CHIEF SCIENTIST OFFICE

CODE: TCS-16-47

RESEARCH PROJECT BRIEFING

Does NB-UVB phototherapy increase the risk of skin cancer development? A 30-year retrospective cohort study in Scotland

AIMS

The main aim of the study was to assess whether or not there is an increased risk of any of the three commonest types of skin cancer in relation to number of treatments and length of follow-up following first treatment with narrowband UVB (NB-UVB) phototherapy. NB-UVB phototherapy is the most widely used form of phototherapy used to treat almost fifty different skin diseases, although particularly for psoriasis, eczema and urticaria.

KEY FINDINGS

This study is still ongoing – the information so far is for the Tayside and Fife populations. We are still seeking linkage between information about patients treated throughout the whole of Scotland with the Scottish Cancer registries. Dr Khaled Bedair, the epidemiologist who was employed through the CSO grant to perform the study is no longer here but working in Qatar, but still spending a lot of time, along with colleagues, on this study. We therefore expect to have some more information available once the study has been extended to the whole of Scotland.

- Regarding squamous cell carcinoma of the skin (SCC) we detected some increased risk amongst those who had also been exposed to PUVA.
- Regarding melanoma of the skin we detected no definite increased risk likely attributable to NB-UVB.
- Regarding basal cell carcinoma of the skin (BCC) we detected some increased risk amongst those who had also been exposed to PUVA.
- Our findings in relation to PUVA exposure match those of previous studies, helping to validate findings of this study. An interesting finding was that although with PUVA exposure

KEY FINDINGS (CONT)

there was no increased risk of melanoma compared to the general population such an increased risk was detectable when comparing with risks in the same population before exposure. This supports the possibility suggested by a large U.S.A. study that PUVA might increase the risk of melanoma skin cancer – a larger study from Sweden did not detect a risk but they only compared risk with the general population rather than within the treated population, so potentially missing a small increased risk.

- We did not detect any association with UVA1 phototherapy and any form of skin cancer. UVA1 phototherapy has been used since the 1980s but is not widely available having until recently been available in the UK only in Dundee (now also in Leeds and London).

WHAT DID THE STUDY INVOLVE?

This study involved linkage of information on number of phototherapy courses, diagnoses and other factors that might be associated with increased risk or not of skin cancers collected in the database of the National Scottish Managed Clinical Network for Phototherapy with the Scottish Skin Cancer registry. All patients who have phototherapy have as part of their consent for phototherapy consented to use of their information for relevant research such as this. In the design of the study public involvement was involved in that patients regularly ask about possible risks of skin cancer with this form of phototherapy and it was mainly to try to provide clearer answers that this study was conducted. Our plan was to link data on all patients treated in Scotland with this form of phototherapy and the Scottish Skin Cancer registry – the procedure for seeking approval for this national linkage has taken much longer than expected but we still plan to do this. Once we have permissions this will be rapid as all the algorithms have now been refined and are ready to be used. Some of the key results are in the tables below.

WHAT WERE THE RESULTS AND WHAT DO THEY MEAN?

Squamous cell carcinoma of the skin (SCC)

		Squamous Cell Carcinoma of the skin																		
		Not Yet UVB									After UVB Exposure									
		O	PYR	E	SIR	95% CI Lower	95% CI Upper	IR	IR 95% CI Lower	IR 95% CI Upper	O	PYR	E	SIR	95% CI Lower	95% CI Upper	IR	IR 95% CI Lower	IR 95% CI Upper
PUVA	Not Yet	27	181527.57	25.01	1.08	0.712	1.571	0.409	0.267	0.627	35	57942.10	27.08	1.29	0.898	1.794	1.663	1.130	2.446
	After Exposure	14	13399.51	7.74	1.81	0.989	3.037	2.876	1.643	5.034	22	16857.95	9.51	2.31	1.447	3.498	3.592	2.262	5.703
Diagnosis	Before Diagnosis	24	180563.81	24.60	0.98	0.628	1.458	0.366	0.234	0.572	NA	NA	NA	NA	-	-	-	-	-
	Psoriasis	8	6634.88	3.28	2.44	1.051	4.808	3.319	1.614	6.823	22	40178.35	15.83	1.39	0.871	2.105	1.507	0.949	2.393
	Photodermatoses	0	257.96	0.07	0.00	-	-	0.000	-	-	0	4558.35	1.08	0.00	-	-	0.000	-	-
	Other dermatoses	9	7470.43	4.80	1.87	0.853	3.550	3.316	1.675	6.563	35	30063.35	19.67	1.78	1.240	2.476	3.204	2.178	4.714
Skin phototype	I	14	34960.93	6.70	2.09	1.142	3.507	1.102	0.630	1.930	21	14888.91	7.19	2.92	1.807	4.464	3.882	2.423	6.219
	II	18	93183.88	15.88	1.13	0.669	1.786	0.532	0.322	0.879	24	34168.12	17.84	1.35	0.865	2.009	1.933	1.237	3.021
	III	9	55586.23	8.06	1.12	0.511	2.126	0.446	0.225	0.882	12	21722.73	9.88	1.22	0.630	2.131	1.520	0.835	2.769
	IV	0	5142.55	0.66	0.00	-	-	0.000	-	-	0	1648.83	0.54	0.00	-	-	0.000	-	-
	V	0	2051.66	0.11	0.00	-	-	0.000	-	-	0	613.53	0.08	0.00	-	-	0.000	-	-
	VI	0	526.91	0.03	0.00	-	-	0.000	-	-	0	152.13	0.09	0.00	-	-	0.000	-	-
Total		41	194927.07	32.75	1.25	0.898	1.698	0.579	0.402	0.834	57	74800.04	36.58	1.56	1.180	2.019	2.097	1.513	2.907

Note: The summation of number of cancers, person years and expected number of cancer are NOT equal to the total number because there were 9 BCC cases with missing skin type

Melanoma of the skin

		Melanoma of the skin																		
		Not Yet UVB									After UVB Exposure									
		O	PYR	E	SIR	95% CI Lower	95% CI Upper	IR	IR 95% CI Lower	IR 95% CI Upper	O	PYR	E	SIR	95% CI Lower	95% CI Upper	IR	IR 95% CI Lower	IR 95% CI Upper
PUVA	Not Yet	9	181527.57	17.95	0.50	0.228	0.949	0.495	0.233	1.053	9	57942.10	13.12	0.69	0.315	1.310	1.552	0.730	3.299
	After Exposure	2	13399.51	3.24	0.62	0.070	2.239	1.491	0.355	6.270	7	16857.95	4.53	1.55	0.621	3.194	4.148	1.806	9.526
Diagnosis	Before Diagnosis	9	180563.81	17.67	0.51	0.233	0.968	0.498	0.234	1.059	NA	NA	NA	NA	-	-	-	-	-
	Psoriasis	0	6634.88	1.43	0.00	-	-	0.000	-	-	9	40178.35	8.95	1.01	0.461	1.917	2.238	1.052	4.758
	Photodermatoses	0	257.96	0.06	0.00	-	-	0.000	-	-	1	4558.35	1.08	0.92	0.012	5.119	2.192	0.298	16.128
	Other dermatoses	2	7470.43	2.03	0.98	0.110	3.538	2.675	0.636	11.247	6	30063.35	7.62	0.79	0.288	1.720	1.994	0.823	4.829
Skin phototype	I	3	34960.93	4.10	0.73	0.147	2.133	0.857	0.260	2.826	3	14888.91	3.47	0.86	0.173	2.513	2.013	0.611	6.634
	II	7	93183.88	10.09	0.69	0.276	1.422	0.750	0.327	1.723	9	34168.12	8.19	1.10	0.502	2.088	2.631	1.238	5.595
	III	0	55586.23	5.74	0.00	-	-	0.000	-	-	4	21722.73	5.15	0.78	0.210	1.997	1.840	0.644	5.257
	IV	0	5142.55	0.50	0.00	-	-	0.000	-	-	0	1648.83	0.32	0.00	-	-	0.000	-	-
	V	0	2051.66	0.13	0.00	-	-	0.000	-	-	0	613.53	0.10	0.00	-	-	0.000	-	-
	VI	0	526.91	0.03	0.00	-	-	0.000	-	-	0	152.13	0.03	0.00	-	-	0.000	-	-
Total		11	194927.07	21.18	0.52	0.259	0.929	0.564	0.280	1.136	16	74800.04	17.66	0.91	0.518	1.471	2.137	1.151	3.966

Note: The summation of number of cancers, person years and expected number of cancer are NOT equal to the total number because there were 9 BCC cases with missing skin type

WHAT WERE THE RESULTS AND WHAT DO THEY MEAN? (CONT)

Basal cell carcinoma of the skin (BCC)

		Basal Cell Carcinoma of the skin																	
		Not Yet UVB									After UVB Exposure								
		O	PYR	E	SIR	95% CI Lower	95% CI Upper	IR	IR 95% CI Lower	IR 95% CI Upper	O	PYR	E	SIR	95% CI Lower	95% CI Upper	IR	IR 95% CI Lower	IR 95% CI Upper
PUVA	Not Yet	84	180935.41	87.98	0.95	0.758	1.176	0.574	0.447	0.741	73	57237.78	72.53	1.01	0.792	1.270	1.581	1.213	2.062
	After Exposure	25	13143.65	21.61	1.16	0.750	1.712	2.358	1.559	3.568	34	16458.53	27.60	1.23	0.852	1.719	2.561	1.784	3.677
Diagnosis	Before Diagnosis	82	18005.85	86.41	0.95	0.756	1.179	0.565	0.438	0.728	NA	NA	NA	NA	-	-	-	-	-
	Psoriasis	12	6476.09	9.30	1.29	0.666	2.254	2.297	1.284	4.108	63	39570.31	49.55	1.27	0.976	1.625	1.974	1.491	2.613
	Photodermatoses	0	257.96	0.36	0.00	-	-	0.000	-	-	4	4491.18	5.13	0.78	0.210	1.997	1.104	0.411	2.969
	Other dermatoses	15	7339.16	13.53	1.11	0.621	1.831	2.534	1.501	4.276	40	29634.82	45.44	0.88	0.629	1.198	1.673	1.194	2.345
Skin phototype	I	20	21081.55	18.39	1.09	0.666	1.684	1.176	0.744	1.860	26	13185.96	17.83	1.46	0.953	2.139	2.444	1.627	3.672
	II	39	58881.63	46.10	0.85	0.604	1.162	0.821	0.584	1.155	39	30275.17	41.03	0.95	0.675	1.299	1.597	1.136	2.246
	III	22	34452.20	25.34	0.87	0.545	1.317	0.792	0.511	1.227	27	19291.87	25.73	1.05	0.692	1.528	1.735	1.163	2.589
	IV	3	3370.84	2.11	1.42	0.285	4.149	1.103	0.353	3.448	0	1460.21	1.45	0.00	-	-	0.000	-	-
	V	0	1396.93	0.43	0.00	-	-	0.000	-	-	0	543.05	0.38	0.00	-	-	0.000	-	-
	VI	1	346.92	0.09	10.54	0.138	58.643	3.573	0.501	25.484	0	128.28	0.11	0.00	-	-	0.000	-	-
Total		109	194079.06	109.58	0.99	0.817	1.200	0.696	0.553	0.877	107	73696.31	100.12	1.07	0.876	1.291	1.800	1.428	2.269

Note: The summation of number of cancers, person years and expected number of cancer are NOT equal to the total number because there were 9 BCC cases with missing skin type

Number of treatments with UVB and PUVA and SCC

		O	PYR	E	SIR	95% CI Lower	95% CI Upper	IR	IR 95% CI Lower	IR 95% CI Upper
UVB group	(-Inf,0)	41	194927.08	32.76	1.25	0.897	1.696	0.579	0.402	0.834
	(0,50)	31	53588.82	25.48	1.22	0.829	1.732	1.592	1.063	2.384
	(50,100)	9	13129.50	6.29	1.43	0.653	2.715	1.887	0.953	3.734
	(100,200)	7	6345.8	3.79	1.85	0.741	3.812	3.036	1.410	6.536
	(200,350)	4	1327.76	0.81	4.93	1.326	12.622	8.292	3.051	22.534
	(350,Inf)	6	408.17	0.21	28.02	10.232	60.990	40.458	17.743	92.256
PUVA group	(-Inf,0)	62	239469.67	52.09	1.19	0.912	1.526	0.713	0.518	0.979
	(0,50)	17	21358.46	12.01	1.42	0.827	2.274	2.191	1.309	3.666
	(50,100)	5	5315.58	2.91	1.72	0.554	4.014	2.589	1.054	6.359
	(100,200)	7	2795.11	1.80	3.90	1.562	8.036	6.893	3.202	14.840
	(200,Inf)	7	788.31	0.53	13.13	5.260	27.054	24.440	11.352	52.616
Total		98	269727.13	69.34	1.41	1.145	1.718	1.000	0.756	1.323

O = observed events (the skin cancer type concerned)
PYR = Person years of follow-up
E = Expected number of events in general Scottish population
SIR = Standard incidence rate, comparing chance of developing squamous cell carcinoma, melanoma or a first basal cell carcinoma (compared to within the general population)
IR = Similar to SIR but an incidence ratio giving estimate as to risks compared to the same population prior to phototherapy exposure

WHAT WERE THE RESULTS AND WHAT DO THEY MEAN? (CONT)

Regarding squamous cell carcinoma of the skin (SCC) we detected no increased risk amongst people only exposed to NB-UVB phototherapy and not exposed to PUVA (another phototherapy treatment, with known increased risk of skin cancer). With PUVA exposure as well as NB-UVB exposure we did not detect a definite increased risk when comparing risks with those for the general Scottish population. When we compared risks amongst the same individuals after exposure and compared with before exposure there is no detectable risk amongst those who have received NB-UVB only but there was a detectable risk in those who had received both PUVA and NB-UVB phototherapy. There was an association between increasing number of treatments over a lifetime with NB-UVB and squamous cell carcinoma although much of this risk was likely attributable to the fact that most of these patients had also had PUVA treatments.

Regarding basal cell carcinoma of the skin (BCC) we detected no increased risk amongst people only exposed to NB-UVB phototherapy and not exposed to PUVA. With PUVA exposure as well as NB-UVB exposure we did not detect a definite increased risk when comparing risks with those for the general Scottish population. When we compared risks amongst the same individuals after exposure and compared with before exposure there is no detectable risk amongst those who have received NB-UVB only but there was a detectable risk in those who had received both PUVA and NB-UVB phototherapy.

Compared with the general population there was no increased risk of melanoma identified in those patients treated with NB-UVB. Only amongst those treated with both NB-UVB and PUVA and comparing with the same population before exposure was an increased risk detectable. The chance of melanoma was lower than that for the general population before exposure – in those also exposed to PUVA it increased after exposure to both forms of phototherapy. It is likely that the small increased risk in those treated with both NB-UVB and PUVA was due to PUVA.

In summary the information contained here showed many interesting things many of which confirm that we found what was expected in relation to PUVA risks and increased risks in people of lower skin phototypes. The interesting new information is in relation to NB-UVB exposure which we have not completely been able to disentangle from PUVA exposure although the data is reassuring in not detecting any very high increased risks. We will once this study has been completed for the whole of Scotland go onto a case control study that should allow us to work out hazard ratios for development of the different skin cancer types according to amount of NB-UVB exposure taking into account PUVA exposure.

WHAT IMPACT COULD THE FINDINGS HAVE?

- Implications for patients: we have not excluded any risk of skin cancer, particularly squamous cell skin carcinoma, with very high NB-UVB exposures and so the current practice of recalling for skin cancer checks those patients who have received a lot of ultraviolet B over the years should continue. The information from this once published will allow us to be more precise in telling potential patients about the likely risks – reassuringly less than with other alternative treatments for most of the conditions concerned.
- The information so far has validated the current national standard in relation to follow-up of patients who have had high NB-UVB exposures. It is unlikely that this policy will be changed.
- NB-UVB phototherapy should continue to be used but with the same precautions as before.

HOW WILL THE OUTCOMES BE DISSEMINATED?

A letter regarding UVA1 phototherapy and skin cancer risks is currently under second review (first manuscript was reviewed and the decision was that this is likely to be accepted subject to some changes) by the British Journal of Dermatology (No association between UVA1 phototherapy and skin cancers in humans: cancer registry linkage study; manuscript ID BJD2019-3095). We are working on a paper regarding the main cohort study – to be offered to a general dermatology journal and, although a lesser priority, we are also planning to submit to an epidemiology or general medical journal information that we are now collecting on associations between phototherapy and other, non-skin cancer types.

The next piece of research should be analysing through the same models data with linkage to the Scottish Cancer registry from the whole of Scotland rather than only Tayside and Fife. Following this, a case-control study to give more information regarding NB-UVB risk, taking into account the risks associated with confounders particularly PUVA exposure, and squamous cell carcinoma will be conducted.

CONCLUSION

So far, the main information continues to be reassuring as regards the relative safety of this widely used (throughout the world) form of phototherapy (which was first introduced in Dundee, Scotland and Utrecht, Netherlands) Standard approaches to informing patients about potential risks and following up those who have had high numbers of NB-UVB treatments will not be greatly changed; however, information given to interested patients will be more precise.

RESEARCH TEAM & CONTACT

Robert S. Dawe
Photobiology Unit
Department of Dermatology
Level 8
Ninewells Hospital and Medical School
Dundee
DD1 9SY

rdawe@nhs.net
r.s.dawe@dundee.ac.uk

01382 632250

Khaled Bedair
Department of Statistics and Mathematics Faculty of Commerce
Tanta University
Tanta 31521
Egypt

Peter Donnan
Department of Population Health Sciences and Medical Research Unit
University of Dundee
Dundee
DD1 9SY

Ahmed Elhadad
Department of Mathematics and Computer Science
Faculty of Science
South Valley University
Qena 83523
Egypt

James Ferguson
Photobiology Unit
Dermatology Department
School of Medicine
University of Dundee
Dundee
DD1 9SY

Safwat Hamad
Department of Scientific Computing
Faculty of Computer and Information Sciences
Ain Shams University
Cairo 11566
Egypt