UNIVERSIDAD NACIONAL AUTÓNOMA DE MÉXICO
FACULTAD DE MEDICINA
DIVISIÓN DE ESTUDIOS DE POSGRADO E INVESTIGACIÓN

SECRETARÍA DE SALUD DE LA CIUDAD DE MÉXICO
DIRECCIÓN DE FORMACIÓN, ACTUALIZACIÓN MÉDICA E INVESTIGACIÓN

CURSO UNIVERSITARIO DE ESPECIALIZACIÓN EN

DERMATOLOGÍA

INTERVENTIONS FOR PREVENTING KERATINOCYTIC CANCER IN PATIENTS WITH HISTORY OF A PREVIOUS KERATINOCYTIC CARCINOMA: A SYSTEMATIC REVIEW.

TRABAJO DE INVESTIGACIÓN

BIBLIOGRÁFICA

PRESENTADO POR

DRA. MARÍA JOSÉ GARCÍA ALONSO

PARA OBTENER EL GRADO DE ESPECIALISTA EN

DERMATOLOGÍA

DIRECTOR DE TESIS

DR. FERMÍN JURADO SANTA CRUZ

CIUDAD DE MÉXICO, 2022

Interventions for preventing keratinocytic cancer in patients with history of a previous keratinocytic carcinoma: A systematic review.

María José García-Alonso, MD, María Luisa Peralta-Pedrero, MD, MSc, Fermín Jurado-Santa Cruz, MD, and Martha Alejandra Morales-Sánchez, MD, MSc

Education and Research Unit, Centro Dermatológico "Dr. Ladislao de la Pascua", México City, Mexico

Correspondence

Martha Alejandra Morales-Sánchez, MD, MSc

Centro Dermatológico "Dr. Ladislao de la Pascua"

Dr. José María Vértiz No. 464 Col. Buenos Aires 06780 Mexico City, Mexico

Telephone: 55 55 38 70 33

E-mail: marthamoralessanchez@gmail.com

Manuscript word count: 3006

Abstract word count: 170

Tables: 1

Figures: 3

Conflict of interest: None.

Funding source: None.

Running head: Interventions to prevent keratinocytic cancer

ABSTRACT

Keratinocyte cancer (KC) is the most common cancer worldwide. To our knowledge, no previous systematic reviews on interventions for their prevention on patients with a previous history of a KC have been published. We aim to review the existent literature to assess the efficacy and safety of interventions to prevent KC in patients with a history of previous KC. We searched clinical trials in which the main outcome was the prevention of KC in patients with previous history of KC using the strategy published in the International Prospective Register of Systematic Reviews (PROSPERO registry), CRD42016045981. We analyzed 18 clinical trials, from which 8 reported a benefit with their respective intervention, but had methodological flaws and a variable risk of bias. Two clinical trials (regarding celecoxib and oral supplementation with nicotinamide) seemed to have the most beneficial results reducing incidence of KC in treated groups. However, all of the studies are highly heterogeneous, which does not allow a meta-analysis to be performed. New studies with greater epidemiological value should be conducted.

INTRODUCTION

Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), also called squamous or epidermoid carcinoma, are usually grouped under the term keratinocytic carcinoma (KC), alluding to the origin of these neoplasms, since both arise from keratinocytes. Keratinocytic carcinoma represents the most common neoplasm in low phototype populations, with up to 3 million cases diagnosed each year worldwide, according to the World Health Organization.[1,2] It has been observed that the incidence of KC has increased in recent years and it is believed to be associated with increased exposure to known risk factors, such as ultraviolet radiation (UVR), among others.[1] This type of neoplasm has an important impact as a burden of disease for both, healthcare systems and patients, due to the morbidity associated with treatments and the disease itself. The personal history of a KC is a predictor for the development of a subsequent KC in up to 29%, depending on the type of carcinoma, and this risk increases with each subsequent KC, reaching up to 93% after the third KC,[3,4] that is why prevention is essential in this group of patients.

Many interventions have been described on prevention of KC, including the use of sunscreen,[5,6,7] DNA repair enzymes,[8,9] retinoids,[10,11]non-steroidal anti-inflammatory drugs (NSAIDs),[12,13,14] antioxidants (beta-carotene, selenium, zinc, vitamin C),[15,16,17,18] photodynamic therapy (PDT),[19] endonuclease, 8-oxoguanine glycosylase, and other dietary compounds such as sulforaphane (SFN), epigallocatechin-3-gallate (EGCG) and nicotinamide have been studied among with educational and lifestyle modification measures.[20,21]

Despite what was found in the literature review, results of studies are contradictory and controversial. There is a systematic review that studies the effect of interventions to prevent skin cancer in high-risk patients,[22] but up to date, no systematic review or meta-analysis has been carried out to determine the most effective intervention for prevention of KC in patients with a previous history of KC. In this regard, the objective of this systematic review is to determine the efficacy and safety of interventions to prevent keratinocytic cancer in patients with a history of previous keratinocytic cancer.

MATERIALS AND METHODS

Search strategy, data extraction, management, and risk of bias

The Cochrane Skin Information Specialist searched the PubMed, OVID, CENTRAL, Clinical Trials, LILACS, and SciELO databases up to July 7th 2021. The search strategy and information on data collection and analysis, including details on unpublished trials, citation indexes, dissertations and theses databases, grey literature, adverse effects, and risk of bias, was made based on the published registry International Prospective Register of Systematic Reviews (PROSPERO), CRD42016045981.

Selection criteria

We only included randomised controlled trials (RCTs) that aim to prevent keratinocyte cancer in patients with personal history of a previous KC (participants of any age, gender, ethnic background, or socioeconomic status). We included studies whose participants have personal history of a KC confirmed by biopsy. Regarding interventions

and outcomes, we included all topical and oral agents used for preventing keratinocyte cancer compared with placebo, no treatment, other topical or oral agents, or a different formulation, concentration, dose, frequency, or duration of the same agent. We also included educational interventions to promote sun protective behaviours and dietary modifications. Primary outcome was the incidence of subsequent KCs and time to subsequent KC.

We excluded quasi-experimental studies, also excluded studies where participants are receiving immunosuppressive therapy, studies whose participants have cutaneous squamous cell carcinoma in situ or Bowen's disease, long-standing ulcer or scar, personal history of long-term psoralen and ultraviolet A (PUVA) treatment, chronic arsenic exposure, history of radiation therapy, genodermatoses or hereditary cancer syndromes, like xeroderma pigmentosum, oculocutaneous albinism, epidermolysis bullosa, epidermodysplasia verruciformis, Fanconi anaemia, dyskeratosis congenita, Rothmund-Thomson syndrome, Bloom syndrome, Werner syndrome, nevoid basal cell carcinoma syndrome, Rombo syndrome, or Basex-Dupré-Christol syndrome.

RESULTS

A total of 14,222 references were identified through electronic database searches and were screened by title and abstract. After exclusion of duplicate and irrelevant references, a total of 223 articles were deemed relevant and were reviewed in full text and assessed for eligibility based on our inclusion and exclusion criteria. All articles

were screened according to the scheme presented in Fig. 1. A total of 18 studies were included and analysed, all of them being prospective controlled trials.

Among the 18 studies included in the review, 13 of them exclusively included primary outcomes about new keratinocyte cancers, and 5 included outcomes about KC and/or actinic keratoses (AK). Table 1 summarizes the studies included in the analysis.

Risk of bias and methodological quality was assessed using the Cochrane Collaboration risk of bias tool. Risk of bias graph and summary are shown in Figs. 2 and 3, respectively.

Retinoids

Five trials studied the effect of retinoids in prevention of new KC, only one of them using a topical formulation. Weinstock *et al*.[11] reported the use of topical retinoid tretinoin 0.1% for up to 5.5 years, but the tretinoin and control groups did not differ in time to occurrence of any of the skin cancer end points or in actinic keratosis counts. The proportion developing either BCC or invasive SCC was 41% and 44% at 2 years and 65% in each group at 5 years, with a non statistically significant p value.

Moon *et al*.[23] treated 2297 patients with oral retinol vs. placebo, and 526 subjects had a new KC. Subjects in the retinol vs placebo group showed a HR for first SCC of 0.74 (95% CI, 0.56-0.99), and HR 1.06 (95% CI, 0.86-1.32) for first BCC, concluding only slight benefit in prevention of SCC (p=0.04) but not BCC or KC as a whole. Levine *et al*.[24] studied administration of oral retinol, isotretinoin or placebo during 3 years on 525

patients, using time to occurrence as outcome measure. Of the 125 total SCC diagnosed during the follow-up period, retinol-treated patients accounted for 32.8%, isotretinoin 32% and placebo 32.8%. While from the 319 BCC, 33.2% corresponded to retinol group, 32.2% isotretinoin and 34.4% placebo. No differences were observed between groups with any of the interventions. Tangrea *et al*.[25] also studied oral administration of isotretinoin in 981 patients, and no statistically significant difference in either the cumulative percent of patients with an occurrence of basal cell carcinoma at a new site or the annual rate of basal cell carcinoma formation existed, but adverse effects such as hypertriglyceridemia, skeletal and mucocutaneous reactions were reported with statistical significance in the intervention group. Kadakia *et al*.[26] treated 70 patients with acitretin vs placebo and no statistically significant reduction in new KC was shown (OR 0.41; 95% CI, 0.15- 1.13; 54% vs 74%), and once again, significantly more adverse reactions were reported in the intervention group.

Topical therapies

Seven trials studied the use of other topical treatments, either alone, combined or in different intervention arms. Three of them compared different modalities of photodynamic therapy (Dixon *et al*., Marcus *et al*. and Sotiriou *et al*.),[19,27,28] Three studies included 5-fluorouracil, either alone, combined or vs other intervention or placebo (Weinstock 2018 *et al*., Rosenberg *et al*., and Hantash *et al*.).[29,30,31] And other agents included calcipotriol, trichloroacetic acid (TCA) and carbon dioxide laser.[30,31]

Dixon *et al*.[19] found that over the 3 year period of their study, 38% of intervention patients and 38% of the control group developed 30 and 22 new KC, respectively. Additionally, intervention patients experienced adverse effects such as pain, scars and blistering, the trial was suspended early. On the other hand Marcus *et al*.[27] compared chemoprevention with δ-Aminolevulinic acid-photodynamic therapy (ALA-PDT) 2 vs 3 sessions vs vehicle-PDT, and found that 3 sessions of ALA-PDT significantly reduced the occurrence of AK and the rate of KC development over time compared to vehicle (post hoc analysis, p= 0.0014). Sotiriou *et al*.[28] studied methyl-aminolevulinate-PDT (MAL-PDT) vs imiquimod 5%, reporting a mean time to occurrence of new lesions was 9.56 (PDT) (95% CI 8.10–11.01) vs. 10.09 months (imiquimod 5%) (95% CI 8.38–10.36), but in terms of new KC, no statistically significant difference between the two fields was found, at any time point of follow-up.

Weinstock 2018 *et al*.[29] studied 5-fluorouracil; during the first year of follow-up, 20 participants of the control group developed a SCC, while only 5 participants of the intervention group did. However, at the end of the 4 year follow-up period, no reduction was seen for the development of either SCC nor BCC. Rosenberg *et al*.[30] on the other hand, reported that 5-fluorouracil in combination with calcipotriol for treatment of AK might be an effective therapy for prevention of new KC through induction of tissue-resident memory T cells. Fewer patients in the intervention arm developed SCC on the treated area within 3 years (2 of 30 vs 11 of 40 on the placebo arm, HR 0.215 95% CI, 0.048-0.972 p=0.032). Resurfacing with different techniques was studied by Hantash *et al*.[31]; 34 patients were initially included, but some of them were finally

excluded because of protocol violations, only including 24 of them on the final analysis. The rate of new KC in the TCA arm was lower by 3.75 to 5.25 fold vs the other two arms, but no statistically significant differences were reported between the treatment groups because of the sample size.

The last topical agent found was studied by Naylor *et al*.,[32] where 50 patients were randomized to use 29 SPF sunscreen vs placebo, data was reported on AK, but KC numbers were too small for statistical analysis.

Oral therapies

Among other oral therapies, multiple preparations were studied, with the aim of acting at different key points along the carcinogenic pathway. Bailey *et al*.[33] conducted a clinical trial using α-difluoro-methylornithine (DFMO) to inhibit the ornithine decarboxylase (ODC) and therefore, decrease tissue concentrations of polyamines. Even though the primary endpoint of new KC was not met, and the subanalysis of new BCC and SCC showed little difference between treatment groups, a significant difference in new BCC was shown with an event rate of 0.28 BCC per person per year in the DMFO group vs 0.40 in the placebo group, p=0.03.

Chen *et al*.[34] reported the use of nicotinamide and the study reported a lower rate of new KC by 23% (95% CI 4 to 38) when compared to placebo, and similar results were shown when analyzed by groups with new BCC 20% lower rate (95% CI, −6 to 39), new SCC by 30% (95% CI, 0 to 51), and AK with 13% lower rate in the intervention groups.

Worth mentioning that the trend toward effectiveness of nicotinamide was shown among patients who had had a higher number of KC in the 5 years before baseline, and the interaction term was significant (P=0.02) when the KC count in the previous 5 years was treated as a continuous covariate, but not significant (P=0.18) it was treated as a categorical covariate. Also, no benefit after nicotinamide discontinuation was shown.

Clark *et al*.[35] found that after selenium supplementation in patients with KC history, RR for a new BCC was 1.14 (95% CI, 0.95-1.28) and a new SCC RR was 1.14 (95% CI, 0.93-1.39), concluding selenium supplementation did not significantly reduced incidence of new KC.

Greenberg *et al*.[36] studied β-carotene supplementation after a 5-year follow-up period and found no difference between the groups in the rate of occurrence of new KC (RR 1.05, 95% CI, 0.91-1.22) nor treated vs control groups in the mean number of new KC per patient-year. Cyclooxygenase 2 (COX-2) inhibition has shown to play an important role in reducing UV-induced carcinogenesis pathways.

Elmets et al.[37] studied celecoxib chemoprevention for AK and KC in 240 subjects. At 11 months after randomization, fewer KC were reported in the intervention group vs placebo (RR 0.43, 95% CI, 0.24 - 0.75), which persisted after adjusting for factors such as age, sex, Fitzpatrick skin type, etc.

Diet

Jaax et al.[38] evaluated the impact of a low-fat diet in reducing occurrence of skin cancer. KC occurrence in control group did not change from baseline period, on the other hand, KC in the intervention group was significantly lower, but only in the last eight-month period of follow-up compared to baseline; cumulative numbers of KC per patient per time period was 0.21 (control) vs 0.19 (intervention) during the first 8-month period of the study, and 0.26 (control) vs 0.02 (intervention) during the last 8 months.

DISCUSSION

All of the studies included in this systematic review show great heterogeneity in terms of outcomes, time to outcome and units of measurement, as well as duration of the interventions themselves, which does not allow a meta-analysis to be performed. Also, there are studies with very small patient samples and a short follow-up period, such as Hantash et al. with 24 patients or Elmets *et al*.[38] which intervention and follow-up period lasted only 10 months, so the methodology of these studies could improve to have more consistent and accurate results.

Of the 18 studies included in the review, 8 studies report a benefit with their respective intervention, that is, a decrease in the incidence of a new keratinocytic skin cancer. Of these studies, 6 of them that evaluated different treatment options, seem promising interventions (use of oral retinol, photodynamic therapy, DMFO, 5-fluorouracil and 5-fluorouracil with calcipotriol),[23,27,29,30,33,38] however, these are studies that have a high risk of bias for different reasons, so no decisive recommendation can be made on the use of the studied treatments.

Regarding the 2 remaining interventions, which are the use of celecoxib and oral supplementation with nicotinamide, these do seem to have a protective effect that reduces the incidence of KC. Finding on Elmets *et al*.[37] study showed that patients treated with celecoxib 200mg twice a day for 9 months developed fewer KC than placebo-treated patients, however, their primary endpoint only considered AK and the effect on new KC incidence was shown in exploratory analyses, however results were very promising and authors conclude that other studies on this medication should be conducted measuring KC as a primary endpoint. It is of interest that results were significant on new SCC but not AK, which are their precursor lesions, and authors propose mechanisms that may explain how celecoxib could inhibit the progression of premalignant keratinocytes to invasive malignancies, including an antiproliferative effect promoting apoptosis, inhibition of myeloid suppressor cells, and suppression of the epithelial–mesenchymal transition process.[37]

Special attention should be paid to the cardiovascular and thrombotic risk concerns on COX-2 selective NSAIDS. The “Prospective Randomized Evaluation of Celecoxib Integrated Safety vs Ibuprofen or Naproxen” (PRECISION) Trial was conducted in 2006; it was a large, randomized, double-blind controlled trial to determine risk of celecoxib when compared to ibuprofen and naproxen in the treatment of arthritis pain, and cardiovascular, gastrointestinal and renal safety were also assessed.[39] Results demonstrated that celecoxib at the lowest dose of 100mg twice daily did not have worse cardiovascular outcomes than the other NSAIDS, but too few patients received higher

doses to evaluate such dose-dependent risks.[39] Considerations must be taken in this regard for future studies, as the dose studied by Elmets et al. was 200mg twice a day.

Findings on Chen *et al*.[34] study showed that nicotinamide, vitamin B3, at dose of 500mg twice daily for 12 months have a protective effect on UV damage and reduces new premalignant and malignant (KC) lesions. Rate of new KC was lower in the intervention arm by 23% and a similar protective effect on SCC and BCC, with a good safety profile, since nicotinamide has been used at pharmacologic doses (up to 3g daily) for long periods of time with minimal side effects. These results shed light on a new form of chemoprevention using a highly accessible and safe vitamin supplement for high-risk patients, but it is important to conduct studies with a longer follow-up period.

The main limitation of this review is the heterogeneity of the studies, their methods and outcomes, which do not allow to perform a meta-analysis. Regarding the characteristics of the studies, the validity of results of randomized clinical trials depend on the quality of performance and reporting of the results; this was issued by Morales *et al*.[40] in a systematic review where they aimed to determine the risk of bias and the quality of published clinical trials on prevention of KC in high risk groups, and found that most of the clinical trials reported in their study (most of them also included in this review) had a high risk of bias, mainly because of lack of important methodological aspects such as performance, attrition and reporting. Therefore, evidence of efficacy and safety of some interventions is compromised because of their high risk of bias. However, many of the interventions showed interesting and promising results with theoretical bases that could

be applied to clinical practice, so the interventions that showed no conclusive results should be retested in studies with greater epidemiological value.

CONCLUSION

In conclusion, the current level of evidence on interventions to prevent new KC on patients with a previous history of a KC is limited and very heterogeneous. From the data available, nicotinamide and celecoxib therapy appear to be the most effective measures, considering some details on dose and time of administration. Taking into account that the population targeted by these interventions are mostly older adults with certain comorbidities, nicotinamide appears to be the preferred option because of its safety profile. Other interventions include oral retinol, photodynamic therapy with aminolevulinic acid, 5-fluorouracil either alone or combined with calcipotriol, α-difluoro-methylornithine, and low-fat diet, but more studies with lower risk of bias and a finer methodological structure with homogeneous outcomes that allow to perform a meta-analysis are needed to make specific recommendations.

REFERENCES

1. Albert MR, Weinstock MA. Keratinocyte carcinoma. CA: A Cancer Journal for Clinicians. 2003;53(5):292–302.
2. Radiation: Ultraviolet (uv) radiation and skin cancer [Internet]. World Health Organization. World Health Organization; [cited 2021Sep7]. Available from: https://www.who.int/news-room/q-a-detail/radiation-ultraviolet-(uv)-radiation-and-skin-cancer

3. Marcil I, Stern RS. Risk of developing a subsequent nonmelanoma skin cancer in patients with a history of nonmelanoma skin cancer. Archives of Dermatology. 2000;136(12).
4. Flohil SC, van der Leest RJT, Arends LR, de Vries E, Nijsten T. Risk of subsequent cutaneous malignancy in patients with prior keratinocyte carcinoma: A systematic review and meta-analysis. European Journal of Cancer. 2013;49(10):2365–75.
5. Hirst NG, Gordon LG, Scuffham PA, Green AC. Lifetime cost-effectiveness of skin cancer prevention through promotion of daily sunscreen use. Value in Health. 2012;15(2):261–8.
6. van der Pols JC, Williams GM, Pandeya N, Logan V, Green AC. Prolonged prevention of squamous cell carcinoma of the skin by regular sunscreen use. Cancer Epidemiology Biomarkers & Prevention. 2006;15(12):2546–8.
7. Silva Esaes, Tavares R, Paulitsch Fda, Zhang L. Use of sunscreen and risk of melanoma and non-melanoma skin cancer: A systematic review and meta-analysis. European Journal of Dermatology. 2018;28(2):186–201.
8. Emanuele E. Reduced ultraviolet-induced dna damage and apoptosis in human skin with topical application of a photolyase-containing dna repair enzyme cream: Clues to skin cancer prevention. Molecular Medicine Reports. 2011.
9. Emanuele E, M Spencer J, Braun M. An experimental double-blind irradiation study of a novel topical product (TPF 50) compared to other topical products with DNA repair enzymes, antioxidants, and growth factors with sunscreens:

implications for preventing skin aging and cancer. J Drugs Dermatol . 2014Mar;13(3):309–14.

10. Alizadeh F, Bolhassani A, Khavari A, Bathaie SZ, Naji T, Bidgoli SA. Retinoids and their biological effects against cancer. International Immunopharmacology. 2014;18(1):43–9.
11. Weinstock MA, Bingham SF, Digiovanna JJ, Rizzo AE, Marcolivio K, Hall R, Eilers D, Naylor M, Kirsner R, Kalivas J, Cole G, Vertrees JE; Veterans Affairs Topical Tretinoin Chemoprevention Trial Group. Tretinoin and the prevention of keratinocyte carcinoma (Basal and squamous cell carcinoma of the skin): a veterans affairs randomized chemoprevention trial. J Invest Dermatol. 2012 Jun;132(6):1583-90. doi: 10.1038/jid.2011.483. Epub 2012 Feb 9. PMID: 22318383.
12. Liebman TN, Stein JA, Polsky D. Cyclo-oxygenase-2 inhibitors for chemoprevention of nonmelanoma skin cancer: is there a role for these agents? J Am Acad Dermatol. 2013 Jan;68(1):173-6. doi: 10.1016/j.jaad.2012.06.037. PMID: 23244374.
13. Clouser MC, Roe DJ, Foote JA, Harris RB. Effect of non-steroidal anti-inflammatory drugs on non-melanoma skin cancer incidence in the SKICAP-AK trial. Pharmacoepidemiol Drug Saf. 2009 Apr;18(4):276-83. doi: 10.1002/pds.1718. PMID: 19226541.
14. Zhang B, Liang X, Ye L, Wang Y. No chemopreventive effect of nonsteroidal anti-inflammatory drugs on nonmelanoma skin cancer: evidence from

meta-analysis. PLoS One. 2014 May 14;9(5):e96887. doi: 10.1371/journal.pone.0096887. PMID: 24828489; PMCID: PMC4020781.

15. Foote JA, Ranger-Moore JR, Einspahr JG, Saboda K, Kenyon J, Warneke J, Miller RC, Goldman R, Xu MJ, Roe DJ, Alberts DS. Chemoprevention of human actinic keratoses by topical DL-alpha-tocopherol. Cancer Prev Res (Phila). 2009 Apr;2(4):394-400. doi: 10.1158/1940-6207.CAPR-08-0210. Epub 2009 Mar 31. PMID: 19336724; PMCID: PMC4154592.
16. Murray JC, Burch JA, Streilein RD, Iannacchione MA, Hall RP, Pinnell SR. A topical antioxidant solution containing vitamins C and E stabilized by ferulic acid provides protection for human skin against damage caused by ultraviolet irradiation. J Am Acad Dermatol. 2008 Sep;59(3):418-25. doi: 10.1016/j.jaad.2008.05.004. Epub 2008 Jul 7. PMID: 18603326.
17. Hercberg S, Galan P, Preziosi P, Roussel AM, Arnaud J, Richard MJ, Malvy D, Paul-Dauphin A, Briançon S, Favier A. Background and rationale behind the SU.VI.MAX Study, a prevention trial using nutritional doses of a combination of antioxidant vitamins and minerals to reduce cardiovascular diseases and cancers. SUpplementation en VItamines et Minéraux AntioXydants Study. Int J Vitam Nutr Res. 1998;68(1):3-20. PMID: 9503043.
18. Hercberg S, Galan P, Preziosi P, Bertrais S, Mennen L, Malvy D, Roussel AM, Favier A, Briançon S. The SU.VI.MAX Study: a randomized, placebo-controlled trial of the health effects of antioxidant vitamins and minerals. Arch Intern Med. 2004 Nov 22;164(21):2335-42. doi: 10.1001/archinte.164.21.2335. Erratum in: Arch Intern Med. 2005 Feb 14;165(3):286. PMID: 15557412.

19. Dixon AJ, Anderson SJ, Mazzurco JD, Steinman HK. Novel photodynamic therapy does not prevent new skin cancers--randomized controlled trial. Dermatol Surg. 2014 Apr;40(4):412-9. doi: 10.1111/dsu.12462. PMID: 24826396.
20. Saha K, Hornyak TJ, Eckert RL. Epigenetic cancer prevention mechanisms in skin cancer. AAPS J. 2013 Oct;15(4):1064-71. doi: 10.1208/s12248-013-9513-3. Epub 2013 Aug 1. PMID: 23904153; PMCID: PMC3787232.
21. Thompson BC, Surjana D, Halliday GM, Damian DL. Nicotinamide enhances repair of ultraviolet radiation-induced DNA damage in primary melanocytes. Exp Dermatol. 2014 Jul;23(7):509-11. doi: 10.1111/exd.12430. PMID: 24798949.
22. Morales-Sanchez MA, Peralta-Pedrero ML, Jurado-Santa Cruz F, et al. Interventions for preventing keratinocyte cancer in high- risk groups not receiving immunosuppressive therapy. Cochrane Database Syst Rev 2016; 7: CD012266.
23. Moon TE, Levine N, Cartmel B, Bangert JL, Rodney S, Dong Q, Peng YM, Alberts DS. Effect of retinol in preventing squamous cell skin cancer in moderate-risk subjects: a randomized, double-blind, controlled trial. Southwest Skin Cancer Prevention Study Group. Cancer Epidemiol Biomarkers Prev. 1997 Nov;6(11):949-56. PMID: 9367069.
24. Levine N, Moon TE, Cartmel B, Bangert JL, Rodney S, Dong Q, Peng YM, Alberts DS. Trial of retinol and isotretinoin in skin cancer prevention: a randomized, double-blind, controlled trial. Southwest Skin Cancer Prevention Study Group. Cancer Epidemiol Biomarkers Prev. 1997 Nov;6(11):957-61. PMID: 9367070.

25. Tangrea JA, Edwards BK, Taylor PR, Hartman AM, Peck GL, Salasche SJ, Menon PA, Benson PM, Mellette JR, Guill MA, et al. Long-term therapy with low-dose isotretinoin for prevention of basal cell carcinoma: a multicenter clinical trial. Isotretinoin-Basal Cell Carcinoma Study Group. J Natl Cancer Inst. 1992 Mar 4;84(5):328-32. doi: 10.1093/jnci/84.5.328. PMID: 1738183.
26. Kadakia KC, Barton DL, Loprinzi CL, Sloan JA, Otley CC, Diekmann BB, Novotny PJ, Alberts SR, Limburg PJ, Pittelkow MR. Randomized controlled trial of acitretin versus placebo in patients at high-risk for basal cell or squamous cell carcinoma of the skin (North Central Cancer Treatment Group Study 969251). Cancer. 2012 Apr 15;118(8):2128-37. doi: 10.1002/cncr.26374. Epub 2011 Aug 31. PMID: 21882176; PMCID: PMC3365547.
27. Marcus S, Piacquadio D, Houlihan A, et al. Photodynamic therapy (PDT) with aminolevulinic acid (ALA) 20% and blue light reduces occurrence of actinic keratoses (AK) and de novo non- melanoma skin cancers (NMSCs) in patients with field cancerization. J Investig Dermatol 2017; 137: B2.
28. SotiriouE,ApallaZ,VraniF,etal.Photodynamictherapyvs. imiquimod 5% cream as skin cancer preventive strategies in patients with field changes: a randomized intraindividual comparison study. J Eur Acad Dermatology Venereol 2015; 29: 325–329.
29. Weinstock MA, Thwin SS, Siegel JA. Chemoprevention of basal and squamous cell carcinoma with a single course of fluorouracil, 5%, cream a randomized clinical trial. JAMA Dermatol 2018; 154: 167–174.

30. Rosenberg AR, Tabacchi M, Ngo KH, Wallendorf M, Rosman IS, Cornelius LA, Demehri S. Skin cancer precursor immunotherapy for squamous cell carcinoma prevention. JCI Insight. 2019 Mar 21;4(6):e125476. doi: 10.1172/jci.insight.125476. PMID: 30895944; PMCID: PMC6483001.
31. Hantash BM, Stewart DB, Cooper ZA, et al. Facial resurfacing for nonmelanoma skin cancer prophylaxis. Arch Dermatol 2006; 142: 976–982.
32. Naylor MF, Boyd A, Smith DW, et al. High sun protection factor sunscreens in the suppression of actinic neoplasia. Arch Dermatol 1995; 131: 170–175.
33. Bailey HH, Kim K, Verma AK, Sielaff K, Larson PO, Snow S, Lenaghan T, Viner JL, Douglas J, Dreckschmidt NE, Hamielec M, Pomplun M, Sharata HH, Puchalsky D, Berg ER, Havighurst TC, Carbone PP. A randomized, double-blind, placebo-controlled phase 3 skin cancer prevention study of {alpha}-difluoromethylornithine in subjects with previous history of skin cancer. Cancer Prev Res (Phila). 2010 Jan;3(1):35-47. doi: 10.1158/1940-6207.CAPR-09-0096. PMID: 20051371; PMCID: PMC2804946.
34. Chen AC, Martin AJ, Choy B, et al. A phase 3 randomized trial of nicotinamide for skin-cancer chemoprevention. N Engl J Med 2015; 373: 1618–1626.
35. Clark LC, Combs GF Jr, Turnbull BW, et al. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. JAMA 1996; 276: 1957.
36. Greenberg ER, Baron JA, Stukel TA, et al. A clinical trial of beta carotene to prevent basal-cell and squamous-cell cancers of the skin. N Engl J Med 1990; 323: 789–795.

37. Elmets CA, Viner JL, Pentland AP, et al. Chemoprevention of nonmelanoma skin cancer with celecoxib: a randomized, double-blind, placebo-controlled trial. J Natl Cancer Inst 2010; 102: 1835–1844.
38. Jaax S, Scott LW, Wolf JE Jr, et al. General guidelines for a low-fat diet effective in the management and prevention of nonmelanoma skin cancer. Nutr Cancer 1997; 27: 150–156.
39. Reed GW, Nissen SE. NSAID choice: lessons from PRECISION. Aging (Albany NY). 2019;11(8):2181-2182. doi:10.18632/aging.101930
40. Morales-Sánchez MA, Barragán-Dessavre M, Peralta-Pedrero ML, Quezada-Morales RP, Jurado-Santa Cruz F. Quality of clinical trials for the prevention of keratinocyte cancer. Int J Dermatol. 2020 Nov;59(11):1332-1340. doi: 10.1111/ijd.14903. Epub 2020 May 7. PMID: 32378199.

TABLES

References	Type of publication	Patients, n	Age mean ± SD med (p25-p75) (min-max)	Sex	Diagnosis	Treatment	Primary outcome	Time to outcome	Results (absolut number of new NMSC, unless specified otherwise)
Bailey 2010	Randomized controlled trial	291	60.9	175 males 116 females	NMSC history - basal or squamous cell cancers (stage 0-2)	Oral DFMO (500 mg/m2/day) or placebo for 4 to 5 years	Rate of new NMSC	5 years	NMSK: DFMO 260 vs placebo 363 BCC DMFO 163 vs placebo 243 †

Chen 2015	Randomized controlled trial*	386	66.4 ± 11.8 (30-91)	243 males 143 females	≥ 2 histologically confirmed KC within the past 5 years	Oral nicotinamide 500mg twice a day or placebo for 12 months	Incidence of new NMSC	12 months (+ 6 months postintervention follow-up)	Nicotinamide 336 vs placebo 463 †
Clark 1996	Randomized, double-blind, placebo-controlled trial*	1312	63.2 ± 10.1 (18-80)	980 males 332 females	History of ≥2 BCCs or 1 SCC with 1 of these carcinomas occurring within the prior year	Oral selenium 200 micrograms per day or placebo, for 4.5 years (mean)	Incidence of basal and squamous cell carcinomas of the skin	Up to 10 years, mean 4.5 years	Selenium 595 vs placebo 540

Dixon 2014	Randomized controlled trial*	63	71	36 males 27 females	≥1 histologically proven invasive KC	PDT with 5-aminolevulonic acid for two treatments and 2 weeks apart, or control group	Incidence of new malignancies in therapy field	3 years	ALA+PDT 30 vs control 22
Elmets 2010	Randomized clinical trial*	240	65.2 ± 10.2 (37.5-87.6)	197 male 43 female	10–40 AK and a previous histological diagnosis of ≥1 AK and/or KC	Celecoxib 200 mg twice a day for 9 months	The number of new actinic keratoses. In exploratory analyses, number of NMSC per	9 months (+2 months following completion)	NMSC Celecoxib 122 vs placebo 118 (Mean number of tumors per patient at month 11) celecoxib 0.14 vs placebo 0.35 †

							patient at 11 months after randomization		
Greenberg 1990	Randomised, double-blind, clinical trial*	1805	63	1251 males 554 females	History of ≥1 biopsy proved of BCC or SCC	Betacarotene 50mg daily or placebo, for 5 years	Incidence of new keratinocyte cancers	5 years	B-carotene 1043 vs placebo 909
Hantash 2006	Randomized, prospective trial	24	72.8 (54–91)	24 males 0 females	History of KC and numerous AKs or significant photoda	Carbon dioxide laser, vs 30% trichloroacetic acid, vs 5% fluorouracil cream twice daily	Reduction in the number of AK. The incidence of new NMSC in treated areas	2 years (2 year follow-up at 3 month intervals)	NMSC Fluorouracil 5 vs TCA 1 vs CO2 laser 3 vs control 24

					mage alone	for 3 weeks	(following 4 years)		
Jaax 1997	Randomized controlled trial	115	51.45 ± 11.45	70 males 45 females	KCs who had no >2 previous KCs	Low-fat diet (Calories from fat 20%, from protein 15%, from carbohydrates 65%), 2 years follow-up	Incidence of new keratinocyte cancers	2 years	(Cumulative skin cancers per patient per time period) Low-fat diet 0.02 vs. usual diet 0.26 †
Kadakia 2012	Randomized controlled trial	70	68.2 ± 9.48	44 males 26 females	History of ≥2 KCs confirmed HP	Acitretin 25mg 5 days weekly for 2 years	Rate of new keratinocyte cancers at 6, 12, 18 and 24 months	2 years	Acitretin 52 vs placebo 119

Levine 1997	Randomized, double-blind controlled trial*	525	238 <66 years 287 >66 years	379 males 146 females	History of ≥4 BCCs and/or SCCs, the most recent diagnosed in the previous year	Retinol 25000 IU/day for 3 years or Isotretinoin 5- 10 mg per day (depending on weight) for 3 years or placebo	Incidence of new keratinocyte cancers (time to occurrence)	3 years	Retinol 147 vs. isotretinoin 143 vs. placebo 151
Marcus 2017	Prospective evaluator-blinded, placebo-controlled study *	166	NI	NI	Facial AKs, history of KCs, and histologic evidence of dysplasi	PDT+ALA 2 doses vs PDT+ALA 3 doses vs PDT+placebo Cryotherapy in clinically	The Incidence of new AK and keratinocyte cancers in treatment field.	52 weeks	NMSC PDT+ALA3 5 vs. placebo 12 †

					a within clinically normal-appearing perilesional skin	evident KA previously. *ALA-2X → one application to the entire facial skin for one hour at baseline and week 4. After ALA's application patients received 10 J/cm2 blue light delivered at 10 mW/cm2			

						for 2 doses **ALA-3X → one application to the entire facial skin for one hour at baseline and week 4. After ALA's application patients received 10 J/cm2 blue light delivered at 10 mW/cm2			

						for 3 doses			
Moon 1997	Randomized, double-blind, controlled trial	2297	63	1618 male 679 female	History of >10 AKs, most recent diagnosed during preceding year, and ≥2 pathologically confirmed SCC or BCC	Oral retinol 25,000 IU daily vs placebo for 5 years	Time to first new SCC or BCC Incidence of new keratinocyte cancers	5 years	Cumulative probability of new NMSC during 5 years of study: SSC: retinol 0.106 vs placebo 0.141 † BCC: retinol 0.22 vs placebo 0.21
Naylor 1995	Controlled trial *	50	63.75 ± 8	43 male	Clinical evidence of AKs or KCs	SPF 29 (octyl methoxycinnamate,	Annual rates of AK formation,	2 years (evaluation at month	NMSC SPF 10 vs placebo 8

				7 female		benzophenone-3, and octyl salicylate) vs placebo daily 5760 ml (240 ml per month) for 2 years	incidence of NMSC	1, 3 and every 3 months up to 2 years)	NMSC numbers were too small for statistical analysis
Rosenberg 2019	Randomized double-blind clinical trial	86	68	65 male 21 female	≥2 KCs (BCC or SCC) in the prior 5 years	Calcipotriol plus 5-FU vs vaseline + 5FU for 4 day-courses, during 3 years as treatment for AK	Histopathologic diagnosis of primary SCC and BCC	3 years (evaluation at 1, 2 and 3 years)	At 1 year: -calcipotriol+5FU: 0.125 -placebo: 0.125 At 2 years: -intervention: 0.193 -placebo: 025 At 3 years: -intervention: 0.2

									-placebo: 0.325 †
Sotiriou 2015	Clinical trial , randomized intraindividual comparison	44	65 ± 6.8	37 male 7 female	Field cancerization + history of ≥1 previous KC	(MAL)-PDT vs IMIQ 5% cream	The number of new “lesions”	12 months	New “lesions” (does not specify if AK or NMSC) PDT 16 vs imiquimod 5% 22
Tangrea 1992	Randomized, double-blind controlled trial*	981	60.8	757 males 224 females	≥2 biopsy-proven BCCs during the last 5 years	Isotretinoin 10 mg daily for 3 years or placebo	Incidence of new keratinocyte cancers	3 years	(Tumor rate per patient per year) Isotretinoin 0.94 vs placebo 0.96
Weinstock 2012	Randomized controlled trial*	1131	NI	1097 males	≥2 KCs in the prior 5 years	Tretinoin 0.1% Cream twice daily	Time to development of new	1.5-5.5 years	Tretinoin 296 vs placebo 310 (at endpoint)

				34 females	but free of KC at enrollment	for 1.5 to 5.5 years	keratinocyte cancers		
Weinstock 2018	Randomized controlled trial*	932	71.1 ± 9.3	916 males 16 females	History of ≥2 KCs in the past 5 years	Fluorouracil 5% cream twice daily to face and ears for 56 doses or placebo (vehicle)	Surgically treated new keratinocyte cancers	Endpoint 1 year, follow-up 4 years	Fluorouracil 317 (62 during first year) vs placebo 330 (91 during first year) †

TABLES AND FIGURES LEGENDS

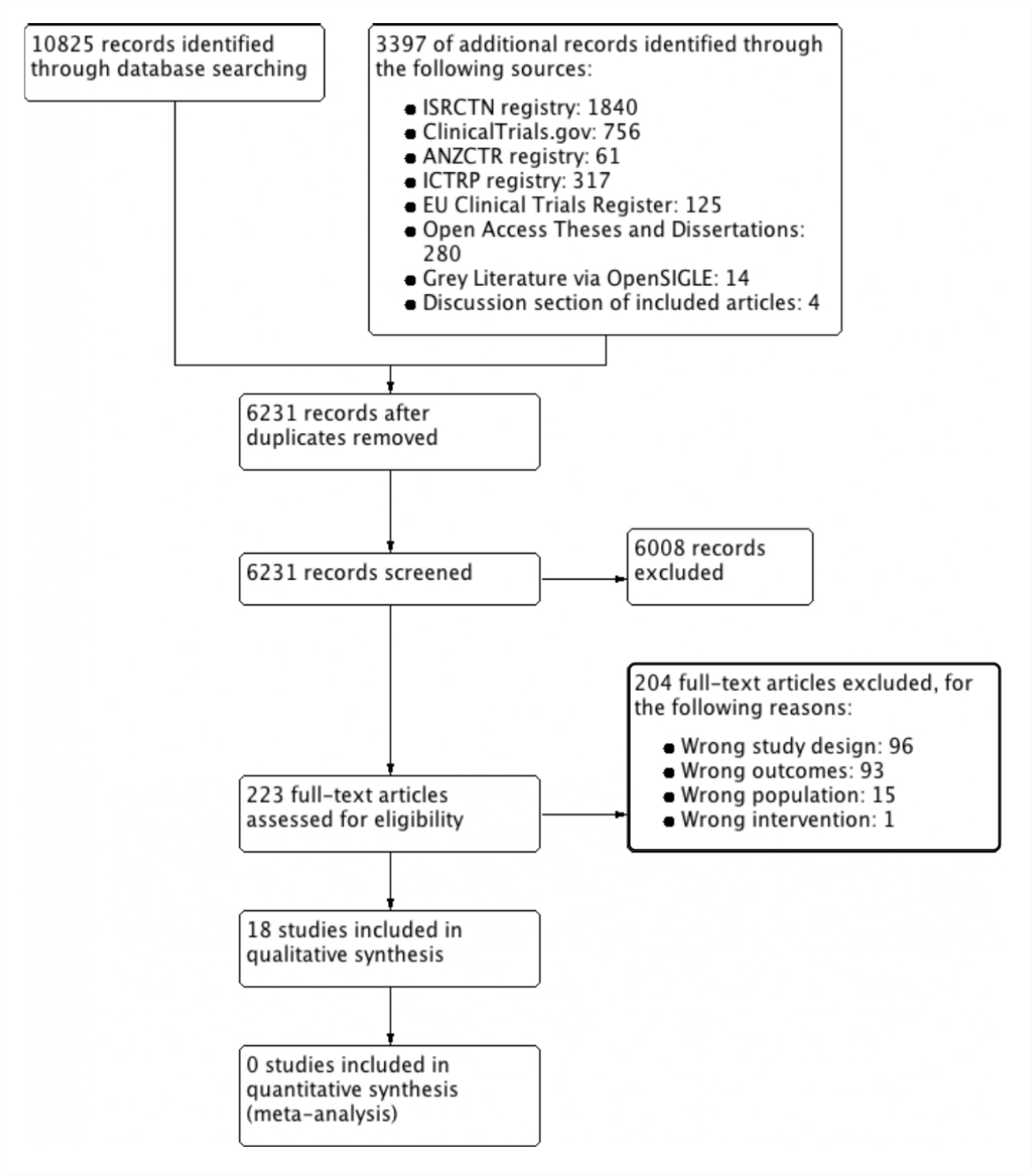
(in order of appearance in text)

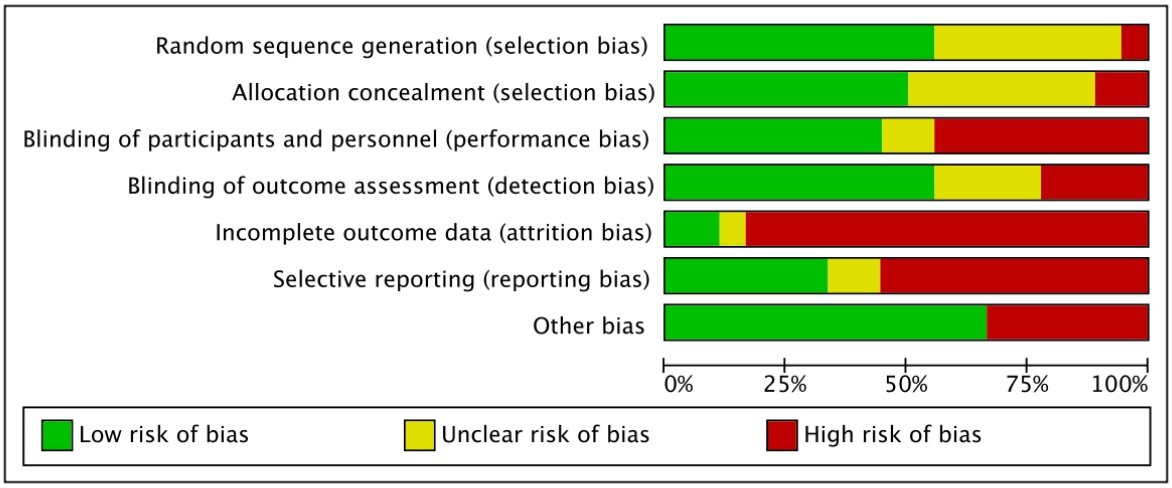
Figure 1. Literature review screening scheme for articles included in the systematic review of interventions for preventing keratinocytic cancer in patients with history of a previous keratinocytic carcinoma.

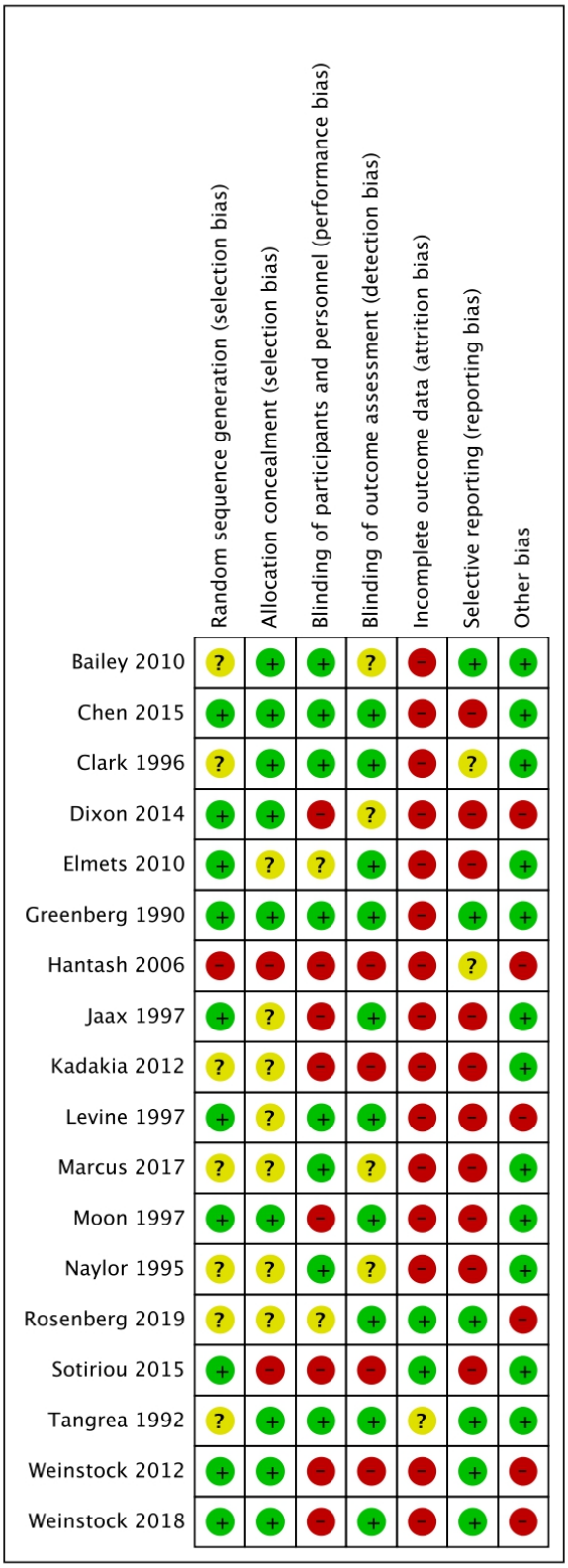
Table 1. General characteristics of the 18 clinical trials included in this review.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study


10825 records identified through database searching
3397 of additional records identified through the following sources:
ISRCTN registry: 1840
ClinicalTrials.gov: 756
ANZCTR registry: 61
ICTRP registry: 317
EU Clinical Trials Register: 125
Open Access Theses and Dissertations: 280
Grey Literature via OpenSIGLE: 14
Discussion section of included articles: 4
6231 records after duplicates removed
6231 records screened
6008 records excluded
204 full-text articles excluded, for the following reasons:
Wrong study design: 96
Wrong outcomes: 93
Wrong population: 15
Wrong intervention: 1
223 full-text articles assessed for eligibility
18 studies included in qualitative synthesis
0 studies included in quantitative synthesis (meta-analysis)


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
0%
25%
50%
75%
100%
Low risk of bias
Unclear risk of bias
High risk of bias


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Bailey 2010
Chen 2015
Clark 1996
Dixon 2014
Elmets 2010
Greenberg 1990
Hantash 2006
Jaax 1997
Kadakia 2012
Levine 1997
Marcus 2017
Moon 1997
Naylor 1995
Rosenberg 2019
Sotiriou 2015
Tangrea 1992
Weinstock 2012
Weinstock 2018