

Supplementary Online Content

Lam M, Zhu JW, Tadrous M, Drucker AM. The association between topical calcineurin inhibitor use and risk of cancer, including lymphoma, keratinocyte carcinoma, and melanoma: a systematic review and meta-analysis. *JAMA Dermatol*. Published online March 31, 2021. doi:10.1001/jamadermatol.2021.0345

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Search Strategy for MEDLINE via Ovid

#	searches
1	exp neoplasms/
2	lymphoma/
3	carcinoma/
4	melanoma/
5	cancer*.mp.
6	malignan*.mp.
7	neoplas*.mp.
8	tumo*.mp.
9	carcinom*.mp.
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11	calcineurin inhibitors/
12	calcineurin inhibitor*.mp.
13	tacrolimus/
14	tacrolimus.mp.
15	protopic.mp.
16	prograft.mp.
17	fk506.mp.
18	aristoderm.mp.
19	tacroderm.mp.
20	pimecrolimus.mp.
21	elidel.mp.
22	argen.mp.
23	douglan.mp.
24	isaplic.mp.
25	rizan.mp.
26	OR 11-25
27	ointment*.mp.
28	cream*.mp.
29	topical*.mp.
30	27 or 28 or 29
31	10 and 26 and 30
32	10 and 26 and 30 (limit to human studies)

Note: / - MeSH search, * - truncation, exp – explode

eTable 2. Search Strategy for Embase via Ovid

#	searches
1	exp neoplasm/
2	exp malignant neoplasm/
3	lymphoma/
4	carcinoma/
5	melanoma/
6	cancer*.mp.
7	malignan*.mp.
8	neoplas*.mp.
9	carcinom*.mp.
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11	calcineurin inhibitor/
12	tacrolimus/
13	pimecrolimus/
14	tacrolimus.mp.
15	protopic.mp.
16	prograft.mp.
17	fk506.mp.
18	aristoderm.mp.
19	tacroderm.mp.
20	pimecrolimus.mp.
21	elidel.mp.
22	argen.mp.
23	douglan.mp.
24	isaplic.mp.
25	rizan.mp.
26	OR 11-25
27	ointment*.mp.
28	cream*.mp.
29	topical*.mp.
30	20 or 21 or 22
31	10 and 26 and 30
32	10 and 26 and 30 (limit to human studies)

Note: / - MeSH search, * - truncation, exp – explode

eTable 3. Search Strategy for Web of Science

#	searches
1	TS=(neoplasm)
2	TS=("neoplas*")
3	TS=(lymphoma)
4	TS=(carcinoma)
5	TS=(melanoma)
6	TS=("malignan*")
7	TS=("cancer*")
8	1 or 2 or 3 or 4 or 5 or 6 or 7
9	TS=(calcineurin inhibitor)
10	TS=(tacrolimus)
11	TS=(pimecrolimus)
12	9 or 10 or 11
13	(TS=("topical*"))
14	TS=("cream*")
15	TS=("ointment*")
16	13 or 14 or 15
17	8 and 12 and 16

eTable 4. Characteristics of Included Case-Control Studies on TCI Use in Participants With Cancer

Study	Participant source	Condition	Cases				Controls			Variables matched
			<i>n</i>	<i>Mean age (SD)</i>	<i>% female</i>	<i>Type of cancer</i>	<i>n</i>	<i>Mean age (SD)</i>	<i>% female</i>	
Arellano, 2006	Atopic dermatitis patients from the PharMetrix database from July 1995 to Jan 2005; USA	AD	294	-	58.8%	Lymphoma	1176	-	58.7%	Duration of follow-up
Arellano, 2009	Patients from The Health Improvement Network database with at least 6 months enrollment from Jan 1, 1992 to March 23, 2006; UK	AD	2738	-	43.5%	Lymphoma	10949	-	43.5%	Age, sex, practice
Margolis, 2007	Patients with history of dermatitis, seen at the Department of Dermatology, University of Pennsylvania from 2002 to 2005; USA	Dermatitis (seborrheic dermatitis, AD, dermatitis NOS, rosacea)	866	66.6 (12.7)	45.0%	KC	1901	59.2 (11.9)	64.5%	-

Abbreviations: AD – Atopic Dermatitis; SD – Standard Deviation; KC – Keratinocyte Carcinoma

eTable 5. Scoring Distribution of Quality Assessment of Studies Using the Newcastle-Ottawa Scale

STUDY	SELECTION	COMPARABILITY	OUTCOME	TOTAL
Cohort studies				
<i>Asgari, 2020</i>	4	2	3	9
<i>Cai, 2016</i>	4	2	3	9
<i>Castellsague, 2018</i>	4	1	1	6
<i>Deleuran, 2016</i>	3	0	2	5
<i>Hui, 2009</i>	4	1	1	6
<i>Margolis, 2015</i>	1	1	1	3
<i>Paller, 2020</i>	1	2	3	6
<i>Schneeweiss, 2009</i>	4	1	1	6
Case-control studies				
<i>Arellano, 2009</i>	3	2	2	7
<i>Arellano, 2006</i>	3	2	2	7
<i>Margolis, 2007</i>	2	1	1	4

eTable 6. Exposure to TCI Outcomes in Cancer Cases and Cancer-Free Controls in Case-Control Studies

Study	Type of cancer	Treatment	n (%) cases exposed to treatment	n (%) control exposed to treatment	Odds Ratio (95% CI)	Adjusted variables
Arellano, 2009	Lymphoma	TAC	0 (0)	3 (0)	N.A.	N.A.
		PIM	0 (0)	0 (0)	N.A.	
		TAC+PIM	0 (0)	0 (0)	N.A.	
Arellano, 2007	Lymphoma	TAC	11 (3.7)	41 (3.5)	0.79 (0.37-1.71)	sex, age, region, specialty, presence of infectious mononucleosis, asthma diagnosis, asthma drug use, oral steroid
		PIM	14 (4.8)	65 (5.5)	0.82 (0.42-1.61)	
		TAC+PIM	4 (1.4)	9 (0.8)	1.01 (0.25-4.12)	
Margolis, 2007	KC	TAC	57 (6.9)	354 (19.6)	0.43 (0.30-0.60)	age, gender, history of AD, previous history of NMSC
		PIM	88 (10.4)	383 (20.7)	0.66 (0.-500.89)	
		TAC+PIM	123 (14.4)	587 (30.7)	0.54 (0.41-0.69)	
Schneeweiss, 2009	Lymphoma	TAC	13 (52.0)	49 (49.0)	Ref.*	Propensity score at cohort entry
		PIM	11 (44.0)	48 (48.0)	0.86 (0.35-2.12)*	
		TAC+PIM	1 (4.0)	3 (3.0)	1.26 (0.12-13.1)*	

Abbreviations: KC – Keratinocyte carcinoma; CI – confidence interval; N.A. – not applicable

*Odds ratio for TCI use comparing Pimecrolimus and Tacrolimus in cases of lymphoma and cancer-free controls

eTable 7. Excluded Full-Text Records

<i>Citation</i>	<i>Reason for exclusion</i>
Gardenier, Jason C; Kataru, Raghu P; Hespe, Geoffrey E; Savetsky, Ira L; Torrissi, Jeremy S; Nores, Gabriela D Garcia; Jowhar, Dawit K; Nitti, Matthew D; Schofield, Ryan C; Carlow, Dean C; Mehrara, Babak J Topical tacrolimus for the treatment of secondary lymphedema. Nature communications / 2017;8(101528555):14345	Animal study
Anderson, Kathryn; Ascanio, Nicole M; Kinney, Megan A; Krowchuk, Daniel P; Jorizzo, Joseph L A retrospective analysis of pediatric patients with lichen sclerosus treated with a standard protocol of class I topical corticosteroid and topical calcineurin inhibitor. The Journal of dermatological treatment / 2016;27(1):64-6	Case report / Case series
Bastida, Jesus; Valeron-Almazan, Pedro; Santana-Molina, Nestor; Medina-Gil, Carolina; Carretero-Hernandez, Gregorio Treatment of folliculitis decalvans with tacrolimus ointment. International journal of dermatology / 2012;51(2):216-20	Case report / Case series
Bernard L.A.; Cunningham B.B.; Al-Suwaidan S.; Friedlander S.F.; Eichenfield L.F. A rosacea-like granulomatous eruption in a patient using tacrolimus ointment for atopic dermatitis [7] Archives of Dermatology / 2003;139(2):229-231	Case report / Case series
Birnbaum F.; Reis A.; Reinhard T. Long term use of topical tacrolimus (FK506) in high-risk penetrating keratoplasty Cornea / 2009;28(6):715-716	Case report / Case series
Fischer, Gayle; Bradford, Jennifer Topical immunosuppressants, genital lichen sclerosus and the risk of squamous cell carcinoma: a case report. The Journal of reproductive medicine / 2007;52(4):329-31	Case report / Case series
Fricain, J. C.; Sibaud, V.; Swetyenga, N.; Tabrizi, R.; Campana, F.; Taieb, A. Long-term efficacy of topical tacrolimus on oral lesions of chronic graft-versus-host disease British Journal of Dermatology 2007;156(3):588-590	Case report / Case series
Garcia-Delgado R.; Escario-Travesedo E.; Sanchez-Romero A. Systemic Absorption of Topical Tacrolimus in Metastatic Crohn Disease With Skin Ulcers Actas Dermo-Sifiliograficas / 2016;107(10):866-867	Case report / Case series
Gordon M.K.; Kraus M.; van Besien K. Interdigitating dendritic cell tumors in two patients exposed to topical calcineurin inhibitors [5] Leukemia and Lymphoma / 2007;48(4):816-818	Case report / Case series
Jung, Ji Won; Lee, Young Ji; Yoon, Sang Chul; Kim, Tae-Im; Kim, Eung Kweon; Seo, Kyoung Yul Long-term result of maintenance treatment with tacrolimus ointment in chronic ocular graft-versus-host disease. American journal of ophthalmology / 2015;159(3):519-27.e1	Case report / Case series

<p>Kelekci, Handan Kiyemet; Uncu, Hikmet Gulsen; Yilmaz, Bulent; Ozdemir, Orcun; Sut, Necdet; Kelekci, Sefa</p> <p>Pimecrolimus 1% cream for pruritus in postmenopausal diabetic women with vulvar lichen simplex chronicus: a prospective non-controlled case series. The Journal of dermatological treatment / 2008;19(5):274-8</p>	Case report / Case series
<p>Lan, C Ce; Wu, C S; Chen, G S; Yu, H S</p> <p>Helium-neon laser and topical tacrolimus combination therapy: novel treatment option for vitiligo without additional photocarcinogenic risks. Journal of the European Academy of Dermatology and Venereology : JEADV / 2009;23(3):344-5</p>	Case report / Case series
<p>Langeland T.; Engh V.</p> <p>Topical use of tacrolimus and squamous cell carcinoma on the penis [8] British Journal of Dermatology, Supplement / 2005;152(1):183-185</p>	Case report / Case series
<p>Lee Y.J.; Kim S.W.; Seo K.Y.</p> <p>Application for Tacrolimus Ointment in Treating Refractory Inflammatory Ocular Surface Diseases American Journal of Ophthalmology / 2013;155(5)</p>	Case report / Case series
<p>Mattsson, Ulf; Magnusson, Bengt; Jontell, Mats</p> <p>Squamous cell carcinoma in a patient with oral lichen planus treated with topical application of tacrolimus. Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics / 2010;110(1):e19-25</p>	Case report / Case series
<p>Miura, Hiroyuki; Itami, Satoshi; Yoshikawa, Kunihiro</p> <p>Treatment of facial lesion of cutaneous plasmacytosis with tacrolimus ointment. Journal of the American Academy of Dermatology / 2003;49(6):1195-6</p>	Case report / Case series
<p>Miyazaki D.; Tominaga T.; Kakimaru-Hasegawa A.; Nagata Y.; Hasegawa J.; Inoue Y.</p> <p>Therapeutic Effects of Tacrolimus Ointment for Refractory Ocular Surface Inflammatory Diseases Ophthalmology / 2008;115(6):988</p>	Case report / Case series
<p>Nikolaou, V; Stratigos, A; Antoniou, C; Kiagia, M; Nikolaou, C; Katsambas, A; Syrigos, K</p> <p>Pimecrolimus cream 1% for the treatment of papulopustular eruption related to epidermal growth factor receptor inhibitors: a case series and a literature review of therapeutic approaches. Dermatology (Basel, Switzerland) / 2010;220(3):243-8</p>	Case report / Case series
<p>Pagliariello C.; Fabrizi G.; Fantini C.; Cortelazzi C.; Boccaletti V.; Annessi G.; Zampetti A.; Feliciani C.; Di Nuzzo S.</p> <p>Calcipotriol/betamethasone dipropionate ointment compared with tacrolimus ointment for the treatment of erosive pustular dermatosis of the scalp: A split-lesion comparison European Journal of Dermatology / 2015;25(2):206-208</p>	Case report / Case series
<p>Pleasant, Latawnya; Skinner, Sean; Pulliam, Joseph; Challa, Harigovinda; D'Orazio, John</p> <p>Burkitt lymphoma in a child with atopic dermatitis and a 7-year history of regular topical tacrolimus use. Cutis / 2012;89(3):117-20</p>	Case report / Case series

Saez M.; Rodriguez-Martin M.; Sidro M.; Carnerero A.; Garcia-Bustinduy M.; Noda A. Successful treatment of erosive pustular dermatosis of the scalp with topical tacrolimus [19] Clinical and Experimental Dermatology / 2005;30(5):599-600	Case report / Case series
Schmook T.; Kraft J.; Benninghoff B.; Nindl I.; Roewert J.; Ulrich C.; Stockfleth E. Treatment of cutaneous chronic graft-versus-host disease with topical pimecrolimus [4] Bone Marrow Transplantation / 2005;36(1):87-88	Case report / Case series
Tam, P M K; Young, A L; Cheng, L L; Lam, P T H Topical 0.03% tacrolimus ointment in the management of ocular surface inflammation in chronic GVHD. Bone marrow transplantation / 2010;45(5):957-8	Case report / Case series
Ueda M.; Makinodan R.; Matsumura M.; Ichihashi M. Successful treatment of amyopathic dermatomyositis with topical tacrolimus [4] British Journal of Dermatology / 2003;148(3):595-596	Case report / Case series
Vecchietti G.; Kerl K.; Hugli A.; Samson J.; Borradori L. Topical tacrolimus (FK506) for relapsing erosive stomatitis in paraneoplastic pemphigus [9] British Journal of Dermatology / 2003;148(4):833-834	Case report / Case series
Vence L.; Thompson C.B.; Callen J.P.; Brown T.S. Giant Porokeratosis with Malignant Transformation to Squamous Cell Carcinoma Dermatologic Surgery / 2018;44(4):580-581	Case report / Case series
Yasuda, Masahito; Amano, Hiroo; Nagai, Yayoi; Tamura, Atsushi; Ishikawa, Osamu; Yamaguchi, Satoru Pyodermatitis-pyostomatitis vegetans associated with ulcerative colitis: successful treatment with total colectomy and topical tacrolimus. Dermatology (Basel, Switzerland) / 2008;217(2):146-8	Case report / Case series
Zhang, Xuepeng; Yang, Kaiying; Chen, Siyuan; Ji, Yi Tacrolimus ointment for the treatment of superficial kaposiform hemangioendothelioma and tufted angioma. The Journal of dermatology / 2019;46(10):898-901	Case report / Case series
Anonymous. Impact of genital lichen sclerosus treatments on occurrence of vulvar neoplasms in 275 adult women Journal of the American Academy of Dermatology / 2018;79(3 Supplement 1):AB158	Conference abstract / poster
Arana A.; Wentworth C.; Conde E. Incidence of lymphoma in a large population of patients with atopic dermatitis, some treated with topical calcineurin inhibitors or topical corticosteroids Allergy: European Journal of Allergy and Clinical Immunology / 2012;67(SUPPL. 96):15	Conference abstract / poster
Arana, A.; Wentworth, C. W.; Rivero, E.; Plana, E.; Conde, E. Lymphoma among Patients with Atopic Dermatitis Treated with Topical Corticosteroids (TCS) and/or Topical Calcineurin Inhibitors (TCIs) Pharmacoepidemiology and Drug Safety 2010;19():S12-S12	Conference abstract / poster

<p>Arana, A.; Wentworth, C. W.; Rivero, E.; Planas, E.; Conde, E.</p> <p>Lymphoma among patients with atopic dermatitis treated with topical corticosteroids and/or topical calcineurin inhibitors</p> <p>Journal of the American Academy of Dermatology 2011;64(2):AB3-AB3</p>	<p>Conference abstract / poster</p>
<p>Arellano, F. M.; Arana, A.; Wentworth, C. E.; Fernandez-Vidaurre, C.; Schlienger, R.; Conde, E.</p> <p>Risk of lymphoma risk among users of topical corticosteroids and topical calcineurin inhibitors. Preliminary results</p> <p>Pharmacoepidemiology and Drug Safety 2007;16():S12-S12</p>	<p>Conference abstract / poster</p>
<p>Arellano, F. M.; Arana, A.; Wentworth, C. E.; Fernandez-Vidaurre, C.; Schlienger, R.; Conde, E.</p> <p>Risk of lymphoma among users of topical corticosteroids and topical calcineurin inhibitors</p> <p>Journal of Investigative Dermatology 2007;127():S62-S62</p>	<p>Conference abstract / poster</p>
<p>Arellano, F. M.; Wentworth, C. E.; Arana, A.; Fernandez, C.; Paul, C.</p> <p>Risk of lymphoma following exposure to calcineurin inhibitors and topical steroids in patients with atopic dermatitis</p> <p>Pharmacoepidemiology and Drug Safety 2006;15():S63-S64</p>	<p>Conference abstract / poster</p>
<p>Armstrong A.; Grabner M.; Stephenson J.; Zhao R.; Mallya U.; Bieszk N.; Miao R.; Gadkari A.; Chao J.</p> <p>Treatment-emergent acute complications from immunosuppressant use in adult patients with atopic dermatitis in the U.S</p> <p>Journal of Managed Care and Specialty Pharmacy / 2018;24(4-A SUPPL.):S78-S79</p>	<p>Conference abstract / poster</p>
<p>Cai S.C.S.; Li W.; Tian E.A.L.; Tang M.B.Y.; Allen J.C.; Tey H.L.</p> <p>Topical tacrolimus in endogenous eczema and cancer association</p> <p>Annals of the Academy of Medicine Singapore / 2014;43(9 SUPPL. 1):S1</p>	<p>Conference abstract / poster</p>
<p>Castellsague J.; Calingaert B.; Rothman K.J.; Gutierrez L.; Van Herk-Sukel M.P.P.; Kuiper J.J.G.; Pottegard A.; Hallas J.; Berglind I.A.; Sundstrom A.; Dedman D.; Gallagher A.; Kaye J.A.; Pardo C.; Perez-Gutthann S.</p> <p>Probabilistic bias analysis for unmeasured confounders in a study of users of topical tacrolimus, pimecrolimus and corticosteroids (JOELLE) study</p> <p>Pharmacoepidemiology and Drug Safety / 2016;25(Supplement 3):142-143</p>	<p>Conference abstract / poster</p>
<p>Castellsague J.; Kuiper J.J.G.; Pottegard A.; Berglind I.A.; Dedman D.; Gutierrez L.; Calingaert B.; Van Herk-Sukel M.P.P.; Hallas J.; Sundstrom A.; Gallagher A.; Kaye J.A.; Pardo C.; Rothman K.J.; Perez-Gutthann S.</p> <p>Risk of lymphoma in users of topical tacrolimus, pimecrolimus and corticosteroids (JOELLE Study)</p> <p>Pharmacoepidemiology and Drug Safety / 2016;25(Supplement 3):494-495</p>	<p>Conference abstract / poster</p>
<p>Castellsague J.; Van Herk-Sukel M.P.P.; Hallas J.; Sundstrom A.; Gallagher A.; Gutierrez L.; Calingaert B.; Kuiper J.J.G.; Pottegard A.; Berglind I.A.; Dedman D.; Kaye J.A.; Pardo C.; Rothman K.J.; Perez-Gutthann S.</p> <p>Risk of skin cancer in users of topical tacrolimus, pimecrolimus and corticosteroids. Joint European Longitudinal Lymphoma and Skin Cancer Evaluation (JOELLE) study</p> <p>Pharmacoepidemiology and Drug Safety / 2016;25(Supplement 3):527</p>	<p>Conference abstract / poster</p>

<p>Craig F.; Greenlaw N.; Harrison E.; Mason J.; Mitchell E.; Norrie J.; Ormerod A.; Thomas K.; Williams H.</p> <p>Clinical outcomes of patients receiving topical treatments for pyoderma gangrenosum: A prospective observational study British Journal of Dermatology / 2014;171(SUPPL. 1):53</p>	<p>Conference abstract / poster</p>
<p>Deleuran, M.; Vestergaard, C.; Thestrup-Pedersen, K.</p> <p>Topical calcineurin inhibitors and cancer in children: a register study British Journal of Dermatology 2014;170(6):E55-E55</p>	<p>Conference abstract / poster</p>
<p>Dell E.; Miest R.; Lohse C.; Torgerson R.</p> <p>Impact of genital lichen sclerosus treatments on occurrence of vulvar neoplasms in 275 adult women Journal of the American Academy of Dermatology / 2018;79(3 Supplement 1):AB158</p>	<p>Conference abstract / poster</p>
<p>Feng, J.; Tsai, A.; Raimondo, D.; Quesenberry, C. P.; Asgari, M.</p> <p>Skin cancer risk among adults with atopic dermatitis exposed to topical calcineurin inhibitors Journal of Investigative Dermatology 2018;138(5):S55-S55</p>	<p>Conference abstract / poster</p>
<p>Godat S.; Fournier N.; Pittet V.; Safroneeva E.; Moradpour D.; Schoepfer A.</p> <p>Frequency and type of side effects of immunomodulating medication in the swiss inflammatory bowel disease cohort Gastroenterology / 2012;142(5 SUPPL. 1):S249</p>	<p>Conference abstract / poster</p>
<p>Gutierrez L.; Booth H.; Dedman D.; Crellin E.; Kaye J.A.; Franzoni C.; Arana A.; Schmitt-Egenolf M.; Sundstrom A.; Bystrom C.</p> <p>Case validation of cutaneous lymphoma to minimize protopathic bias Pharmacoepidemiology and Drug Safety / 2019;28(Supplement 2):315</p>	<p>Conference abstract / poster</p>
<p>Kiiski V.; Remitz A.; Reitamo S.; Peltonen S.; Mandelin J.; Kari O.</p> <p>Safety and efficacy of tacrolimus ointment in the longterm use for atopic blepharoconjunctivitis Acta Ophthalmologica / 2012;90(SUPPL. 250):14</p>	<p>Conference abstract / poster</p>
<p>Kuiper J.G.; Van Herk-Sukel M.P.; Castellsague J.; Pottegard A.; Anveden Berglind I.; Dedman D.; Gutierrez L.; Calingaert B.; Hallas J.; Sundstrom A.; Gallagher A.M.; Kaye J.A.; Pardo C.; Perez-Guttham S.</p> <p>Utilization of topical tacrolimus and topical pimecrolimus in Europe: Results from the joint European longitudinal lymphoma and skin cancer evaluation (Joelle) study Value in Health / 2016;19(7):A573</p>	<p>Conference abstract / poster</p>
<p>Leite M.I.B.A.P.; Leitao C.; Ribeiro A.; Leite A.L.; Osorio E.</p> <p>Childhood granuloma annulare. A 16-year clinical perspective from a Pediatric Hospital Dermatology Department Cogent Medicine / 2017;4(1):</p>	<p>Conference abstract / poster</p>
<p>Liau M.Q.M.; Leung A.J.; Aw C.W.D.</p> <p>5-Year retrospective study of topical calcineurin inhibitor use in a Singaporean tertiary hospital Annals of the Academy of Medicine Singapore / 2016;45(9 Supplement 1):S262</p>	<p>Conference abstract / poster</p>

<p>Manthripragada A.D.; Pinheiro S.P.; MaCurdy T.E.; Saneinejad S.; Graham D.J.</p> <p>Characteristics and patterns of topical calcineurin inhibitor use in children Pharmacoepidemiology and Drug Safety / 2011;20(SUPPL. 1):S76-S77</p>	<p>Conference abstract / poster</p>
<p>Margolis, D.; Hoffstad, O.; Bilker, W.</p> <p>Is there an association between the use of topical calcineurin inhibitors and skin cancer? Journal of Investigative Dermatology 2006;126():48-48</p>	<p>Conference abstract / poster</p>
<p>Margolis, D. J.; Hofstad, O.; Bilker, W.</p> <p>A potential protective effect of topical calcineurin inhibitors with respect to non melanoma skin cancer Pharmacoepidemiology and Drug Safety 2006;15():S257-S258</p>	<p>Conference abstract / poster</p>
<p>Mashiah J.; Kutz A.; Bodemer C.; Rabia S.H.; Goldberg I.; Sprecher E.; Harel A.</p> <p>Topical pimecrolimus for pediatric cutaneous mastocytosis Pediatric Dermatology / 2016;33(SUPPL. 1):S52</p>	<p>Conference abstract / poster</p>
<p>Negoita M.; Sugarman I.; Puntis J.W.L.; Zamvar V.; Vora R.; Grange S.</p> <p>Genital Crohn's disease case series-natural history Journal of Pediatric Gastroenterology and Nutrition / 2017;64(Supplement 1):522-523</p>	<p>Conference abstract / poster</p>
<p>Scarlsbrick J.J.; Dignan F.L.; Tulpule S.; Das gupta E.; Shah G.; Pagliuca A.; Malladi R.; Raj K.</p> <p>A multicentre retrospective UK study detailing onset of graft versus host disease, responses to treatment and outcome after donor lymphocyte infusion following haemopoietic stem cell transplantation: Rates of GVHD are high but death from GVHD infrequent Blood / 2013;122(21):</p>	<p>Conference abstract / poster</p>
<p>Tey H.L.; Cai S.; Li W.; Allen J.</p> <p>Topical calcineurin inhibitors in endogenous eczema and cancer association: A cohort study Acta Dermato-Venereologica / 2015;95(7):891</p>	<p>Conference abstract / poster</p>
<p>Tjahjono L.; Davis M.D.; Tollefson M.; Khan S.; Rodriguez V.; Lehman J.</p> <p>Cutaneous manifestations of pediatric graft-versus-host disease Journal of the American Academy of Dermatology / 2018;79(3 Supplement 1):AB94</p>	<p>Conference abstract / poster</p>
<p>Cooper S.M.; Wojnarowska F.</p> <p>Influence of treatment of erosive lichen planus of the vulva on its prognosis Archives of Dermatology / 2006;142(3):289-294</p>	<p>did not examine association b/n TCI+cancer</p>
<p>Fahy C.M.R.; Torgerson R.R.; Davis M.D.P.</p> <p>Lichen planus affecting the female genitalia: A retrospective review of patients at Mayo Clinic Journal of the American Academy of Dermatology / 2017;77(6):1053-1059</p>	<p>did not examine association b/n TCI+cancer</p>
<p>Godat, Sebastien; Fournier, Nicolas; Safroneeva, Ekaterina; Juillerat, Pascal; Nydegger, Andreas; Straumann, Alex; Vavricka, Stephan; Biedermann, Luc; Greuter, Thomas; Fraga, Montserrat; Abdelrahman, Karim; Hahnloser, Dieter; Sauter, Bernhard; Rogler, Gerhard; Michetti, Pierre; Schoepfer, Alain M; Swiss IBD Cohort Study Group</p> <p>Frequency and type of drug-related side effects necessitating treatment discontinuation in the Swiss Inflammatory Bowel Disease Cohort. European journal of gastroenterology & hepatology / 2018;30(6):612-620</p>	<p>did not examine association b/n TCI+cancer</p>

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Simpson R.C.; Littlewood S.M.; Cooper S.M.; Cruickshank M.E.; Green C.M.; Derrick E.; Yell J.; Chiang N.; Bell H.; Owen C.; Javed A.; Wilson C.L.; McLelland J.; Murphy R. Real-life experience of managing vulval erosive lichen planus: A case-based review and U.K. multicentre case note audit British Journal of Dermatology / 2012;167(1):85-91	did not examine association b/n TCI+cancer
Weyers W. Hypertrophic lichen sclerosus with dyskeratosis and parakeratosis - A common presentation of vulvar lichen sclerosus not associated with a significant risk of malignancy American Journal of Dermatopathology / 2013;35(7):713-721	did not examine association b/n TCI+cancer
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Marquezan M.C.; Nascimento H.; Vieira L.A.; Serapiao M.; Ghanem R.C.; Belfort R.; Freitas D. Effect of Topical Tacrolimus in the Treatment of Thygeson's Superficial Punctate Keratitis American Journal of Ophthalmology / 2015;160(4):663-668	did not examine association b/n TCI+cancer
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Gordon, Melinda K; Kraus, Madeleine; van Besien, Koen Interdigitating dendritic cell tumors in two patients exposed to topical calcineurin inhibitors. Leukemia & lymphoma / 2007;48(4):816-8	duplicate
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Haley, C. T.; Mui, U. N.; Tying, S. K. Safety of Topical Calcineurin Inhibitors for Hailey-Hailey Disease Reply Jama-Journal of the American Medical Association 2018;320(11):1200-1201	Letter/editorial no original data
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Yew Y.W.; Tey H.L. Association between leukemia and topical use of pimecrolimus JAMA Dermatology / 2015;151(12):1390-1391	Letter/editorial no original data
Ribero, S.; Stieger, M.; Quaglino, P.; Hongang, T.; Bornstein, M. M.; Naldi, L.; Borradori, L. Efficacy of topical tacrolimus for oral lichen planus: real-life experience in a retrospective cohort of patients with a review of the literature Journal of the European Academy of Dermatology and Venereology 2015;29(6):1107-1113	no comparator group
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<p>children Acta Dermato-Venereologica / 2007;87(1):54-61</p>	
<p>Tan J.; Langley R. Safety and efficacy of tacrolimus ointment 0.1% (Protopic™) in atopic dermatitis: A Canadian open-label multicenter study Journal of Cutaneous Medicine and Surgery / 2004;8(4):213-219</p>	no comparator group
<p>Dayal, Surabhi; Sahu, Priyadarshini; Gupta, Nidhi Treatment of Childhood Vitiligo Using Tacrolimus Ointment with Narrowband Ultraviolet B Phototherapy. Pediatric dermatology / 2016;33(6):646-651</p>	Outcome - not assessing cancer
<p>Elad S.; Or R.; Resnick I.; Shapira M.Y. Topical tacrolimus - A novel treatment alternative for cutaneous chronic graft-versus-host disease Transplant International / 2003;16(9):665-670</p>	Outcome - not assessing cancer
<p>Fleischer Jr. A.B.; Ling M.; Eichenfield L.; Satoi Y.; Jaracz E.; Rico M.J.; Maher R.M. Tacrolimus ointment for the treatment of atopic dermatitis is not associated with an increase in cutaneous infections Journal of the American Academy of Dermatology / 2002;47(4):562-570</p>	Outcome - not assessing cancer
<p>Hanifin J.M.; Paller A.S.; Eichenfield L.; Clark R.A.; Korman N.; Weinstein G.; Caro I.; Jaracz E.; Rico M.J. Efficacy and safety of tacrolimus ointment treatment for up to 4 years in patients with atopic dermatitis Journal of the American Academy of Dermatology / 2005;53(2 SUPPL. 2):S186-S194</p>	Outcome - not assessing cancer
<p>Kapoor, R.; Hoffstad, O.; Bilker, W.; Margolis, D. J. The Frequency and Intensity of Topical Pimecrolimus Treatment in Children with Physician-Confirmed Mild to Moderate Atopic Dermatitis Pediatric Dermatology 2009;26(6):682-687</p>	Outcome - not assessing cancer
<p>Kuiper J.G.; van Herk-Sukel M.P.P.; Castellsague J.; Pottegard A.; Berglind I.A.; Dedman D.; Gutierrez L.; Calingaert B.; Hallas J.; Sundstrom A.; Gallagher A.M.; Kaye J.A.; Pardo C.; Rothman K.J.; Perez-Gutthann S. Use of Topical Tacrolimus and Topical Pimecrolimus in Four European Countries: A Multicentre Database Cohort Study Drugs - Real World Outcomes / 2018;5(2):109-116</p>	Outcome - not assessing cancer
<p>Kyriakou, A.; Patsialas, C.; Patsatsi, A.; Sotiriadis, D. Treatment of male genital lichen sclerosus with clobetasol propionate and maintenance with either methylprednisolone aceponate or tacrolimus: a retrospective study Journal of Dermatological Treatment 2013;24(6):431-434</p>	Outcome - not assessing cancer
<p>Lubbe J.; Friedlander S.F.; Cribier B.; Morren M.-A.; Garcia-Diez A.; Gelmetti C.; Hofmann H.; Houwing R.H.; Kownacki S.; Langley R.G.B.; Virtanen M.; Wolff K.; Wisseh S.; McGeown C.; Abrams B.; Schneider D. Safety, Efficacy, and Dosage of 1% Pimecrolimus Cream for the Treatment of Atopic Dermatitis</p>	Outcome - not assessing cancer

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<p>MacMillan M.L.; Weisdorf D.J.; Davies S.M.; DeFor T.E.; Burns L.J.; Ramsay N.K.C.; Wagner J.E.; Blazar B.R.</p> <p>Early antithymocyte globulin therapy improves survival in patients with steroid-resistant acute graft-versus-host disease Biology of Blood and Marrow Transplantation / 2002;8(1):40-46</p>	<p>Outcome - not assessing cancer</p>
<p>Mandelin J.; Remitz A.; Virtanen H.; Reitamo S.</p> <p>Recall antigen reactions in patients with atopic dermatitis treated with tacrolimus ointment for 1 year Journal of Allergy and Clinical Immunology / 2008;121(3):777-779</p>	<p>Outcome - not assessing cancer</p>
<p>Mashiah, J; Harel, A; Bodemer, C; Hadj-Rabia, S; Goldberg, I; Sprecher, E; Kutz, A</p> <p>Topical pimecrolimus for paediatric cutaneous mastocytosis. Clinical and experimental dermatology / 2018;43(5):559-565</p>	<p>Outcome - not assessing cancer</p>
<p>Nivenius, E.; van der Ploeg, I.; Jung, K.; Chrissanthou, E.; van Hage, M.; Montan, P. G.</p> <p>Tacrolimus ointment vs steroid ointment for eyelid dermatitis in patients with atopic keratoconjunctivitis Eye 2007;21(7):968-975</p>	<p>Outcome - not assessing cancer</p>
<p>Oskay T.; Kaya Sezer H.; Genc C.; Kutluay L.</p> <p>Pimecrolimus 1% cream in the treatment of vulvar lichen sclerosus in postmenopausal women International Journal of Dermatology / 2007;46(5):527-532</p>	<p>Outcome - not assessing cancer</p>
<p>Patrascu, V; Giurca, Claudia; Ciurea, Raluca Niculina; Georgescu, Claudia Valentina</p> <p>Disseminated granuloma annulare: study on eight cases. Romanian journal of morphology and embryology = Revue roumaine de morphologie et embryologie / 2013;54(2):327-31</p>	<p>Outcome - not assessing cancer</p>
<p>Pereira N.; Brites M.M.; Goncalo M.; Tellechea O.; Figueiredo A.</p> <p>Pyoderma gangrenosum - A review of 24 cases observed over 10years International Journal of Dermatology / 2013;52(8):938-945</p>	<p>Outcome - not assessing cancer</p>
<p>Resende J.P.M.; Das Chaves M.G.A.M.; Aarestrup F.M.; Aarestrup B.V.; Olate S.; Netto H.D.</p> <p>Oral lichen planus treated with tacrolimus 0.1% International Journal of Clinical and Experimental Medicine / 2013;6(10):917-921</p>	<p>Outcome - not assessing cancer</p>
<p>Song J.S.; London W.B.; Hawryluk E.B.; Guo D.; Sridharan M.; Fisher D.E.; Lehmann L.E.; Duncan C.N.; Huang J.T.</p> <p>Risk of melanocytic nevi and nonmelanoma skin cancer in children after allogeneic hematopoietic stem cell transplantation Bone Marrow Transplantation / 2017;52(7):989-997</p>	<p>Outcome - not assessing cancer</p>

<p>Villanueva, Fernanda N; Perez-Simon, Jose Antonio; Silva, Fernando F; Caballero-Velazquez, Teresa T; Sanchez-Guijo, Fermin F; Canizo, Conzuelo C; Vazquez, Lourdes L; Caballero, Dolores D; San Miguel, Jesus F</p> <p>Oral beclomethasone dipropionate for the treatment of gastrointestinal chronic graft-versus-host disease.</p> <p>Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation / 2009;15(10):1331-6</p>	<p>Outcome - not assessing cancer</p>
<p>Wataya-Kaneda, M; Tanaka, M; Nakamura, A; Matsumoto, S; Katayama, I</p> <p>A topical combination of rapamycin and tacrolimus for the treatment of angiofibroma due to tuberous sclerosis complex (TSC): a pilot study of nine Japanese patients with TSC of different disease severity.</p> <p>The British journal of dermatology / 2011;165(4):912-6</p>	<p>Outcome - not assessing cancer</p>
<p>Albert, Michael H; Becker, B; Schuster, F R; Klein, B; Binder, V; Adam, K; Nienhoff, C; Fuhrer, M; Borkhardt, A</p> <p>Oral graft vs. host disease in children--treatment with topical tacrolimus ointment.</p> <p>Pediatric transplantation / 2007;11(3):306-11</p>	<p>Outcome - not assessing cancer</p>
<p>Xu, A. E.; Zhang, D. M.; Wei, X. D.; Huang, B.; Lu, L. J.</p> <p>Efficacy and safety of tacrolimus cream 0.1% in the treatment of vitiligo</p> <p>International Journal of Dermatology 2009;48(1):86-90</p>	<p>Outcome - not assessing cancer</p>
<p>Albuquerque A.; Cappello C.; Cuming T.; De Masi A.; Bowring J.; Rosenthal A.N.; Nathan M.</p> <p>Anal high-grade squamous intraepithelial lesions in pharmacologically immunocompromised patients followed in a referral center</p> <p>Diseases of the Colon and Rectum / 2018;61(11):1267-1272</p>	<p>not treated with TCI</p>
<p>Damento G.M.; Pulido J.S.; Abbott B.A.; Hodge D.O.; Dalvin L.A.</p> <p>TNF-Alpha Inhibition and Other Immunosuppressants in the Development of Uveal and Cutaneous Melanoma</p> <p>Mayo Clinic Proceedings / 2019;94(7):1287-1295</p>	<p>not treated with TCI</p>
<p>Gu Y.; Nordstrom B.L.</p> <p>The risk of malignancy among biologic-naive pediatric psoriasis patients: A retrospective cohort study in a US claims database</p> <p>Journal of the American Academy of Dermatology / 2017;77(2):293</p>	<p>not treated with TCI</p>
<p>Kesic, L.; Obradovic, R.; Mihailovic, D.; Radicevic, G.; Stankovic, S.; Todorovic, K.</p> <p>Incidence and treatment outcome of oral lichen planus in southeast Serbia in a 10-year period (1997-2007)</p> <p>Vojnosanitetski Pregled 2009;66(6):435-439</p>	<p>not treated with TCI</p>
<p>Kirtschig, G.; Wakelin, S. H.; Wojnarowska, F.</p> <p>Mucosal vulval lichen planus: outcome, clinical and laboratory features</p> <p>Journal of the European Academy of Dermatology and Venereology 2005;19(3):301-307</p>	<p>not treated with TCI</p>
<p>Michajlowski I.; Panek D.; Sobjanek M.; Michajlowski J.; Wlodarkiewicz A.</p> <p>Malignant transformation in patients with penile lichen sclerosis</p> <p>Przegląd Dermatologiczny / 2012;99(4):390-391</p>	<p>not treated with TCI</p>

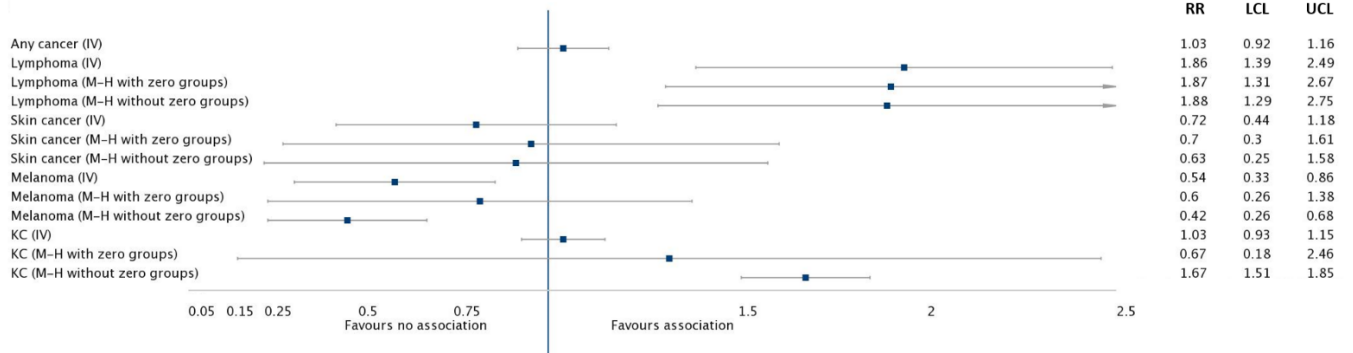
Mithoefer A.B.; Supran S.; Freeman R.B. Risk factors associated with the development of skin cancer after liver transplantation Liver Transplantation / 2002;8(10):939-944	not treated with TCI
Saigal S.; Norris S.; Muiesan P.; Rela M.; Heaton N.; O'Grady J. Evidence of differential risk for posttransplantation malignancy based on pretransplantation caused in patients undergoing liver transplantation Liver Transplantation / 2002;8(5):482-487	not treated with TCI
Dyer, R. K.; Weinstock, M. A.; Cohen, T. S. D.; Rizzo, A. E.; Bingham, S. F.; Grp, Vattc Trial Predictors of Basal Cell Carcinoma in High-Risk Patients in the VATTC (VA Topical Tretinoin Chemoprevention) Trial Journal of Investigative Dermatology 2012;132(11):2544-2551	not treated with TCI
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Bernard L.A.; Eichenfield L.F. Topical immunomodulators for atopic dermatitis Current Opinion in Pediatrics / 2002;14(4):414-418	Review article
DePry J.L.; Reed K.B.; Cook-Norris R.H.; Brewer J.D. Iatrogenic immunosuppression and cutaneous malignancy Clinics in Dermatology / 2011;29(6):602-613	Review article
Fleischer, Alan B Jr Black box warning for topical calcineurin inhibitors and the death of common sense. Dermatology online journal / 2006;12(6):2	Review article
Furue M.; Uchi H.; Moroi Y.; Ogawa S.; Nakahara T.; Urabe K. Topical tacrolimus in the management of atopic dermatitis in Japan Dermatologic Therapy / 2006;19(2):118-126	Review article
Hultsch, Thomas; Kapp, Alexander; Spergel, Jonathan Immunomodulation and safety of topical calcineurin inhibitors for the treatment of atopic dermatitis. Dermatology (Basel, Switzerland) / 2005;211(2):174-87	Review article
Kapp A.; Allen B.R.; Reitamo S. Atopic dermatitis management with tacrolimus ointment (Protopic) Journal of Dermatological Treatment / 2003;14(SUPPL. 1):5-16	Review article
Kida A.; McDonald G.B. Gastrointestinal, hepatobiliary, pancreatic, and iron-related diseases in long-term survivors of allogeneic hematopoietic cell transplantation Seminars in Hematology / 2012;49(1):43-58	Review article
Kuijken I.; Bouwes Bavinck J.N. Skin cancer risk associated with immunosuppressive therapy in organ transplant recipients:	Review article

Epidemiology and proposed mechanisms BioDrugs / 2000;14(5):319-329	
Langa, Y.; Van der Merwe, E. Atopic dermatitis: tacrolimus vs. topical corticosteroid use Sa Pharmaceutical Journal Incorporating Pharmacy Management 2016;83(3):11-+	Review article
Langa Y.; Van Der Merwe E. Atopic dermatitis - Tacrolimus vs topical corticosteroid use SA Pharmaceutical Journal / 2010;77(10):50-56	Review article
Lebwohl, Mark; Gower, Tara A safety assessment of topical calcineurin inhibitors in the treatment of atopic dermatitis. MedGenMed : Medscape general medicine / 2006;8(4):8	Review article
Lok C.; Viseux V.; Denoeux J.P.; Bagot M. Post-transplant cutaneous T-cell lymphomas Critical Reviews in Oncology/Hematology / 2005;56(1 SPEC. ISS.):137-145	Review article
McPherson, Tess; Cooper, Susan Vulval lichen sclerosus and lichen planus. Dermatologic therapy / 2010;23(5):523-32	Review article
Munzenberger, Paul J; Montejo, Jenny M Safety of topical calcineurin inhibitors for the treatment of atopic dermatitis. Pharmacotherapy / 2007;27(7):1020-8	Review article
Nicholson S. Management of metastatic skin cancers in organ transplant recipients Skin Cancer after Organ Transplantation Cancer Treatment and Research / 2009;146((Nicholson) University Hospitals of Leicester, Leicester, United Kingdom):467-481	Review article
Qureshi A.A.; Fischer M.A. Topical calcineurin inhibitors for atopic dermatitis: Balancing clinical benefit and possible risks Archives of Dermatology / 2006;142(5):633-637	Review article
Saraswat A. Topical corticosteroid use in children: Adverse effects and how to minimize them Indian Journal of Dermatology, Venereology and Leprology / 2010;76(3):225-228	Review article
Schreve B.S.; Anliker M.; Arnold A.W.; Kempf W.; Laffitte E.; Lapointe A.-K.; Mainetti C.; Pelloni F.; Oberholzer P.; Serra A.; Streit M.; Hofbauer G.F.L. Pre- and posttransplant management of solid organ transplant recipients: Risk-adjusted follow-up Transplantation Dermatology Current Problems in Dermatology / 2012;43((Schreve, Kempf, Serra, Hofbauer) Dermatologische Klinik, Universittsspital Zurich, Gloriastrasse 31, CH-8091 Zurich, Switzerland (Anliker) Kantonsspital St. Gallen, Lausanne, Switzerland (Arnold) Universitatsspital Basel, Lausanne, Switzerland (Laffitte) Ho):57-70	Review article

<p>Stockfleth, E; Ulrich, C; Meyer, T; Christophers, E</p> <p>Epithelial malignancies in organ transplant patients: clinical presentation and new methods of treatment. Recent results in cancer research. Fortschritte der Krebsforschung. Progres dans les recherches sur le cancer / 2002;160(r1y, 0044671):251-8</p>	Review article
<p>Thaci, Diamant; Salgo, Rebekka</p> <p>The topical calcineurin inhibitor pimecrolimus in atopic dermatitis: a safety update. Acta dermatovenerologica Alpina, Pannonica, et Adriatica / 2007;16(2):58-62</p>	Review article
<p>Thaci, Diamant; Salgo, Rebekka</p> <p>Malignancy concerns of topical calcineurin inhibitors for atopic dermatitis: facts and controversies. Clinics in dermatology / 2010;28(1):52-6</p>	Review article
<p>Weischer, Maren; Rocken, Martin; Berneburg, Mark</p> <p>Calcineurin inhibitors and rapamycin: cancer protection or promotion?. Experimental dermatology / 2007;16(5):385-93</p>	Review article
<p>Werfel T.</p> <p>Topical use of pimecrolimus in atopic dermatitis JDDG - Journal of the German Society of Dermatology / 2009;7(9):739-742</p>	Review article
<p>Wolff K.; Stuetz A.</p> <p>Pimecrolimus for the treatment of inflammatory skin disease Expert Opinion on Pharmacotherapy / 2004;5(3):643-655</p>	Review article
<p>Yesudian, Paul D</p> <p>The role of calcineurin inhibitors in the management of lichen sclerosus. American journal of clinical dermatology / 2009;10(5):313-8</p>	Review article

eFigure 1. Summary of Meta-analyses of Cancer Risk With TCI Treatment and Nonactive Comparator in Cohort Studies

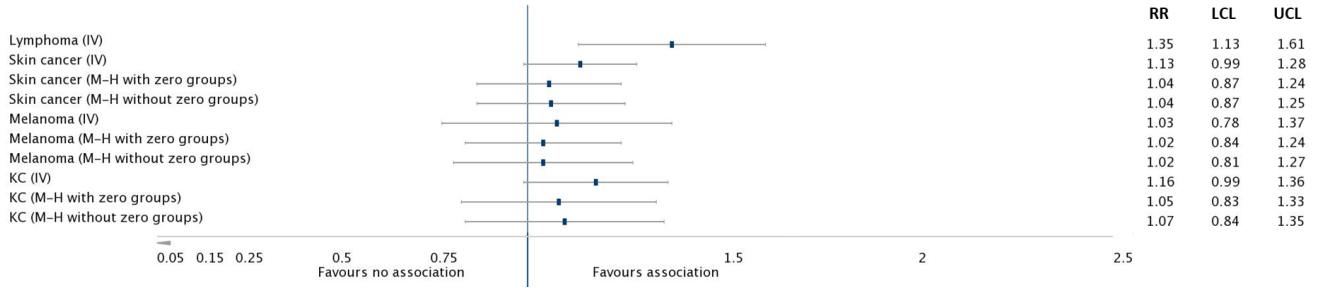
TCI Cancer Risk with Non-Active Comparator



Abbreviations: IV, Inverse Variance; M-H, Mantel-Haenszel; KC, Keratinocyte Carcinoma; RR, Relative Risk; Plot generated by DistillerSR Forest Plot Generator from Evidence Partners

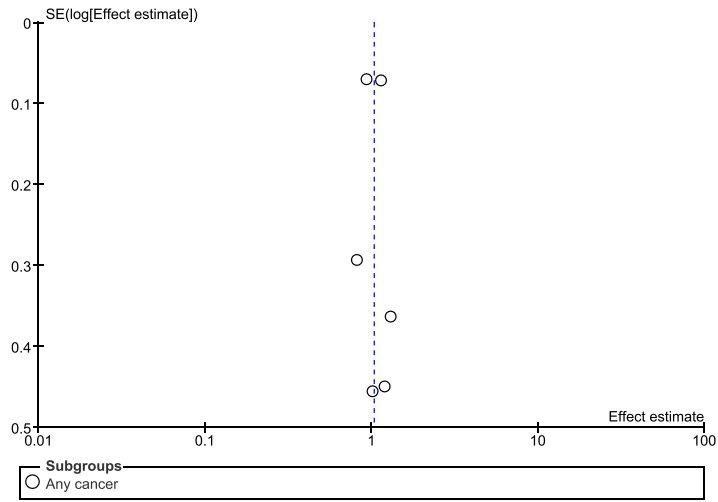
eFigure 2. Summary of Meta-analyses of Cancer Risk With TCI Treatment and TCS Comparator in Cohort Studies

TCI Cancer Risk with Active Comparator

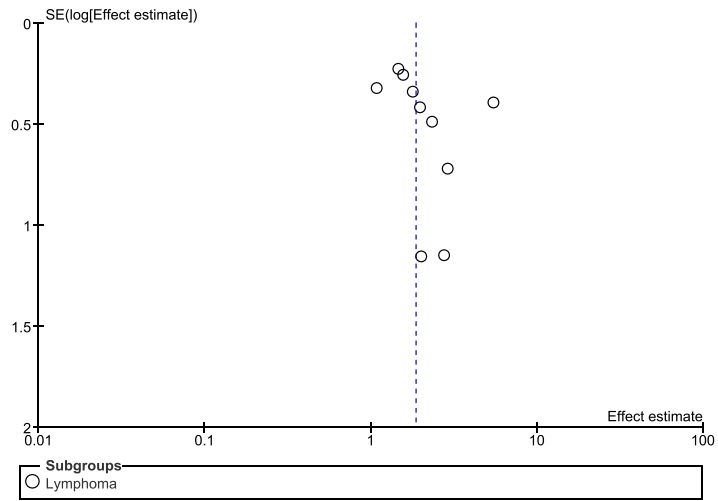


Abbreviations: IV, Inverse Variance; M-H, Mantel-Haenszel; KC, Keratinocyte Carcinoma; Plot generated by DistillerSR Forest Plot Generator from Evidence Partners

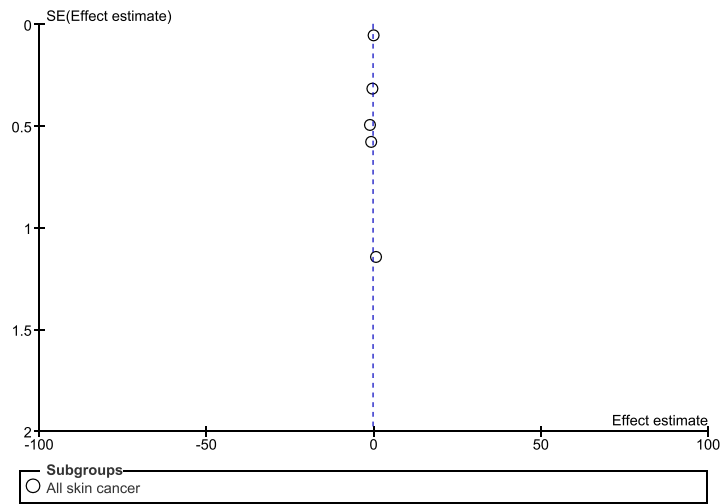
eFigure 3. Funnel Plot for Any Cancer With Nonactive Comparator



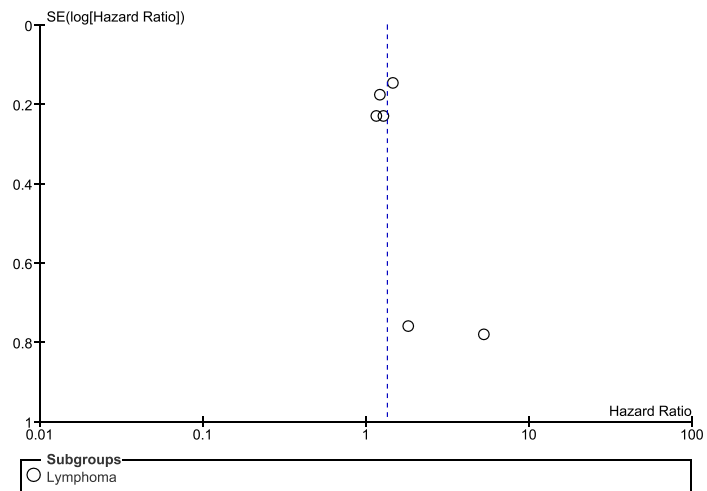
eFigure 4. Funnel Plot for Lymphoma With Nonactive Comparator



eFigure 5. Funnel Plot for Skin Cancer With Nonactive Comparator



eFigure 6. Funnel Plot for Lymphoma With TCS Comparator



eFigure 7. Funnel Plot for Skin Cancer With TCS Comparator

