
				Followed for ≥ 15 years (*n* = 1 046)	7	1.7 (0.7–3.4)		
				Total-body treatment for psoriasis (*n* = 1 357)				
				Women				
				Total cohort (*n* = 2 456)	7	0.8 (0.5–2.2)		
				Subgroups				
				Followed for ≥ 15 years (*n* = 821)	2	0.8 (0.1–2.8)		
				Total treatment for psoriasis (*n* = 1 090)	4	1.4 (0.4–3.6)		

Table 2.1. Cohort studies of treatment with methoxsalen plus UV radiation and cutaneous and extracutaneous cancers

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Stern (2001), USA The PUVA Follow-up Study	Prospective cohort study of 1 380 predominantly white individuals (892 men, 488 women) first treated for psoriasis with PUVA during 1974–76 at 16 university centres; cancer incidence follow-up to 1999 (mean: 22.4 years)	Total number of PUVA treatments	Malignant melanoma of skin as reported by patient or study dermatologist and confirmed histologically			**IRR**	Age, sex and calendar period	Reference rates from the US SEER Program 1992–1996. Multivariate analysis.
				Number of treatments				
				≥ 200 vs < 200	18	2.6 (1.0–6.6)	In addition prior exposure to topical tar, UVB therapy, methotrexate, and ionizing radiation	All cases of malignant melanoma included (one patient had three melanomas; an additional case of ocular melanoma in study group.
						RR		
				Number of treatments				
				≥ 200 vs < 200	18	1.9 (0.7–4.9)		
				Yrs since 1st treatment ≥ 15 vs < 15	18	5.0 (1.6–15.5)		

Table 2.1. Cohort studies of treatment with methoxsalen plus UV radiation and cutaneous and extracutaneous cancers

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Other cancer sites								
Lindelöf et al. (1999) Sweden The Swedish PUVA-cancer Study	Retrospective cohort study of 4 799 individuals (2 343 men, 2 456 women) treated for psoriasis or other skin disorders with PUVA during 1974–85 in 11 dermatological centres; extended cancer incidence follow-up through 1994 (mean: 15.9 years for men, 16.2 for women); 77% of patients were treated with oral 8-methoxypsoralen and UV-A, while the remaining patients were treated with other types of photochemotherapy (mainly trimethoxypsoralen and UV-A)	Ever treated with PUVA	Noncutaneous cancer sites as notified in national cancer registry	Men (*n* = 2 343)		**SMR**	Age, sex and calendar period	Reference rates from national cancer registry. No adjustment for other anti-psoriatic treatment regimens.
				All noncutaneous sites	229	[1.05 (0.9–1.2)]		
				Lung and pleura	42	1.8 (1.3–2.4)		
				Kidney	7	0.8 (0.3–1.6)		
				Women (*n* = 2 456)				
				All noncutaneous sites	215	[1.26 (1.1–1.5)]		
				Lung and pleura	20	2.5 (1.5–3.8)		
				Kidney	11	2.3 (1.2–4.2)		

SMR, Standard Morbidity Ratio; **RR**, Relative Risk