Squamous cell carcinoma of the skin (non-metastatic)

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ABSTRACT

INTRODUCTION: Cutaneous squamous cell carcinoma is a malignant tumour of keratinocytes arising in the epidermis, with histological evidence of dermal invasion. Incidence varies by country, skin colour, and outdoor behaviour, and is as high as 400/100,000 in Australia. People with fair skin colour who have high sun exposure and sunburn easily with little or no tanning, people with xeroderma pigmentosum, and people who are immunosuppressed are most susceptible to squamous cell carcinoma. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: Does the use of sunscreen help prevent cutaneous squamous cell carcinoma and actinic (solar) keratosis? What is the optimal margin for primary excision of cutaneous squamous cell carcinoma (non-metastatic)? Does radiotherapy after surgery affect local recurrence of cutaneous squamous cell carcinoma in people with squamous cell carcinoma of the skin (non-metastatic)? We searched: Medline, Embase, The Cochrane Library, and other important databases up to August 2013 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found five studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review, we present information relating to the effectiveness and safety of the following interventions: sunscreens, primary excision, and radiotherapy after surgery.

QUESTIONS

INTERVENTIONS

SUNSCREEN TO PREVENT SQUAMOUS CELL CARCINOMA AND ACTINIC (SOLAR) KERATOSES

Likely to be beneficial

PRIMARY EXCISION MARGIN

Unknown effectiveness

RADIOTHERAPY AFTER SURGERY

Unknown effectiveness

Key points

- Cutaneous squamous cell carcinoma is a malignant tumour of keratinocytes arising in the epidermis, with histological evidence of dermal invasion.

  Incidence varies by country, skin colour, and outdoor behaviour, and is as high as 400/100,000 in Australia.

  People with fair skin colour who have high sun exposure and sunburn easily with little or no tanning, people with xeroderma pigmentosum, and people who are immunosuppressed are most susceptible to squamous cell carcinoma.

- Regular sunscreen application to the head, neck, arms, and hands seems to reduce the incidence of squamous cell carcinoma more than discretionary use or no use.

  The evidence regarding regular use of sunscreen to reduce squamous cell carcinoma is from an RCT of adults in a subtropical community in Queensland, Australia, half of whom had previous actinic keratoses. The generalisability of these findings will be influenced by climate and seasonality, among other factors.

  Regular sunscreen application to the head, neck, arms, and hands also seems to reduce the rate of acquisition of actinic (solar) keratoses more than discretionary or no use. Daily sunscreen application seems to reduce the incidence of new actinic keratoses in people who had previous actinic keratoses.

- With regard to surgery, we found no RCTs to assess the optimal primary excision margin required to prevent recurrence of squamous cell carcinoma.

  As with all kinds of surgery, there is a potential for tissue destruction and scarring, particularly of vital structures such as eyelids, lip margins, and motor and sensory nerves.

- We do not know whether radiotherapy after surgery reduces local recurrence compared with surgery alone.

  Although not measured, there is potential for long-term scar deterioration with post-radiation depigmentation and gradual development of chronic radiodermatitis, including telangiectasiae, thinning of the skin, and hyperkeratosis.

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DEFINITION

Cutaneous squamous cell carcinoma is a malignant tumour of keratinocytes arising in the epidermis, showing histological evidence of dermal invasion.

INCIDENCE/ PREVALENCE

Incidence rates on exposed skin vary markedly around the world according to latitude, skin colour, and outdoor behaviour. Reported incidence thus ranges from negligible in black populations, to rates of around 23/100,000 in England (though 33/100,000 in the South West) and 37/100,000 in Scotland in 2003, to 60/100,000 in Canada in 2006, to 290/100,000 in Arizona in 1991 and up to around 400/100,000 in Australia in 2002. [1]

AETIOLOGY/ RISK FACTORS

People with fair skin colour who have high sun exposure and sunburn easily with little or no tanning, people with xeroderma pigmentosum, [2] [3] [4] and those who are immunosuppressed [5] are susceptible to squamous cell carcinoma. The strongest environmental risk factor for squamous cell carcinoma is chronic sun exposure, such that those who work outdoors are at higher risk than those who work indoors. [6] Clinical signs of chronic skin damage, especially actinic (solar) keratoses, are also predictive factors for cutaneous squamous cell carcinoma. [3] [4] [7] In people with multiple actinic keratoses (more than 15), the risk of squamous cell carcinoma is 10 to 15 times greater than in people with no actinic keratoses. [3] [4]

PROGNOSIS

Prognosis is related to the location and size of tumour, histological pattern, depth of invasion, perineural involvement, and immunosuppression. [8] [9] The most common site of squamous cell carcinoma is the head and neck. Follow-up of 315 consecutive patients with primary cutaneous squamous cell carcinoma of the head and neck for an average of 4 years in Thessaloniki, Greece, showed grade of differentiation, perineural involvement, the presence of inflammation, and T-stage were independent predictors for overall survival. [10] Stage, inflammation, and perineural involvement predicted recurrence-free survival. Factors associated with poor outcomes for squamous cell carcinoma with perineural invasion were studied in a hospital series of 114 adults in Boston, MA (US). [11] Tumours with large nerve invasion (at least 0.1 mm in calibre) rather than small (unspecified) nerve invasion were more likely to have other risk factors, including tumour diameter of 2 cm or greater, invasion beyond the subcutaneous fat, multiple nerve involvement, infiltrative growth, or lymphovascular invasion. Tumour diameter of 2 cm or greater predicted local recurrence; having multiple (of the above) risk factors predicted nodal metastasis; and lymphovascular invasion predicted death from disease. [11]

AIMS OF INTERVENTION

To prevent the occurrence of squamous cell carcinoma; to achieve cure by eradicating local disease, including micro-invasive disease; to reduce mortality.

OUTCOMES

Prevention: Incidence rates of cutaneous squamous cell carcinoma and prevalence rates of actinic (solar) keratoses; mortality from squamous cell carcinoma. **Primary excision:** Local recurrence (i.e., recurrence of original lesion at original site up to 5 years post-excision); cosmetic outcome (i.e., scarring, effect on facial expression, necessity for skin grafts); survival. **Radiotherapy after surgery:** Local recurrence (i.e., recurrence of original lesion at original site up to 5 years post-radiotherapy); regional recurrence (i.e., recurrence in an area drained by the regional lymph node up to 5 years post-radiotherapy); survival.

METHODS

Clinical Evidence search and appraisal August 2013. The following databases were used to identify studies for this systematic review: Medline 1966 to August 2013, Embase 1980 to August 2013, and The Cochrane Database of Systematic Reviews 2013, issue 8 (1966 to date of issue). Additional searches were carried out in the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) database. We also searched for retractions of studies included in the review. Titles and abstracts identified by the initial search, run by an information specialist, were first assessed against predefined criteria by an evidence scanner. Full texts for potentially relevant studies were then assessed against predefined criteria by an evidence analyst. Studies selected for inclusion were discussed with an expert contributor. All data relevant to the review were then extracted by an evidence analyst. Study design criteria for inclusion in this review were: published RCTs and systematic reviews of RCTs in the English language, at least single-blinded, and containing >20 individuals of whom >80% were followed up. There was no minimum length of follow-up. We excluded all studies described as 'open', 'open label', or not blinded unless blinding was impossible. We included RCTs and systematic reviews of RCTs where harms of an included intervention were assessed, applying the same study design criteria for inclusion as we did for benefits. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 10). The categorisation

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of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **Does the use of sunscreen help prevent cutaneous squamous cell carcinoma and actinic (solar) keratosis?**

OPTION **SUNSCREEN TO PREVENT DEVELOPMENT OF SQUAMOUS CELL CARCINOMA**

- For GRADE evaluation of interventions for Squamous cell carcinoma of the skin (non-metastatic), see table, p 10 .
- Regular use of sunscreen on the head, neck, arms, and hands seems to be more effective than discretionary or no use.
- The evidence regarding regular use of sunscreen to reduce squamous cell carcinoma is from an RCT of adults in a subtropical community in Queensland, Australia, half of whom had previous actinic keratoses. The generalisability of these findings will be influenced by climate and seasonality, among other factors.

Benefits and harms

Sunscreen use versus placebo:

We found no systematic review or RCTs (see Comment below).

Regular sunscreen use versus discretionary or no use:

We found one RCT that compared allocation to regular use of sunscreen (sun protection [SPF] 15+) with allocation to discretionary or no use of sunscreen. [12] We found one follow-up report of the RCT. [13]

Incidence rates

Regular sunscreen use compared with discretionary or no sunscreen use Regular use of sunscreen on the head, neck, arms, and hands seems to be more effective than discretionary or no use of sunscreen at reducing the incidence of squamous cell carcinoma at 4.5 years, and during an 8-year follow-up period, in people in a subtropical community in Queensland, Australia, half of whom had had previous actinic (solar) keratoses (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Incidence					
[12] RCT	1621 adults in a subtropical community in Queensland, about half of whom had previous actinic (solar) keratoses	**Incidence of cutaneous squamous cell carcinoma tumours , 4.5 years** 22 people with 28 new squamous cell carcinomas with regular sunscreen use (sun protection factor [SPF] 15+) 25 people with 46 new squamous cell carcinomas with discretionary or no sunscreen use	RR 0.61 95% CI 0.46 to 0.81 Subgroup analysis found no significant difference in the incidence of squamous cell carcinoma tumours between regular sunscreen users with, or regular sunscreen users without, a history of skin cancer (P = 0.42)	●○○	daily sunscreen use
[13] RCT	1621 adults in a subtropical community in Queensland, about half of whom had previous actinic (solar) keratoses Further report of reference [12]	**Incidence of cutaneous squamous cell carcinoma , 12.5 years** 40 people with new squamous cell carcinomas with regular sunscreen use (sun protection factor [SPF] 15+) 60 people with new squamous cell carcinomas with discretionary or no sunscreen use	RR 0.65 95% CI 0.43 to 0.98	●○○	daily sunscreen use

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Denominators not clear New squamous cell carcinoma incidence rates were reported as 625/100,000 person-years at risk with regular sunscreen use compared with 934/100,000 person-years at risk with discretionary or no sunscreen use			

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[12] RCT	1621 adults in a subtropical community in Queensland, about half of whom had previous actinic (solar) keratoses	**Adverse effects , 4.5 years** with regular sunscreen use (sun protection factor [SPF] 15+) with discretionary or no sunscreen use	No analysis between groups reported Following regular sunscreen use, 25 people reported contact allergy or skin irritation (1 person withdrew because of skin irritation), 10 people reported skin greasiness, and 6 people reported interference with perspiration or stinging eyes after facial perspiration		

No data from the following reference on this outcome. [13]

Further information on studies

[12] People allocated to regular sunscreen were told to apply it to the head, neck, arms, and hands every morning and to reapply it after heavy sweating, bathing, or long sun exposure. They were reminded of this advice every 3 months by research staff when sunscreen supplies were replenished. People not allocated to daily sunscreen use were asked to continue application of sunscreen at their usual discretionary rate, which included no use but for most people was recreational use. After the end of the RCT, all participants were followed up for a further 8 years. [13]

Comment: In a long-term prevention trial with skin cancer as the outcome, placebo sunscreen may be regarded as unethical. It would also be difficult to mask treatment allocation. The evidence regarding regular use of sunscreen to reduce squamous cell carcinoma is from an RCT of adults in a subtropical community in Queensland, Australia, half of whom had previous actinic keratoses. The prolonged effectiveness of regular sunscreen use in reducing the incidence of squamous cell carcinoma was enhanced by more frequent use of sunscreen persisting in the regular sunscreen treatment group compared with discretionary or no sunscreen users (25% with regular sunscreen use *v* 18% with discretionary or no sunscreen use; P = 0.004). [13] The generalisability of these findings will be influenced by climate and seasonality, among other factors.

The RCT used a broad-spectrum SPF 15+ sunscreen which filters 94% of solar ultraviolet-B radiation and is recommended by the World Health Organization. [14] SPF 30+ sunscreens filter 96.7% of solar ultraviolet-B and are also widely recommended. The efficacy of sunscreen protection depends more on the application of a liberal quantity than its precise absorption spectrum. [15] [16]

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OPTION SUNSCREEN TO PREVENT DEVELOPMENT OF ACTINIC (SOLAR) KERATOSES

- For GRADE evaluation of interventions for Squamous cell carcinoma of the skin (non-metastatic), see table, p 10 .
- Daily use of sunscreen seems to be more effective than placebo at reducing the risk of new actinic (solar) keratoses at 7 months and at increasing lesion remission.
- Regular use of sunscreen on the head, neck, arms, and hands seems to be more effective than discretionary or no use of sunscreen at reducing the increase in the number of actinic (solar) keratoses.
- The evidence regarding regular use of sunscreen to reduce actinic keratoses comes from two RCTs of people living in Australia, many of whom had previous actinic keratoses. The generalisability of these findings will be influenced by climate and seasonality, among other factors.

Benefits and harms

Daily sunscreen use versus placebo:

We found one RCT that compared daily use of sunscreen (sun protection factor [SPF] 17) with placebo. [17]

Incidence rates

Daily sunscreen use compared with placebo Daily use of sunscreen on the head, neck, forearms, and hands seems to be more effective than placebo at reducing the risk of new actinic (solar) keratoses at 7 months and at increasing lesion remission in people aged over 40 years in Victoria, Australia, with previous actinic keratoses (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Incidence of actinic (solar) keratosis					
[17] RCT	588 people with previous solar keratoses, aged over 40 years, living in Victoria, Australia	**Mean number of new lesions per person , 7 months** 1.6 with daily sunscreen use (sun protection factor [SPF] 17) 2.3 with placebo (base cream with no active ingredient) Daily use of sunscreen significantly increased lesion remission (OR 1.5, 95 % CI 1.29 to 1.8)	RR 0.62 95% CI 0.54 to 0.71	●○○	daily sunscreen use

Regular sunscreen use versus discretionary or no use:

We found one RCT that compared regular use of sunscreen (sun protection factor [SPF] 15+) with discretionary or no use of sunscreen. [12] Results relating to the incidence of actinic (solar) keratoses were published in a subsequent report. [18]

Incidence rates

Regular sunscreen use compared with discretionary or no sunscreen use Regular use of sunscreen on the head, neck, arms, and hands seems to be more effective than discretionary or no use of sunscreen at reducing the increase in the number of actinic (solar) keratoses over the whole body at 2.5 years in people in a subtropical community in Queensland, Australia, half of whom had had previous actinic keratoses (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Incidence of actinic (solar) keratosis					
[18] RCT	1621 adults in a subtropical community in Queensland, about half of whom had previous actinic (solar) keratoses	**Increase in actinic (solar) keratoses , 2.5 years** 20% with regular sunscreen use (sun protection factor [SPF] 15+) 57% with discretionary or no sunscreen use	Adjusted ratio 76% P <0.05 Results were adjusted for confounding factors (see Comments) The rate of increase of actinic (solar) keratoses was lower with	●○○	daily sunscreen use

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	Further report of reference [12]	Absolute numbers not reported	regular use of sunscreen over the subsequent 2-year period compared with discretionary or no use, but the difference between groups was not statistically significant (adjusted ratio 95%; P >0.05)		

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[17] RCT	588 white people with 1–30 actinic (solar) keratoses	**Skin reactions** 32/210 (15%) with sunscreen (sun protection factor [SPF] 17) 28/221(13 %) with placebo (base cream with no active ingredient)			

No data from the following reference on this outcome. [18]

Further information on studies

[17] People were instructed to apply sunscreen (sun protection factor [SPF] 17), or placebo, to the head, neck, forearms, and hands once every morning, and to reapply during the day, if necessary. The placebo consisted of base cream minus the two active ingredients of the sunscreen. Mineral oil (10% wt/wt) was added to the base cream so that it would have the same consistency as the sunscreen.

[18] People allocated to regular sunscreen were told to apply it to the head, neck, arms, and hands every morning and to re-apply it after heavy sweating, bathing, or long sun exposure. They were reminded of this advice every 3 months by research staff, when sunscreen supplies were replenished.

Comment:

In a long-term prevention trial with skin cancer as the outcome, placebo sunscreen may be regarded as unethical. It would also be difficult to mask treatment allocation. The evidence regarding regular use of sunscreen to reduce actinic keratoses comes from two RCTs of people living in Australia, many of whom had previous actinic keratoses. The generalisability of these findings will be influenced by climate and seasonality, among other factors.

In the RCT comparing regular versus discretionary or no sunscreen use in the development of actinic (solar) keratoses, outcome measures were adjusted for confounding factors, including sex, age, beta carotene use, eye and hair colour, skin reaction to acute sun exposure, lifetime occupational sun exposure, smoking, and history of skin cancer. [12]

The RCTs used broad-spectrum SPF 15+ sunscreen [12] [18] and SPF 17 sunscreen. [17] SPF 15+ sunscreen filters 94% of solar ultraviolet-B radiation and is recommended by the World Health Organization. [14] SPF 30+ sunscreens filter 96.7% of solar ultraviolet-B and are also widely recommended. The efficacy of sunscreen protection depends more on the application of a liberal quantity than its precise absorption spectrum. [15] [16]

See Comments of Sunscreen in preventing development of squamous cell carcinoma, p 3 .

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QUESTION **What is the optimal margin for primary excision of cutaneous squamous cell carcinoma (non-metastatic)?**

OPTION **OPTIMAL PRIMARY EXCISION MARGIN**

- For GRADE evaluation of interventions for Squamous cell carcinoma of the skin (non-metastatic), see table, p 10 .
- We found no direct information from RCTs.
- As with all kinds of surgery, there is a potential for tissue destruction and scarring, particularly of vital structures such as eyelids, lip margins, and motor and sensory nerves.

Benefits and harms

Optimal primary excision margin:

We found no systematic review or RCTs assessing the effect of different primary excision margins in the treatment of people with squamous cell carcinoma of the skin (non-metastatic).

Comment: One case series using micrographically controlled surgery (Mohs' surgery) assessed excision margins in relation to histological extension of the tumour and found a 95% clearance rate of squamous cell carcinomas <2 cm in diameter with a margin of 4 mm of normal skin, and a 96% clearance rate of tumours >2 cm with a margin of 6 mm. [19] The sites of scalp, ears, eyelid, nose, and lip were found to have more deeply invasive tumours. Another study reported on 37 tumours that had a 4 mm margin of clinically normal skin removed at the time of primary excision. It was estimated that this margin would result in complete excision of 97% of squamous cell carcinomas suitable for excision in an outpatient facility. [20] Numerous case series suggest that primary excision of cutaneous squamous cell carcinoma has a likelihood of local recurrence varying from 5% to 20% depending on tumour size, site, histopathological differentiation, perineural involvement, and depth of invasion. [21] [22] [23] [24] [25] [26] [27]

QUESTION **Does radiotherapy after surgery affect local recurrence of cutaneous squamous cell carcinoma in people with squamous cell carcinoma of the skin (non-metastatic)?**

OPTION **RADIOTHERAPY AFTER SURGERY**

- For GRADE evaluation of interventions for Squamous cell carcinoma of the skin (non-metastatic), see table, p 10 .
- We found no direct information from RCTs.
- Although not measured, there is potential for long-term scar deterioration with post-radiation depigmentation and gradual development of chronic radiodermatitis, including telangiectasiae, thinning of the skin, and hyperkeratosis.

Benefits and harms

Radiotherapy after surgery versus surgery alone:

We found no systematic review or RCTs assessing the effect of radiotherapy after surgery in the treatment of people with squamous cell carcinoma of the skin (non-metastatic).

Comment: In rare instances, squamous cell carcinomas cannot be excised completely, and these have local recurrence rates of over 50%. [28] [29] Case series of inadequately excised squamous cell carcinomas, especially those with microscopic perineural invasion found at the time of curative surgery, have reported recurrence rates of 20% to 25% after 5 years when surgery was followed by radiotherapy. [30] [31] Ability to detect advanced perineural invasion can be enhanced by computerised tomography or magnetic resonance imaging. [32]

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GLOSSARY

Micrographically controlled surgery Does not use standard excision margins as the basis for achieving tumour clearance. The visible tumour and a thin margin of apparently normal skin are removed, mapped, and examined microscopically using a specialised sectioning technique at the time of surgery, and the surgery continues until there is microscopic confirmation of complete tumour clearance, at which stage the wound is closed. [33]

Perineural invasion Tumour invasion along (not in) a nerve.

Xeroderma pigmentosum An inherited disorder with defective repair of DNA damage caused by ultraviolet radiation, resulting in sun related skin cancers of all types at an early age.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

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Competing interests: AG was paid by L'Oreal to run a research project and had research staff paid for by the company. She is an author of references cited in this review. PM declares that she has no competing interests.
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GRADE **Evaluation of interventions for Squamous cell carcinoma of the skin (non-metastatic).**

Important outcomes			Incidence rates						
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
Does the use of sunscreen help prevent cutaneous squamous cell carcinoma and actinic (solar) keratosis?									
1 (1621) [12] [13]	Incidence rates	Regular sunscreen use versus discretionary or no use	4	0	0	–1	0	Moderate	Directness point deducted for restricted population (subtropical)
1 (588) [17]	Incidence rates	Daily sunscreen use versus placebo	4	0	0	–1	0	Moderate	Directness point deducted for restricted population (all participants had previous actinic [solar] keratoses)
1 (1621) [12] [18]	Incidence rates	Regular sunscreen use versus discretionary or no use	4	0	0	–1	0	Moderate	Directness point deducted for restricted population (subtropical, half of participants had previous actinic [solar] keratoses)

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.

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