

Skin Cancer Risk of Narrow-Band UV-B (TL-01) Phototherapy: A Multi-Center Registry Study with 4,815 Patients

Petra ÅKERLA^{1,2}, Eero PUKKALA^{3,4}, Mika HELMINEN^{3,5}, Niina KORHONEN^{1,2} and Toni KARPPINEN²

¹Department of Dermatology, Tampere University Hospital, Tampere, ²Faculty of Medicine and Health Technology, Tampere University, Tampere, ³Health Sciences Unit, Faculty of Social Sciences, Tampere University, Tampere, ⁴Finnish Cancer Registry, Institute for Statistical and Epidemiological Cancer Research, Helsinki, and ⁵Tays Research Services, Tampere University Hospital, Tampere, Finland

Narrow-band TL-01 ultraviolet B phototherapy (TL-01) is an effective and widely used treatment for many skin diseases. The purpose of the investigation was to assess the risk of skin cancers in patients treated with TL-01 phototherapy who have not received any other phototherapy modalities. This cohort study included 4,815 TL-01 treated patients in Finland with psoriasis or atopic dermatitis. Clinical information was collected from the hospital records and linked with Finnish Cancer Registry data. The follow-up started from the first TL-01 treatment and the mean follow-up time was 8.4 years. Standardized incidence ratios were calculated for basal cell carcinoma, cutaneous melanoma, and squamous cell carcinoma. The standardized incidence ratio for basal cell carcinoma was 2.5 (95% confidence interval 1.8–3.5), for cutaneous melanoma 4.0 (95% confidence interval 2.1–6.8) and for squamous cell carcinoma 3.7 (95% confidence interval 1.7–7.0). For basal cell carcinoma and squamous cell carcinoma, the standardized incidence ratios remained similar during the whole follow-up time while the standardized incidence ratio for cutaneous melanoma was markedly higher during the first 5 years of follow-up. In conclusion, an increased incidence of skin cancers was observed among TL-01 treated patients. It should be confirmed in the future whether the skin cancer risk of TL-01 phototherapy will remain high in a longer follow-up.

Key words: basal cell carcinoma; cutaneous squamous cell carcinoma; cutaneous melanoma; narrow-band UVB radiation; skin cancer risk; TL-01 phototherapy.

Submitted Jan 21, 2024. Accepted after review Mar 19, 2024

Published April 17, 2024. DOI: 10.2340/actadv.v104.39927

Acta Derm Venereol 2024; 104: adv39927.

Corr: Petra Åkerla, Department of Dermatology, Tampere University Hospital and Faculty of Medicine and Health Technology, Tampere University, Elämäntie 2, FI-33520 Tampere, Finland. E-mail: petra.akerla@tuni.fi

Phototherapy has been used for decades to treat various skin conditions. In the early 1980s Parrish and Jaenicke showed that the wavelengths around 311 nm had the best therapeutic effect when treating psoriasis and caused less erythema than previously used broadband ultraviolet B (UVB) treatment (1). It took several years until a commercial lamp (Philips ultraviolet B narrow-band TL 100W/01 lamp) at this wavelength was available

SIGNIFICANCE

Phototherapy has been used for decades to treat various skin conditions. On the other hand, ultraviolet radiation is known to be carcinogenic to humans. Nowadays, narrow-band TL-01 ultraviolet B phototherapy is the major phototherapy modality for many skin diseases but the long-term carcinogenic risk of TL-01 phototherapy has still not been fully established. Our aim was to assess the risk of skin cancers in patients treated with TL-01 but not with other phototherapy modalities. An increased incidence of skin cancers was observed among TL-01 treated patients. The results need to be confirmed in future studies.

as narrowband TL-01 ultraviolet B phototherapy (TL-01 phototherapy) (2). Nowadays, over 30 years after development of TL-01 phototherapy, it is still the major phototherapy for psoriasis but also used for many other skin diseases due to its ease and effectiveness.

According to the International Agency for Research on Cancer (IARC) classification, UVB radiation is carcinogenic to humans (Group 1 carcinogen) (3). In animals TL-01 radiation has been shown to be more carcinogenic than broadband UVB (4–6). Psoralen-ultraviolet A photochemotherapy (PUVA) is associated with an increased risk of skin cancers (especially squamous cell carcinoma, SCC) in a dose-dependent way (7–9) and this is one of the reasons why TL-01 phototherapy moved towards replacing PUVA for the treatment of skin diseases. An increased risk of cutaneous melanoma (CM) has also been reported among PUVA-treated patients, especially after high exposure to PUVA (10, 11). The increased risk had a long latency: it showed up 15 years after the first exposure to PUVA treatment.

So far, the long-term carcinogenic risk of TL-01 phototherapy has not been fully established. Previous studies have not found a firm association between TL-01 phototherapy and skin cancer risk. No evidence of an increased skin cancer risk was found among 126 German, 484 Irish, 1,908 or 3,867 Scottish patients treated with TL-01 phototherapy (12–15). However, it takes decades to develop skin cancer and the follow-up times in these studies were quite short. It is possible that an increased risk of skin cancer due to TL-01 phototherapy will be noticed only in studies with longer follow-up and larger sample size (16). Our study has those characteristics.

The aim of this study was to gain more knowledge regarding the carcinogenic risk of TL-01 phototherapy in patients who have not received any other phototherapy modalities previously.

MATERIALS AND METHODS

Patients

To explore the carcinogenicity of TL-01 monotherapy we retrospectively collected data of 4,835 individuals treated with TL-01 phototherapy in Finland during 1999–2019. We investigated the patient phototherapy registers of 17 Finnish Central and University Hospitals (Tampere University Hospital, HUS Helsinki University Hospital, Turku University Hospital, Kuopio University Hospital, Päijät-Häme Central Hospital, Kanta-Häme Central Hospital, North Karelia Central Hospital, South Karelia Central Hospital, Sataairaala Hospital, Central Finland Hospital Nova, Lapland Central Hospital, Länsi-Pohja Central Hospital, Vaasa Central Hospital, Seinäjoki Central Hospital, Central Ostrobothnia Central Hospital, Mikkeli Central Hospital, Kainuu Central Hospital) to identify all psoriasis and atopic dermatitis patients (with ICD-10 codes L20 and L40) who received TL-01 therapy and no other phototherapy modalities (e.g. PUVA treatment) in these hospitals. There are a total of 5 University Hospitals and 16 Central Hospitals in Finland, and we were able to collect data extensively from 4 and 13 of them. Only 19 patients (0.4 % of all) were treated in more than 1 different hospital. Personal clinical information (personal identity codes, phototherapy details, history of skin cancers) was collected from the hospital records and linked with the Finnish Population Information System to confirm the accuracy of the personal identity codes and to obtain the dates of death and emigration. The 19 patients who were not found in the Population Information System and 1 person with distinctly incorrect phototherapy dates were excluded, so a total of 4,815 TL-01 treated patients were included in the analyses.

Skin cancers

The patient data were linked with the Finnish Cancer Registry (FCR) data for the years 1999 to 2020 to obtain information on the patients' skin cancers. The FCR is a population-based national registry of all cancer cases diagnosed since 1953. FCR receives cancer data from several sources such as hospitals, private physicians, pathological laboratories, and death certificates (17). The cancer cases have been coded using ICD-O-3 codes (International Classification of Diseases for Oncology, third edition). In the case of multiple cancers with the same morphological groups, only the first diagnosed cancer within each topography is considered during the patient's life. Among the skin cancers, only histologically verified ones are registered. The three most common types of skin cancers, i.e. basal cell carcinoma (BCC), cutaneous SCC, and CM, were selected for analysis.

Narrow-band ultraviolet B phototherapy

Narrow-band UVB phototherapy (TL-01 phototherapy) is a widely used treatment modality in Finland for psoriasis, atopic dermatitis, and other skin diseases. The Finnish Dermatological Society has created the guidelines concerning treatment initiation, frequency, and dose increments. Recommendations have been made separately for psoriasis and atopic dermatitis, and depending on patients' skin phototype.

Typically, treatments are given 2 to 3 times per week and greater doses are used when treating psoriasis. Genitals and full face (or at least the eyes if the face is involved with dermatitis) should be

protected. A dermatologist has usually inspected the whole skin before starting treatments. TL-01 phototherapy is not recommended for patients with very fair or photodamaged skin, or a history of extensive exposure to UV radiation. The phototherapy period normally consists of 15 to 30 therapeutic sessions depending on treatment response. A maximum of 2 phototherapy periods per year is recommended.

Statistical analysis

Follow-up of the patients was started from the first TL-01 treatment and ended at death, emigration, or on 31 December 2020, whichever was first. Standardized incidence ratios (SIRs) were calculated for different skin cancers as a ratio of observed and expected numbers of cases. The observed numbers of cases and person-years were calculated separately for 2 follow-up periods (the first 5 years after the first TL-01 administration, and the period after that) by gender and 5-year age group. The expected numbers of cases were calculated by multiplying the number of person-years in each age and sex stratum by the respective national skin cancer incidence rate derived from the FCR data. The 95% confidence intervals (CIs) for SIRs were calculated assuming that the observed number of cases followed the Poisson distribution. Statistical analyses were performed with R (R Core Team, 2019; R Foundation for Statistical Computing, Vienna, Austria) and RStudio (Posit Team, 2023), the package "popEpi" was used for SIR calculations. *P*-values less than 0.05 were considered statistically significant.

RESULTS

Of the 4,815 patients treated with TL-01 phototherapy, 2,443 (51%) were female and 2,372 (49%) were male. In all, 54% were treated for psoriasis and 46% for atopic dermatitis. The mean age at the first TL-01 radiation was 46 years among patients with psoriasis (range 4–93) and 30 years among atopic patients (range 1–87). Age distribution of the cohort patients at the first TL-01 radiation is represented in **Fig. 1**. The mean follow-up time was 8.4 years for the entire cohort (range 0.03–21.6) and the total number of person-years was 40,230 (**Table I**).

During the follow-up, 38 BCC, 13 CM, and 9 SCC cases were observed versus 15 BCC, 3 CM, and 2 SCC expected. The SIR for BCC was 2.5 (95% CI 1.8–3.5), for CM 4.0 (95% CI 2.1–6.8), and for SCC 3.7 (95% CI

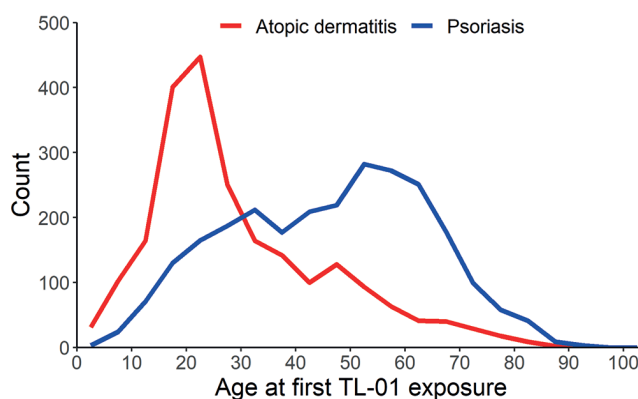


Fig. 1. Number of patients with atopic dermatitis and psoriasis in the cohort, by 5-year age categories at first TL-01 exposure.

Table I. Number of patients under follow-up and number of person-years up to 31 December 2020, by sex and age

Age	Men		Women	
	No. ^a	Person-years ^b	No. ^a	Person-years ^b
0–14 years	197	764	198	884
15–29 years	613	4,544	968	6,726
30–44 years	538	4,835	466	5,263
45–59 years	609	5,124	448	3,825
60–74 years	352	3,534	286	2,983
≥ 75 years	63	794	77	954

^aAge at the beginning of follow-up. ^bAge during follow-up.

1.7–7.0) (**Table II**). The SIRs for BCC and CM were higher among patients with psoriasis than among atopic patients while the SIR of SCC was higher in atopic dermatitis (**Table II**).

Most of the CMs (11/13) were diagnosed during the first 5 years after the first treatment (SIR 7.0, 95% CI 3.5–12.5) and only 2 cases after that (SIR 1.2, 95% CI 0.1–4.2). For BCC and SCC, SIRs remained quite similar during the whole follow-up time (**Table III**).

DISCUSSION

In our study we found an increased incidence of BCC, CM, and SCC among the 4,815 TL-01 treated patients. The SIR of BCC was increased only among patients with psoriasis while the risk of SCC was especially high among persons with atopic dermatitis.

This study is based on the largest cohort receiving TL-01 phototherapy alone so far, with a follow-up of up to almost 22 years. Data were available extensively around Finland and our cohort includes TL-01 treated patients from 17 of the 21 University and Central Hospitals in Finland. Only 0.4% of patients in the cohort had received TL-01 phototherapy in more than 1 study hospital. Hence, it is unlikely that many of the patients would have received TL-01 or other phototherapy modalities in the 4 missing hospitals.

Previous studies have not found any increased risk of skin cancers related to TL-01 phototherapy, but they had a small sample size and quite short follow-up times. The earliest of these studies was a German study including 126 TL-01 treated patients with a mean follow-up of 5.7 years and a total of 726 person-years. No other skin cancers were observed during the follow-up except 1 in situ melanoma, which was diagnosed within the first year after the phototherapy initiation (12). Among 484 TL-01 treated patients from Northern Ireland (some

Table III. Observed (Obs) and expected (Exp) numbers of skin cancers and standardized incidence ratios (SIR) with 95% confidence intervals (CI), by time since the first TL-01 exposure

Skin cancer type	Time since first exposure							
	<5 years				≥5 years			
	Obs	Exp	SIR	95% CI	Obs	Exp	SIR	95% CI
BCC	15	7.3	2.1	1.2–3.4	23	7.8	3.0	1.9–4.4
Cutaneous melanoma	11	1.6	7.0	3.5–12.5	2	1.7	1.2	0.1–4.2
SCC	4	1.1	3.6	1.0–9.2	5	1.3	3.8	1.2–8.8

BCC: basal cell carcinoma; SCC: squamous cell carcinoma.

also treated with PUVA), the incidence of skin cancers during follow-up of a maximum of approximately 10 years was similar to that in the general population (13). In a Scottish study with 3,867 TL-01 treated patients and a median follow-up time of 5.5 years no difference was found in CM risk between the TL-01 patients and the age- and sex-matched population in the same region (SIR 0.99, 95% CI 0.12–3.59) (15). The SIRs for BCC and SCC were closer to our findings, being 1.63 (95% CI 0.89–2.73) and 1.94 (95% CI 0.53–4.97), respectively. As the follow-up time of the Scottish study started 6 months after the first TL-01 exposure, we also performed a comparable analysis excluding the first 6 months after the TL-01 phototherapy initiation. The SIRs from this analysis were quite similar to our original results; the SIR for CM was 3.5 (95% CI 1.8–6.3), for BCC 2.5 (95% CI 1.7–3.5), and for SCC 3.8 (95% CI 1.7–7.2). Hence both our own and the Scottish study suggest an elevated risk of BCC and SCC among TL-01 phototherapy patients while for CM the CI for the Scottish finding is so wide that comparison with our finding cannot really be done.

It is difficult to assess the precise role of exposure to TL-01 phototherapy in the observed increase in incidence of skin cancers. Patients treated with other phototherapy modalities (e.g. PUVA, broadband UVB, or solarium) were excluded but patients with psoriasis especially are likely to be exposed to excessive sunlight, which may be an additional risk factor. We were not able to contact the patients to examine their sunbathing habits. Some patients may have had immunosuppressive therapies and patients with psoriasis have also been shown to have a 1.12 to 1.72 times higher risk of SCC and BCC compared with reference populations (18, 19). An association has been shown between the higher risk of keratinocyte skin cancer and the severity of psoriasis, and some studies have indicated that the risk of SCC is higher than the risk of BCC among patients with psoriasis (18). The risk of skin cancers among patients with atopic dermatitis

Table II. Observed (Obs) and expected (Exp) numbers of skin cancers 1999–2020 and standardized incidence ratios (SIR) with 95% confidence intervals (CI) among 4,815 TL-01 phototherapy-treated patients

Skin cancer type	Psoriasis				Atopic dermatitis				All			
	Obs	Exp	SIR	95% CI	Obs	Exp	SIR	95% CI	Obs	Exp	SIR	95% CI
Basal cell carcinoma	35	11.5	3.1	2.1–4.3	3	3.7	0.8	0.2–2.4	38	15.1	2.5	1.8–3.5
Cutaneous melanoma	10	2.3	4.4	2.1–8.1	3	1.0	3.0	0.6–8.8	13	3.3	4.0	2.1–6.8
Squamous cell carcinoma	5	1.9	2.6	0.8–6.0	4	0.5	7.8	2.1–19.9	9	2.5	3.7	1.7–7.0

is not as well established but previous data suggest an association between atopic dermatitis and keratinocyte skin cancers (20–22).

To investigate the temporal impact of TL-01 therapy on skin cancer risk we calculated SIRs separately for the first 5 years after the first TL-01 administration and the period after the first 5 years of exposure. The SIRs for BCC and SCC remained quite similar throughout the follow-up but for CM, the SIR was markedly higher during the first 5 years of follow-up. The typical latency between exposure and cancer diagnosis is long and therefore it is unlikely that phototherapy initiated shortly before a diagnosis of skin cancer would be causally related. One explanation for the increased incidence of CM during the first years after phototherapy initiation may be that patients receiving phototherapy are under regular dermatological follow-up and they are more likely to have their skin cancers diagnosed earlier.

Limitations

Our study also has limitations. Although the number of patients in the study is large, patients were relatively young to have skin cancer. The mean age at first radiation was 38 years. Patients with psoriasis in our cohort were somewhat older than atopic patients when receiving their first TL-01 administration. The median cumulative numbers of TL-01 treatments until the end of the follow-up were 20 for psoriasis (range 1–376) and 18 for atopic dermatitis (range 1–214), and median cumulative UV-B doses 15.3 J/cm² (range 0.2–374.5) and 10.4 J/cm² (range 0.1–219.3), respectively. The strength of the study would have increased if we had had more patients with long exposure to UV radiation. Unfortunately, in Finland, TL-01 phototherapy was not used before the late 1990s when it became available for treating psoriasis and other skin diseases and soon replaced PUVA as a major phototherapy modality for many skin diseases. Because we wanted to study the effects of TL-01 treatment as a monotherapy and therefore excluded patients who had received other phototherapy modalities previously, there are no patients with longer exposure or follow-up than we managed to collect in our cohort. It takes several years or even decades from initiation to develop skin cancers and multiple genetic mutations are necessary to establish a malignant phenotype and advance the tumorigenesis of UV-associated skin cancers (23, 24). Because of latency, the true carcinogenic risk related to TL-01 exposure can be seen only after a longer follow-up than is currently possible in Finland.

Conclusion

Although a slightly increased incidence of skin cancers was observed among TL-01 treated patients, the carcinogenic role of TL-01 phototherapy needs further examination. For future studies, we have planned to

compare TL-01 exposures more closely between patients with skin cancers and controls in a nested case-control study. We will also continue to follow up our cohort and repeat the study in the future to determine whether the skin cancer risk of TL-01 phototherapy will change after longer follow-up.

ACKNOWLEDGEMENTS

The authors would like to thank the European Academy of Dermatology and Venereology and the Finnish Dermatological Society for the project fundings that made this work possible. They also thank all nurses responsible for gathering the project data.

The project is funded by the European Academy of Dermatology and Venereology Project Funding no. PPRC-2017-8. The study was also supported financially by the Finnish Dermatological Society (grant awarded to Dr. Åkerla).

The study protocol was approved by the Ethics Committee of Tampere University Hospital (N:o R17133).

The authors have no conflicts of interest to declare.

REFERENCES

1. Parrish JA, Jaenicke KF. Action spectrum for phototherapy of psoriasis. *J Invest Dermatol* 1981; 76: 359–362.
2. Hönigsmann H. History of phototherapy in dermatology. *Photochem Photobiol Sci* 2013; 12: 16–21.
3. Solar and ultraviolet radiation. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man, Vol. 55. International Agency for Research on Cancer, 1992.
4. Flindt-Hansen H, McFadden N, Eeg-Larsen T, Thune P. Effect of a new narrow-band UVB lamp on photocarcinogenesis in mice. *Acta Derm Venereol* 1991; 71: 245–248.
5. Wulf HC, Hansen AB, Bech-Thomsen N. Differences in narrow-band ultraviolet B and broad-spectrum ultraviolet photocarcinogenesis in lightly pigmented hairless mice. *Photodermatol Photoimmunol Photomed* 1994; 10: 192–197.
6. Gibbs NK, Traynor NJ, MacKie RM, Campbell I, Johnson BE, Ferguson J. The phototumorigenic potential of broad-band (270–350 nm) and narrow-band (311–313 nm) phototherapy sources cannot be predicted by their edematogenic potential in hairless mouse skin. *J Invest Dermatol* 1995; 104: 359–363.
7. Stern RS, Laird N, Melski J, Parrish JA, Fitzpatrick TB, Bleich HL. Cutaneous squamous-cell carcinoma in patients treated with PUVA. *N Engl J Med* 1984; 310: 1156–1161.
8. Hannuksela-Svahn A, Pukkala E, Läärä E, Poikolainen K, Karvonen J. Psoriasis, its treatment, and cancer in a cohort of Finnish patients. *J Invest Dermatol* 2000; 114: 587–590.
9. Stern RS. PUVA follow-up study: the risk of squamous cell and basal cell cancer associated with psoralen and ultraviolet A therapy: a 30-year prospective study. *J Am Acad Dermatol* 2012; 66: 553–562.
10. Stern RS, Nichols KT, Väkevä LH. Malignant melanoma in patients treated for psoriasis with methoxsalen (psoralen) and ultraviolet A radiation (PUVA). *N Engl J Med* 1997; 336: 1041–1045.
11. Stern RS. The risk of melanoma in association with long-term exposure to PUVA. *J Am Acad Dermatol* 2001; 44: 755–761.
12. Weischer M, Blum A, Eberhard F, Röcken M, Berneburg M. No evidence for increased skin cancer risk in psoriasis patients treated with broadband or narrowband UVB phototherapy: a first retrospective study. *Acta Derm Venereol* 2004; 84: 370–374.
13. Black RJ, Gavin AT. Photocarcinogenic risk of narrowband ultraviolet B (TL-01) phototherapy: early follow-up data. *Br J Dermatol* 2006; 154: 566–567.
14. Man I, Crombie IK, Dawe RS, Ibbotson SH, Ferguson J. The photocarcinogenic risk of narrowband UVB (TL-01)

phototherapy: early follow-up data. *Br J Dermatol* 2005; 152: 755–757.

15. Hearn RMR, Kerr AC, Rahim KF, Ferguson J, Dawe RS. Incidence of skin cancers in 3867 patients treated with narrow-band ultraviolet B phototherapy. *Br J Dermatol* 2008; 159: 931–935.
16. Archier E, Devaux S, Castela E, Gallini A, Aubin F, Le Maître M, et al. Carcinogenic risks of psoralen UV-A therapy and narrowband UV-B therapy in chronic plaque psoriasis: a systematic literature review. *J Eur Acad Dermatol Venereol* 2012; 26: 22–31.
17. Pukkala E, Engholm G, Højsgaard Schmidt LK, Storm H, Khan S, Lambe M, et al. Nordic Cancer Registries: an overview of their procedures and data comparability. *Acta Oncol* 2018; 57: 440–455.
18. Wang X, Liu Q, Wu L, Nie Z, Mei Z. Risk of non-melanoma skin cancer in patients with psoriasis: an updated evidence from systematic review with meta-analysis. *J Cancer* 2020; 11: 1047–1055.
19. Chiesa Fuxench ZC, Shin DB, Ogdie Beatty A, Gelfand JM. The risk of cancer in patients with psoriasis: a population-based cohort study in the Health Improvement Network. *JAMA Dermatol* 2016; 152: 282–290.
20. Jensen AO, Svaerke C, Körmendiné Farkas D, Olesen AB, Kragballe K, Sørensen HT. Atopic dermatitis and risk of skin cancer: a Danish nationwide cohort study (1977–2006) *Am J Clin Dermatol* 2012; 13: 29–36.
21. Wang L, Bierbrier R, Drucker AM, Chan AW. Noncutaneous and cutaneous cancer risk in patients with atopic dermatitis: a systematic review and meta-analysis. *JAMA Dermatol* 2020; 156: 158–171.
22. Hedderson MM, Asgari MM, Xu F, Quesenberry CP, Sridhar S, Geier J, et al. Rates of malignancies among patients with moderate to severe atopic dermatitis: a retrospective cohort study. *BMJ Open* 2023; 13: e071172.
23. Reichrath J, Rass K. Ultraviolet damage, DNA repair and vitamin D in nonmelanoma skin cancer and in malignant melanoma: an update. *Adv Exp Med Biol* 2014; 810: 208–233.
24. Benjamin CL, Ananthaswamy HN. p53 and the pathogenesis of skin cancer. *Toxicol Appl Pharmacol* 2007; 224: 241–248.