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No association between whole-body UVA1 phototherapy and skin cancers in humans: a cancer registry linkage study

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Dear Sir,

Ultraviolet A1 (UVA1) phototherapy was first developed in the 1980s.¹ Its use started in the UK in Dundee in 1996.² It is not available in most centres despite being useful for some of the sclerosing/fibrosing conditions and granulomatous conditions. Where available, for some individuals, it can be very helpful for other indications such as atopic eczema.³ A concern is that sufficient exposures might increase the risk of skin cancer.⁴ It has been shown to produce cyclobutane-pyrimidine dimers in humans,⁵ and so has the potential to be carcinogenic.

There are case reports of people who have had UVA1 who have then developed cutaneous melanoma and Merkel cell carcinoma but there is no clear evidence that this form of phototherapy increases the risk of any form of skin cancer in humans.^{6,7}

As part of a Chief Scientist Office, Scottish Government, study linking treatment with phototherapies and the Scottish cancer registry we assessed UVA1 exposure in patients who had been exposed to UVA1 between 1996 and 2016 in Dundee. Most courses of whole-body UVA1 are delivered with a high output metal halide “bed” rather than our lower output UVA1 cabinet.

Photosys (the database of Photonet, the national managed clinical network for phototherapy) data were linked to national Scottish cancer registry data for patients from Tayside and Fife (using deterministic data linkage by the University of Dundee Health Informatics Centre). We followed up using this registry linkage 297 patients receiving 419 whole-body UVA1 courses (mean age at first UVA1 treatment 46.5 years [range 12.9 to 91.4 years], women [199 (67%)]); the majority of sun-reactive skin phototypes I [52 patients, 18%], II [136, 46%], and III [89, 30%]) 1) from 1/6/1979 until first UVA1 exposure then 2) from first UVA1 exposure until 31/12/2016 (or earlier ‘censoring’ due to, for example, death).

Of the 297 patients in this cohort followed up for up to 20 years after first UVA1, 232 had received a cumulative <50 UVA1 treatments, 61 between 51 and 350 and 4 ≥ 351 whole-body UVA1 treatments. We did not collect data on doses (considering number of treatments likely more relevant especially as doses are individualised for each patient); a typical course involves about 200 J/cm² UVA1. We identified 6 skin cancers in 5 separate patients. None of these patients had also received ultraviolet B phototherapy or PUVA. Of the two patients (one who received 30 UVA1 exposures for morphea and one who had a course of 17 exposures for widespread granuloma annulare) with basal cell carcinoma one developed this 4 years after UVA1 but one at the same time as first UVA1 (so implausible that UVA1 should have caused the BCC). Of those who developed cutaneous SCC, one (who received a single course of 10 treatments for morphea) was diagnosed with 2 SCCs simultaneously 3 years after UVA1, one was diagnosed with an SCC 6 years after first exposure to UVA1 (of which she had a cumulative 152 treatments for eczema) and one (who had received 31 treatments for morphea who had also developed cancer before first phototherapy) had SCC 10 years after first UVA1.

We estimated standardised incidence ratios (SIRs) and 95% CIs for basal cell carcinoma (only the first of these is recorded in the Scottish cancer registry, all of the other cancer types are recorded), cutaneous squamous cell carcinoma (SCC), cutaneous melanoma, non-Hodgkin's lymphoma, and, amongst the men, prostate cancer compared with the general population of Scotland, taking into account age and sex, both before and after UVA1 exposure. The standard incidence ratios (SIRs) for each tumour type are in **Table 1**. It is reassuring that none of the SIRs after UVA1 was statistically significant, that the absolute numbers of skin cancers were small and that they were not found especially in those who had many treatments.

The numbers are still modest and follow-up was for no more than 20 years. Therefore, we cannot discount any increased risk amongst patients treated with UVA1. It is of interest that in this cohort there was an increased risk of cutaneous SCC and of non-Hodgkin's lymphoma before UVA1 suggesting a risk in this cohort of patients (perhaps in part because many are on systemic immunosuppressive drugs for conditions such as morphea). Furthermore, although these were not significant (they might have been due to chance) there were decreased risks of melanoma

and prostate cancer and a slightly increased risk of BCC before the UVA1 exposure: the SIRs were lower after UVA1. Thus, UVA1 could be related to the lack of increased risks or, potentially, could even be associated with decreasing the risks of these cancer types.

With all interventions, it is necessary to balance risks against expected benefits and for many of the indications for UVA1, such as widespread morphea, alternative treatments carry greater risks.

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Table 1 Cancers in people in Tayside and Fife treated with UVA1, adjusted for sex and age

Cancer type	Compared with the age and sex adjusted population of Scotland before first exposure to UVA1 phototherapy					Compared with the age and sex adjusted population of Scotland after first exposure to UVA1 phototherapy				
	PY*	O _z	E _z	SIR* ¹	95% CI [#]	PY*	O _z	E _z	SIR* ¹	95% CI [#]
Basal cell carcinoma	265808	214	206.83	1.03	0.90 to 1.18	1967	2	2.88	0.69	0.08 to 2.49
Squamous cell carcinoma	267709	95	68.54	1.39	1.12 to 1.70	2018	3	0.8	3.75	0.91 to 10.96
Melanoma	267709	27	38.29	0.71	0.47 to 1.03	2018	0	0.54	0 (no melanomas)	No events so unable to calculate
Non-Hodgkin's lymphoma	187063	63	87.45	2.10	1.61 to 2.69	2018	1	0.92	2.42	0.032 to 13.46
Prostate cancer	84641	63	87.45	0.75	0.56 to 0.99	687	0	0.92	0 (no prostate cancers)	No events so unable to calculate

PY*: number of person-years

O_z: number of observed cancer cases

E_z: number of expected cancer cases

SIR*¹: standardised incidence rate (comparison with the general Scottish population adjusted for age and sex)

CI[#]: confidence interval

No Merkel cell carcinomata or melanomas were found after UVA1 treatment.