Synthetic Retinoid Interventions and Outcomes in People with Cancer or Potentially Malignant Disorders of the Upper Aerodigestive Tract: A Systematic Review and Meta-analysis

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Published in:
Oral Surgery

Publication date:
2014

Synthetic Retinoid Interventions and Outcomes in People with Cancer or Potentially Malignant Disorders of the Upper Aerodigestive Tract: A Systematic Review and Meta-analysis

Running title: Systematic review of synthetic retinoid treatments

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Keywords: Retinoids, upper aerodigestive tract cancer, systematic review, meta-analysis, oral leukoplakia

Abstract

Background & Aims: Retinoids may have a role in the chemoprevention of potentially malignant disorders of the upper aerodigestive tract. Therefore, we conducted a systematic review of randomised controlled trials to examine the effect of synthetic retinoid interventions in people with cancer or potentially malignant disorders of the upper digestive tract.

Methods: We searched five electronic databases and reference lists to locate all eligible trials and analysed trial quality. Outcome measures were all-cause and cancer mortality, disease-free survival, second primary cancer, cancer and potentially malignant disorder recurrence and progression to cancer. Results of individual trials were combined by use of random-effects meta-analyses.

Results & Conclusions: We identified 15 trials, eight in people with upper aerodigestive tract cancer and seven in people with potentially malignant disorders, respectively. The results provide little evidence that retinoids have a beneficial effect on disease-free survival (OR=0.74, 95% CI =0.51, 1.09), all cause mortality (OR = 1.28, 95% confidence interval [CI] =1.00 to 1.65), recurrence of cancer (OR = 1.47, 95% CI = 0.95, 2.26), development of second primary cancers (OR = 0.96, 95% CI = 0.76, 1.20) or the progression to malignancy (OR = 0.69, 95% CIs = 0.22, 2.15). There was even a suggestion of harm for some outcomes. There was also a suggestion that retinoids may decrease the recurrence of potentially malignant disorders (OR = 0.22, 95% CIs = 0.03, 1.34). For now there is no evidence to support the use of retinoids in people with upper aerodigestive tract cancer.

Clinical Relevance:

Scientific rationale for study: Previous trials have identified retinoids as effective treatments for cancers of the upper aerodigestive tract and potentially malignant oral disorders. This systematic review assessed the effectiveness of these treatments.

Principal findings: The review found no evidence for the effectiveness of retinoids with upper aerodigestive tract cancers. There was some evidence that retinoids may be effective in reducing the recurrence of potentially malignant oral disorders.

Practical implications: This review concludes that retinoids should not be used for treating cancers of the aerodigestive tract but further research is needed into their effectiveness for potentially malignant oral disorders.

Introduction

Head and neck squamous cell carcinoma (HNSCC) affects more than 600,000 people annually worldwide[1]. HNSCC is frequently preceded by potentially malignant disorders [2] and increased risks of second primary cancers persist 10 years after diagnosis of the first primary, with the incidence of second primary tumours being high especially within the first year of diagnosis[3]. HNSCC includes cancer of the upper aerodigestive tract (this includes the lips, tongue, mouth, throat and larynx)[2]. Although there have been advances in the treatment of upper aerodigestive tract cancer, the existence of potentially malignant disorders and the occurrence of second primary tumours suggest chemopreventive strategies could play an important role in the management of this disease.

Recent studies have shown that loss of epithelial differentiation is an important driver in the pathogenesis of upper aerodigestive tract cancer[4]. Agents that are known to modify epithelial differentiation, therefore, may be useful adjuncts to conventional therapy[5]. The cancer-related chemopreventive effects of vitamin A and its derivatives such as 13-cis-retinoic acid (13-cRA) and etretinate are well recognised, but side effects such as dry skin, cheilitis, conjunctivitis, teratogenicity and retinoid resistance have limited their therapeutic value[6, 7, 8]. By contrast, the newer derivatives such as retinoid N-(4-hydroxyphenyl) retinamide (Fenretinide; 4-HPR) have minimal pharmacological toxicity[9, 10] and have been used successfully in the control of cancers both in animal models[11, 12, 13] and in clinical trials[14, 15].

A systematic review in 2006[16] of the impact of interventions for treating oral leukoplakia ("white plaques of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer"[16]) concluded that treatments may be effective in the resolution of leukoplakia. However, it found that relapses and adverse effects are common and there is no evidence of effective treatment in

preventing malignant transformation of leukoplakia[16]. Further, a systematic review of nutritional interventions in cancers at any site found no evidence to support the effectiveness of dietary interventions for improving survival or enhancing disease prognosis [17].

The purpose of the present study was to assess the effectiveness of synthetic retinoid intervention as a stand-alone treatment in people with potentially malignant disorders, cancer and second primary tumours of the upper aerodigestive tract and to review the potential side effects of this treatment.

Material and Methods

Search strategy

MEDLINE, EMBASE, AMED, ISI Web of Knowledge and the Cochrane Library were searched from inception to April 2014. The search terms included indexing and textwords associated with upper aerodigestive tract cancer and retinoid treatments (See Appendix A for the MEDLINE strategy). No language restrictions were applied. In addition, the references of identified studies were screened.

Inclusion Criteria

We considered any Randomised Controlled Trials (RCTs) to be eligible for inclusion if they recruited people with cancer, second primaries or potentially malignant disorders of the upper aerodigestive tract and included any synthetic retinoid-based intervention. A person with cancer was defined as anyone with a primary cancer, second primaries or recurrence of cancer from the time of diagnosis through to the rest of life[18]. Retinoid interventions included synthetic retinoids taken directly (oral intake, topical application) in excess of the normal diet. We included any RCT with placebo, no treatment or treatment-as-usual as control. We included trials that reported one or more of the following primary outcomes: all-cause mortality, cancer mortality, disease-free survival, cancer recurrence and second primary cancer or

recurrence of a potentially malignant disorder or progression to malignancy. We also recorded information on the following secondary outcomes: number of days in hospital, recurrence of potentially malignant disorders, progression from potentially malignant disorders to cancer, compliance and adverse effects of treatment. There were no restrictions according to language of publication, age of the people, ethnicity or type or stage of cancer.

Exclusion Criteria

This review excluded any trial of interventions used perioperatively, interventions used in combination with chemotherapy, radiotherapy or natural intake of retinoids directly from foodstuffs and in combination with interferons. Beta-carotene was also excluded. It is conceivable that if effective, retinoids would be used as an adjunct to these conventional treatments but in order to accurately assess effectiveness, for the purpose of this review, retinoid treatment was included as a stand-alone treatment

Risk of Bias Assessment

Two reviewers (AN and either RP or HCH) independently assessed studies using the Cochrane Risk of Bias tool[19] to rate each of the following six components as high, low or unclear risk of bias: method of sequence generation, method of allocation concealment, method of blinding of participant and blinding of outcome assessor, selective reporting of outcome data and completeness of outcome data. We considered the method of sequence generation and allocation concealment to be adequate if the resulting sequences were random and if participants and enrolling investigators could not predict the assignment[20]. Adequate blinding was considered to have taken place if both participants and the outcome assessors had been masked to the participant's treatment allocation. Completeness of outcome data was considered to have taken place when studies employed an intention-to-treat (ITT

analysis). We take a strict definition of ITT where the analysis is based on *all* randomised participants in the group to which they are originally assigned[19]. Selective reporting of outcome data is where papers only report outcomes that had a favourable result. Selective reporting of outcomes was considered to have taken place if the outcome measures assessed did not include standard measures that experts in the area would expect to have been reported[19].

Statistical Methods

We analysed trials that recruited participants with second primary tumours, cancer and potentially malignant disorders separately. The overall lack of data for any particular second primary or primary tumour or potentially malignant disorder meant that anatomic sites were combined for all analyses. Where papers had reported outcomes at more than one time point, the outcomes nearest the end of the active intervention period were extracted. We used odds ratios (ORs) together with the 95% Confidence Intervals (CIs) to quantify the intervention effects. In cases where studies reported on more than one retinoid intervention versus no treatment or placebo control, data from the intervention arms were treated as one group to avoid the control group being included in the same meta-analysis twice. Meta-analyses were conducted only after ensuring the results from each arm compared to the control group were consistent in size and direction of effect. Random-effects meta-analyses were conducted by the method of der Simonian and Laird[20]. We derived tests for heterogeneity by referring the heterogeneity statistic Q to the chi-squared distribution, and we quantified the amount of heterogeneity in each meta-analysis by use of the I^2statistic[21] which gives the percentage of variance in the meta-analysis explained by heterogeneity. All analyses were performed in Stata 8 (StataCorp, College Station, TX; http://www.stata.com) and Revman 5 (Cochrane Collaboration; http://ims.cochrane.org/revman). Funnel plots were produced using Revman 5.

Results

The numbers of studies that we included or excluded at each stage of the review are listed in Figure 1; a total of 31 publications met the full inclusion criteria. Further investigation revealed that multiple publications reported on the same studies. Seventeen unique studies were initially identified for inclusion.

Three cancer trials had multiple publications so the data from the following papers were combined and referred to in the text and tables by the latest paper; Khuri et al 2006[22] (with Khuri et al 2003[23], Khuri et al 2001[24], Khuri et al 2002[235] and Benner et al 1993[26]); Bolla et al 1996[27] (with Bolla et al 1994[28] and Bolla et al 1991[29]) and finally Benner et al 1994[30] with Hong et al 1990[31]. Two potentially malignant disorder trials had multiple publications so the data from the following papers were combined: Chiesa et al 2005[15] (with Costa et al 1995[32], DePaulo 1995[33], Chiesa et al 1992a[34], Chiesa et al 1992b[35,] and Chiesa et al 1991[36]) and Lippman et al 1993[37] (with Lippman et al 1992[38] and Lippman et al 1990[39]).

Sankaranarayanan et al 1997[(40)] compared two control groups with one retinoid intervention group. Only the placebo arm was used in the meta-analysis against the retinoid intervention.

Papadimitrakopoulou et al 2009[41], Perry et al 2005[42] and Gaeta et al 2000[43] contained two retinoid interventions and one control group. The retinoid groups were combined and compared against the control groups. Papadimitrakopoulou et al 2009[41], was removed from the meta-analysis as it compared retinoids treatments with an active treatment arm. Toma et al 2004[44] originally consisted of three arms; the third arm (13-cRA + interferon) was removed from the analysis because it used retinoids in combination with another treatment. The van Zandwijk et al 2000[45] study was excluded from the data analysis as data for people with upper aerodigestive tract cancer could not be extracted separately. The Boisnic et al study[46] was also excluded from the analysis because it was not possible to separate out

those with lesions caused by trauma from those with lesions caused by potentially malignant disorders. As such only eight cancer trials were included in the review and seven potentially malignant disorder trials.

Trials assessed the development of second primary tumours[22, 27,30,42,44,47,48], recurrence of cancer[22, 27,30,42, 44, 47, 48, 49], development of potentially malignant disorders[15,40, 41], and the response of potentially malignant disorders[15, 37, ,40,41,43,50 ,51]. The general characteristics of the eight cancer trials and seven potentially malignant disorders trials are summarised separately in Tables 1 and 2, respectively. The majority of the trials reported on compliance and these results can be found in Table 3.

Insert tables 1,2,3 here

General Characteristics of Trials that Evaluated Patients with Cancer

Eight of the 15 trials enrolled people with a primary upper aerodigestive tract cancer, with eight also assessing development of second primary tumours. All studies looked at squamous cell carcinoma of the upper aerodigestive tract, with three studies focusing on specific areas, such as the oral cavity[27,30,] oropharnyx[27,30], hypopharnyx[30] and larynx[30]. Staging was reported in five of the trials[22,27,44,47,49] with two including advanced disease[44,49]. The interventions consisted of a range of different synthetic retinoid supplements including 13-cis retinoic acid[22,30,42,44,47,49], etretinate[27], and retinyl palmitate[48].

General Characteristics of Trials that Evaluated Patients with potentially malignant disorders

Seven of the 15 trials focused on people with potentially malignant disorders, with three assessing the development of these lesions into malignant tumours. All studies looked at oral leukoplakias, with one

study also looking at erythroplakias[41]. The trials included the following types of retinoid interventions: 13cRA[37,41,50,51], acitretin[43], retinyl palmitate[40], and Fenretinide[15].

Quality of Trials

We assessed the trials using the Cochrane Risk of Bias tool (Higgins & Green, 2011[19]). One of the cancer trials were rated as being at low risk of bias[42]. None of the potentially malignant disorder trials were rated as being at low risk of bias. Sequence generation was adequately controlled in six out of 15 of the studies (three cancer trials and three pre-cancer trials [15,27, 30,37,42,50]). Adequate allocation concealment took place in five trials (three cancer and two potentially malignant disorder trials[15,27, 30,42,50]). Blinding took place in seven trials [27,40,42,43,48,50,51] (three cancer trials and four potentially malignant disorder trials). Attrition rates were adequately explained and addressed in two trials[42,43]. Complete reporting of outcomes was observed in 14 of the trials. No protocols were available for these studies so it is unclear whether these outcomes measures reflect those originally highlighted for assessment. The full Risk of Bias analysis can be seen in Table 4.

Insert Table 4 here

Outcomes

Papers reported multiple outcomes, including cancer-related mortality[44], all-cause mortality[22,27,30,44,49], disease-free survival[22, 27,30,44], tumour response[27,30, 48,49,] development of second primary tumours[22,27,30,42,44,47,48], potentially malignant disorder response[15, 37, ,40,41,43, 50,51] and development of cancer from pre-malignancy[15,40 ,41].

No trials reported the number of days in hospital. Fourteen studies reported adverse reactions to treatment (see Table 4). The list of side effects of the retinoid treatments was extensive. These included dermatological toxicity (sun sensitivity, dry, chapped, bleeding and slow healing skin, onycholysis

alopecia), mucosal toxicity (cheilitis, bleeding gums, mucositis, stomatitis, rhinorrhoea.) , ocular symptoms (conjunctivitis, dry eyes, blurred vision,) haematologic and biochemical disorders (triglyceridemia, elevated cholesterol, increased liver enzyme levels) and other general symptoms (dizziness, fatigue, flu-like symptoms, headaches, mood changes, nausea, diarrhoea, constipation. One trial[50] reduced the dosage of retinoic acid part way through the trial in 47% of participants due to high levels of side effects. This resulted in a reduction of cutaneous symptoms. Hypertriglyceridema seemed unaffected by the dosage level and occurred as frequently at both 1 and 2mg[50]. Although the dose used in this trial was higher than some, it was not higher than other studies reporting only moderate side effects[49]. Compliance to treatment was reported in 12 studies and was generally good.

Disease-Free Survival, Cancer-Related Mortality and All-Cause Mortality

Five studies reported disease-free survival [22,27,30,42,44], four of which are included in the meta-analysis (Figure 2). There was a great level of heterogeneity in the studies. The analysis found evidence that retinoid intervention increased disease-free survival in comparison to control, but the analysis had wide confidence intervals (OR = 0.74, 95% CIs = 0.51, 1.09). Perry et al[42] also assessed the effectiveness of 13cRA compared with placebo. The trial found no difference in disease-free survival between the conditions ($X^2 = 2.3$) but no risk estimate was provided so was not included in the meta-analysis.

Only one study included information on cancer-related mortality[44]. Toma et al[44] assessed the effectiveness of 13cRA compared to a no-treatment control. This trial originally contained a third arm consisting of 13cRA combined with interferon alpha 2a. This arm of the trial was abandoned due to being combined with an interferon. The study found no evidence for the effectiveness of 13cRA (OR = 1.05, 95% Confidence intervals (CIs) = 0.61, 1.83).

Five studies reported all-cause mortality [22,27,30,44,49], three of which contained sufficient data to be included in the meta-analysis (Figure 2). Toma et al[44] assessed 13cRA versus no treatment control, Khuri

et al[22] assessed the effectiveness of 13cRA compared with placebo, whilst Bolla et al[27] assessed etretinate against placebo. The combined meta-analyses did not support the effectiveness of the retinoid interventions on overall survival and in fact suggests possible evidence for harm from retinoid treatments (OR = 1.28, 95% CIs = 1.00, 1.65). Benner et al[30] and Lippman et al[49] assessed 13cRA against placebo and 13c RA against methotrexate (an antimetabolite used to counteract autoimmune responses), respectively. Benner et al[30] reported a median mortality of 55 months for the placebo. At this time point, 70% of the 13cRA group were still alive. Lippman et al[49] found a median survival time of 4.5 months and 4 months in the intervention and control groups, respectively.

Cancer recurrence and second primary cancers in patients with cancer

Eight studies assessed retinoid effectiveness in people with cancer and included the following interventions: 13-cRA[22,30,37,42,44,47], etretinate[27], and retinyl palmitate[48]. Of these, the effectiveness of retinoid interventions at reducing the rate of recurrence of upper aerodigestive tract squamous cell cancer was assessed in four studies. The Lippmann[49] study was removed from the meta-analysis as it compared retinoid treatment against an active control arm. The meta-analysis (Figure 2) did not support the effectiveness of retinoids at reducing the rate of recurrence and if anything increased risk (OR = 1.47 95% CIs = 0.95, 2.26). Eight studies assessed the rate of second primary tumour development amongst patients with cancer. The meta-analysis found no evidence to support the use of retinoid interventions to reduce the rate of second primary tumours (OR = 0.96, 95% = 0.76, 1.20).

Development of cancer in patients with potentially malignant disorders (progression to malignancy)

Four studies reported data on the development of cancer in people with potentially malignant disorders and included the following interventions: 13-cRA [37,41], retinyl palmitate[40], fenretinide[15]. The Lippman et

al 1993[37] study was excluded from the meta-analysis as the study included a run-in phase which assessed patient suitability to retinoids prior to trial. The Papadimitrakopoulou et al study 2009[41], was removed from the meta-analysis as it compared retinoids treatments with an active treatment arm. The meta-analysis (Figure 2) found no evidence to suggest reduction in risk of progressions of potentially malignant disorders to cancer from retinoid treatments, and excess risk cannot be excluded (OR = 0.69, 95% CIs = 0.22, 2.15).

Recurrence of potentially malignant disorders

Seven studies reported data on potentially malignant disorders and included the following interventions: 13cRA[37, 41,50,51], acitretin[43], retinyl palmitate[40,] and Fenretinide[15]. One study could not be included due to a lack of data[43]. Gaeta 2000[43] found no change in the lesions of patients who received the placebo. The findings in the acitretin group identified no sign of disease in 6/14 patients, mild signs in 6/14, and moderate or severe symptoms in 2/14 patients. Only those who responded to high dose 13cRA were randomised. The Lippman et al 1993[37] study was excluded from the meta-analysis as the study included a run-in phase which assessed patient suitability to retinoids prior to trial. The Papadimitrakopoulou et al study 2009[41], was removed from the meta-analysis as it compared retinoids treatments with an active treatment arm.

Four studies are included in the meta-analysis in Figure 2. Again the studies contained wide heterogeneity. The meta-analysis suggests reduction in risk of the recurrence of potentially malignant oral disorders from retinoid treatments, but wide confidence intervals highlight that an excess risk cannot be excluded (OR = 0.22, 95% CIs = 0.03, 1.34).

Discussion

A number of trials have investigated the effects of retinoids in people with a previous diagnosis of upper aerodigestive tract cancer or potentially malignant disorders. These trials provide no evidence that specific interventions, or groups of interventions, have any effect on survival, recurrence, development of second primary upper aerodigestive tract cancers or progression of potentially malignant disorders to cancer and in fact there is a suggestion of harm. There is a suggestion that retinoids decrease the recurrence of potentially malignant disorders.

Our review had several limitations. Although the review was systematic and used extensive searches of several databases and inclusive search terms, it did not include unpublished results. We think it is implausible, however, that there are large unpublished trials that demonstrate a protective association between retinoid interventions and upper aerodigestive tract cancer. Funnel plots were conducted which do not suggest a strong likelihood of publication bias (see Appendix B). Inclusion of unpublished results in systematic reviews typically has only a modest impact on intervention effect estimates, which tend to move toward the null. We did not exclude trials on the basis of methodological quality, but exclusion of poor-quality trials would also tend to move effect estimates toward the null[52,53]. The major limitations of our review related to the limitations of the relevant literature. The diversity of the retinoid interventions that have been used mean that decisions on when it is appropriate to use meta-analysis to combine results are difficult. Different retinoid interventions may not have equal effects. Cancer stage, timing of the intervention in relation to treatment and the duration of the intervention varied between trials. It may be difficult to detect any effects on cancer incidence — beneficial or harmful — in trials conducted at a late stage of disease. The interventions included in our meta-analysis lasted between 4 weeks and 10 years, some studies may not have been long enough for effects to become evident.

Most trials had methodological limitations. The aspects of trial quality that have been demonstrated consistently to be associated with treatment effect estimates in randomised controlled trials are concealment of the allocation sequence and double blinding[52,53]. We found that only a few trials reported the methods used to conceal allocation in sufficient detail to allow an assessment of their adequacy by use of standard criteria[20]. Even when allocation concealment was assessed as adequate, there was no guarantee that bias was prevented, because most concealment processes can be subverted[54]. Similarly, we assumed that a trial that was reported as double-blind successfully blinded both participants and outcome assessors. In most trials reported as double-blind, no further detail on methods of blinding was given. The majority of studies did not report ITT analysis, only two[42,43] actually reported ITT according to its strict definition. Finally, many of the studies included in the meta-analyses had relatively small sample sizes. This makes it difficult to draw any firm conclusions from these studies over larger populations.

Although previous reviews examining the role of retinoid supplements in patients with upper aerodigestive tract cancer have been non-systematic, they have reached broadly similar conclusions to those in our study. Smith and Saba 2005[55] concluded that the need to overcome innate and acquired retinoid resistance as well as minimizing toxicity, will be left to the new generation of receptor-selective, synthetic retinoids. A previous meta-analysis[16] concluded that treatments may be effective in the resolution of leukoplakia but relapses and adverse effects are common and there is no evidence of effective treatment in preventing malignant transformation of leukoplakia. Our review deals specifically with the role of retinoids in this context and has the benefit of more contributing studies. The evidence for retinoids preventing malignant transformation of potentially malignant disorders shows some evidence of benefit but the meta-analysis had wide confidence intervals.

Nutritional interventions should not be assumed to be benign. Such interventions, notably antioxidant supplementation in the primary prevention setting, have yielded unexpected adverse effects, particularly with respect to β-carotene supplementation and lung cancer in smokers[56,57]. High rates of toxicity have been reported with earlier retinoid derivatives. Although dose restriction can reduce the risk of severe adverse effects, the studies in this review report side effects that should be taken very seriously by people receiving retinoids and those prescribing them.

Retinoids had little, if any, effect on overt malignancy as demonstrated by the fact that disease free survival and rate of recurrence after conventional treatment remained unchanged despite retinoid intervention, and in fact in some cases increased risk. Further, there was no evidence that retinoids decreased the rate of formation of second primary tumours. We found little evidence that retinoids decreased recurrence of potentially malignant disorders. There is some evidence from clinical observations of tumours at diverse sites[57,58,59], animal studies of skin carcinogenesis and our own laboratory-related investigations[Error! Reference source not found.] that potentially malignant disorders may be susceptible to retinoids whilst overt cancers are refractory. In conclusion, this review found no evidence for the use of retinoids in cancer prevention. There is a suggestion that retinoids may affect early stage disease (potentially malignant disorders transforming to cancer) that is supported by laboratory data but little evidence for this meta-analysis to support this. In the future a targeted pharmacogenetic approach could help select people or cancers that would benefit from retinoids. For now there is no evidence to support the clinical use of the presently available retinoids in people with upper aerodigestive tract cancer.

Acknowledgments

This publication presents independent research commissioned by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research scheme (RP-PG-0707-10034). The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

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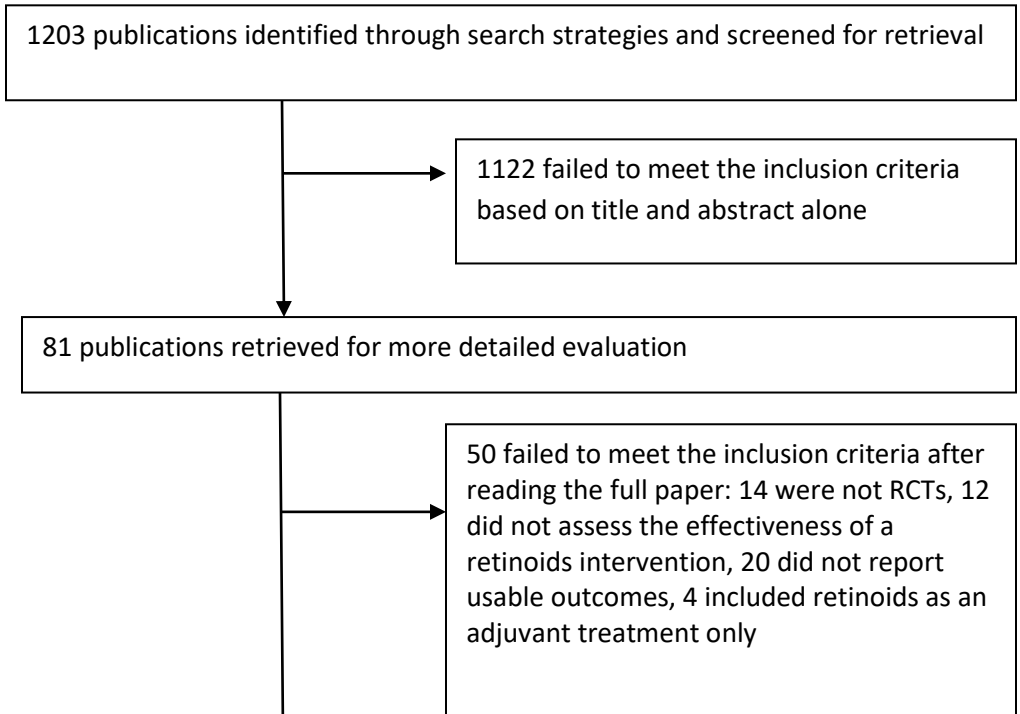
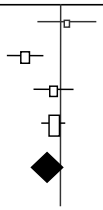

1203 publications identified through search strategies and screened for retrieval
1122 failed to meet the inclusion criteria based on title and abstract alone
81 publications retrieved for more detailed evaluation
50 failed to meet the inclusion criteria after reading the full paper: 14 were not RCTs, 12 did not assess the effectiveness of a retinoids intervention, 20 did not report usable outcomes, 4 included retinoids as an adjuvant treatment only

Disease-free

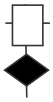
survival

Study	Intervention	Events / Total Int.	Control	Odds Ratio 95% CI
Benner et al 1994	13-cis RA	28/49	27/51	1.19 [0.54, 2.61]
Bolla et al 1996	Etretinate	35/156	65/160	0.42 [0.26, 0.69]
Toma et al 2004	13-cis RA	78/123	82/124	0.89 [0.53, 1.50]
Khuri et al 2006	13-cis RA	87/590	105/600	0.82 [0.60, 1.11]
Total 95%CI				**0.74 [0.51, 1.09]**
Test for overall effect (I^2 = 58.0)				



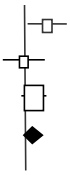
Cancer-related mortality

Toma et al 2004	13-cis RA	36/12	35/124	1.05 [0.61, 1.83]
Total (95% CI)				**1.05 [0.61, 1.83]**



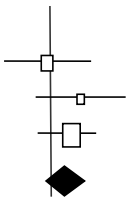
All-Cause Mortality

Bolla et al 1996	Etretinate	56/156	40/160	1.68 [1.03, 2.73]
Toma et al 2004	13-cis RA	44/123	45/124	0.98 [0.58, 1.64]
Khuri et al 2006	13-cis RA	497/590	485/600	1.27 [0.94, 1.71]
Total (95% CI)				**1.28 [1.00, 1.65]**
Overall effect (I^2 = 11.0)				



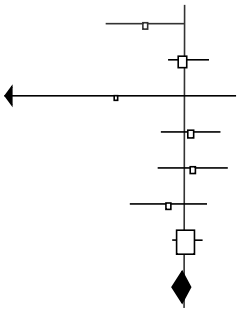
Recurrence of Cancer

Benner et al 1994	13-cis RA	16/49	17/51	0.97 [0.42, 2.23]
Jyothirmayi et al 1996	RP	11/56	5/50	2.20 [0.71, 6.84]
Bolla et al 1996	Etretinate	37/156	26/160	1.60 [0.92, 2.80]
Total (95% CI)				**1.47 [0.95, 2.26]**
Overall effect (I^2 = 0.0)				

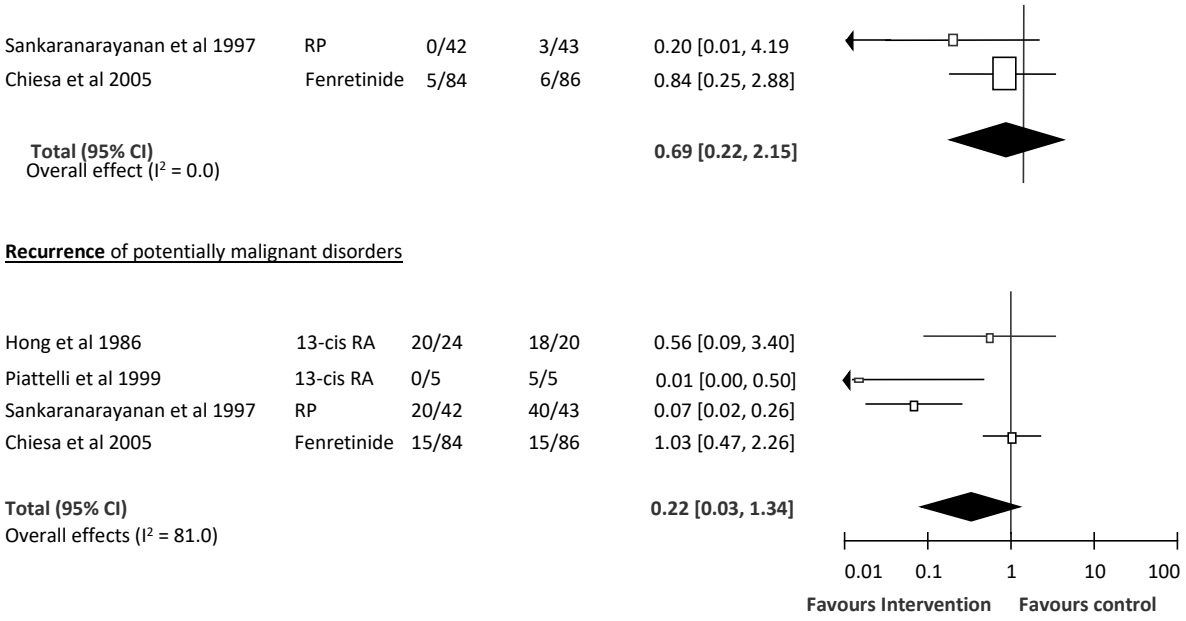


Second Primary Development

Benner et al 1994	13-cis RA	7/49	16/51	0.36 [0.13, 0.99]
Bolla et al 1996	Etretinate	28/156	29/160	0.99 [0.56, 1.75]
Jyothirmayi et al 1996	RP	0/56	2/50	0.17 [0.01, 3.66]
Pinto et al 2001	13-cis RA	18/94	16/95	1.17 [0.56, 2.46]
Toma et al 2004	13-cis RA	12/123	10/124	1.23 [0.51, 2.97]
Perry et al 2005	13-cis RA	12/103	8/48	0.66 [0.25, 1.74]
Khuri et al 2006	13-cis RA	141/590	141/600	1.02 [0.78, 1.34]
Total (95% CI)				**0.96 [0.76, 1.20]**
Overall effect (I^2 = 4.0)				



Progression to malignancy



RA = retinoic Acid, RP = retinyl palmitate

Figure 2: Meta-analysis examining the effects of retinoids on cancer-related mortality, disease–free survival, all-cause mortality, cancer recurrence and second primary occurrence in people with cancer and the recurrence of and development from potentially malignant disorders to cancer in people.

Table 1: General characteristics of the 8 trials in people with cancer

Author	Stage/site	Eligibility	Intervention	Length of follow up
Khuri 2006 USA M = 940, F = 250 Intervention: Mean age = 60.9, SD = 10.9 (n = 590) Comparison: Mean age = 60.7, SD = 11.2 (n = 600)	Relapse of primary and 2nd primary tumour formation (stage I or II HNSCC)	Stage I or II HNSCC treated surgery and/or radiotherapy. Disease free 16+ weeks after treatment. Karnofsky: 80%+, acceptable haemotologic and biochemical parameters.	**Intervention:** 13-CRA. 3 years delivery, 30mg per day. **Comparison:** Placebo delivered for 3 years daily.	8 years
Perry, 2005 Australia M = 115, F = 36, 18-70 years	Relapse of primary and 2nd primary tumour formation (HNSCC)	Invasive HNSCC. Karnofsky: 60+.	Intervention: 1 mg/kg per day 13-CRA (80 mg men, 60 mg women) for 12 months. 2 further years on lower dose 0.5 m/kg per day. Administered in 10mg capsules (n = 54) Comparisons: A: 13-CRA 40mg/kg per day dose for 36 months (n = 49) B: Placebo taken daily for 36 months (n = 48)	3 years
Toma 2004 Italy male = 240, female = 21. 25-75 years.	Relapse of primary and 2nd primary tumour formation (stage III-IV HNSCC)	Stage III-IV, HNSCC, complete response after 1st line treatment, performance status 0-2 ECOG adequate hepatic, renal and cardiac function	Intervention: 13-CRA = orally 0.5mg/kg per day. Comparison: No treatment control (n = 126)	10 years
Pinto 2001 USA Age and gender not reported N = 189	Second primary formation, disease progression (stage I-II HNSCC)	Not stated- abstract only	Intervention: 13-CRA 7.5 mg or 10 mg/kg daily for 2 years (n = 94) Comparison: placebo daily for 2 years (n = 95)	Not reported (median = 5.3 years)
Jyothirmayi 1996 France 73 m, 33 f. Intervention Mean age = 58.2, Comparison Mean age = 56.3 years	Relapse of primary and 2nd primary tumour formation (HNSCC)	Complete clinical regression, no clinical evidence of disease, normal liver function and kidney function	Intervention: Vitamin A oral administration in chewable tablet form. 200,000 IU per week retinyl palmitate for 1 year (n = 56) placebo: Capsules of tapioca powder daily for 1 year (n = 50)	3 years
Bolla 1996 France m = 299, f = 17 Intervention mean age = 53 years Comparison mean age = 54 years	Second primary formation, disease progression, and (histologically confirmed primary SCC of oral cavity & oropharnyx T1/T2, N0/N1 $\leq$ 3cm, M0)	Primary SCC of oral cavity & oropharynx, classified as T1/T2, N0/N1 less than or equal to 3 cm, M0, according to the TNM clinical classification of the UICC	Intervention: Etretinate 50 mg daily in first month, 25 mg daily for remaining 23 months (n = 156) Comparison: Placebo daily for 24 months (n = 160)	5 years
Benner 1994 USA	Second primary formation, disease progression	Not reported	Intervention: 13-cRA 50-100 mg/m2 per day for 12 months (n = 51). First 44 patients received 100mg reduced to 50	7 years

Gender and Age not reported n = 103	(HNSCC) Relapse of primary and 2nd primary tumour formation (primary SCC of oral cavity, oropharnyx, hypopharnyx, larynx)		mg, This was due to toxic effects in 13 patients (n = 49) Comparison: Placebo daily for 12 months (n = 52)	
Lippman 1988 USA 33 males 5 females 42-76 years	Tumour response (change in size), disease progression (locally advanced or metastatic HNSCC)	Head and neck SCC, locally advanced or metastatic. Karnofsky: 50%+. Life expectancy of at least 8 weeks. Adequate renal and liver function	Intervention: 13-cRA for as long as tumour response or stabilisation of disease was present. Completed at least 6 weeks treatment. 3mg dose (n = 20) Comparison: methotrexate for as long as tumour response or stabilisation of disease was present. Completing at least 2 courses (n = 20)	Not reported (median = 4.5months)

Table 2: General characteristics of the 7 trials in people with potentially malignant disorders

Author	Site/ Lesion type	Clinical Outcomes	Eligibility	Intervention	Length of follow up
Papadimitrakopoulou, 2009 USA F=77 M=85 mean 56 yrs	Response of Oral Leukoplakia (oral leukoplakias and/or erythroplakia confirmed by pretreatment biopsies)	Disease free survival. Oral pre-malignant lesion clinical response (complete, partial, progressive, no change).	18yrs+, Histology showing dysplasia or extensive leukoplakia with hyperplasia and symptoms	Intervention A: 13cRA 0.5mg/kg/d orally. For 1 yr followed by 0.25mg/kg/d orally for 2 years (n = 81) Intervention B: retinyl palmitate 25,000 U/d orally for 3 years (n = 36) Comparison A: Beta carotene 50mg/d orally and retinyl palmitate 25,000 U/d orally for 3 years and later once concerns about BC and lung cancer emerged this group were advised to discontinue BC and take RP alone. All subsequent participants randomised to 13cRA or RP alone (n= 45)	5 years/ 3 months
Chiesa 2005 Italy M = 121, F = 49 <75 years	Prevention of recurrence and new occurence of Oral Leukoplakia and development of carcinomas	Disease free survival, recurrence/new leukoplakia (yes/no)	Previously untreated oral leukoplakias. Normal metabolic and liver function tests.	Intervention: 4-HPR administration (n 4 - hydroxyphenyl retinamide) for 1 year (n = 84) Comparison: No treatment control (n = 86)	5 years
Gaeta, 2000 Italy F=5 M=16 42-75 (mean 52.5)	Response of Oral Leukoplakia (confirmed by pretreatment biopsies)	1) lesion severity (no disease, mild, moderate, severe)	Oral Leukoplakia clinically and histologically confirmed not showing severe dysplasia on biopsy	Intervention: Acitretin 10mg in Methocel E5 55mg (n = 7). Comparison: A: Acitretin 10mg in Methocel E5 33mg/ lactose 23mg (n = 7) Placebo: Methocel E5 33MG/ lactose 23mg (n = 7)	4 weeks
Sankaranarayanan 1997 India M = 103, F = 57 (Mean age) placebo - 48.7, Vit A - 54.2, Bc - 50.3 years	Response of Oral Leukoplakia (confirmed by pretreatment biopsies)	Clinical response of lesion at 1 year: complete, partial, no response, malignant transformation	Presence of oral leukoplakia and a tobacco chewing habit	Intervention: Vitamin A (water dispersible beadlets) 300,000 IU/ week for 1 year as capsules containing Retinyl palmitate 50,000 IU (n = 50) Comparison: A: Oral Beta-carotene 360 mg/week as a 30mg beta-carotene capsule (n = (55) B: Placebo (n = 55)	1 year
Piattelli 1999 Italy F= 4, M = 6 Age = 40-71 years	Response of oral Leukoplakia	Clinical response of lesions at 4 months: complete, partial, no response, worse	Oral leukoplakia 6-month+ No treatment for 4 weeks+.	Intervention: 13-cis-retinoic acid 0.1% gel 3x daily (n= 10 (control received treatment after trial)) Comparison: plain gel for 4 month (n = 5)	None

Lippman 1993 USA F = 69, M = 60 Intervention: =24-83 median 59, Comparison A: 34-83, median 60. Comparison B: 31-80 Median 61	Response of Oral Lesions (dysplastic, symptomatic hyperplastic lesions histologically confirmed as premalignant)	Clinical response (complete, partial, stable, progression)	Presence of oral leukoplakia histologically confirmed as pre-malignant. Normal renal and hepatic function. Acceptable fasting triglyceride levels at entry.	Intervention: 13cRA 1.5mg/kg of body weight daily for 3/12 (n = 70) Comparison: A: 13cRA 1.5mg/kg of body weight daily for 3/12 + 13cRA 0.5mg/kg body weight daily for additional 9/12 (n = 26) B: 13cRA 1.5mg/kg of body weight daily for 3/12 + B-carotene 30mg/day for additional 9/12 (n = 33).	28 months
Hong 1986 USA F = 13, M=31 9 = under 50 years, 29 = 50-69, 6 = 70+	Response of Oral Leukoplakia (confirmed by pretreatment biopsies)	clinical response: Complete, partial, stable, progression, no response	Histologically confirmed measurable oral PM lesion	Intervention: 13-cis-retinoic acid 1-2mgs/ kg of body weight/ day for 3/12 (n = 24) Comparison: Placebo given for 3/12 (n = 20)	9 months

Table 3: Trial Risk of Bias Assessment the 15 trials (8 of cancer and 7 of potentially malignant disorders)

Trial Type	Trial	Sequence Generation	Allocation Concealment	Blinding Of participants and personnel	Blinding of outcome assessor	Completeness of Outcome Data	Selective Outcome Reporting
Cancer	**Khuri 2006**	Unclear	Unclear	Unclear	Low	High (not ITT)	Low*
Cancer	**Perry, 2005**	Low	Low[1]	Low	Low	Low	Low*
Cancer	**Toma 2004**	Unclear	Unclear	Unclear	Unclear	High[2]	Low*
Cancer	**Pinto 2001**[3]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Cancer	**Jyothirmayi 1996**	Unclear	Unclear	Low	Low[4]	High (not ITT)	Low*
Cancer	**Bolla 1996**	Low	Low	Low	Low	High (not ITT)	Low*
Cancer	**Benner 1994**	Low	Low	Unclear[5]	Unclear[5]	Unclear	Low*
Cancer	**Lippman 1988**	Unclear	Unclear	High[6]	High[6]	High not ITT	Low*
PMD	**Papadimitrakopoulou, 2009**	Unclear	Unclear	Unclear	Unclear	High[7]	Low*
PMD	**Chiesa 2005**	Low	Low	High[8]	High[8]	High	Low*
PMD	**Gaeta, 2000**	Unclear	Unclear	low [9]	Unclear	Low	Low*
PMD	**Sankaranarayanan 1997**	Unclear	Unclear	Low	Low	High	Low*
PMD	**Piattelli 1999**	Unclear	Unclear	Low	Unclear	High (not ITT)	Low*
PMD-	**Lippman 1993**	Low	Unclear	Unclear	Low	High	Low*
PMD	**Hong 1986**	Low	Low	Low	Low	High	Low*

*: Although these studies were considered to be at low risk of bias, protocols were not available for any study to check that the outcome measures were the same as those originally intended; PMD – potentially malignant disorder

1) It was unclear if envelopes were opaque as specified for true concealment.
2) 6 participants were excluded from analysis after randomisation as no data was available
3) Abstract only
4) It was stated that the clinicians were blinded suitably to treatment allocation
5) The study states that both patients and clinicians were blinded however blinding is likely to have been broken by existence of high rates of adverse events in treatment condition
6) No attempt to blind patients to intervention
7) Not all outcomes measures used ITT
8) Surgeons were blinded but no other investigators or participants
9) Described as double blind trial using identical placebo

Table 4: Rates of compliance and adverse events across all studies

	Rate of compliance across cancer trials	**Adverse Events reported in cancer trials**
Khuri 2006	Compliance was tested using an 8-12 week run-in (take 3 capsules of placebo daily) those that took at least 75% of the placebo pills were randomised. Adherence: 85.1% in intervention and 90.8% in placebo maintained a level of adherence of at least 80%.	More grade 2,3,4 toxicity was found in isotretinoin gp than placebo (P<0.0001). Most toxic effects were skin, chelitis, conjunctivitis and all resolved upon withholding/withdrawing. More dose reduction/discontinuation in isotretinoin gp (29.5% v 9.2%: OR=4.15, 95%CI = 2.98-5.76)
Perry 2005	In each treatment group 85% to 95% of pps were assessed as having taken their medication.	No statistically significant between-gp differences in adverse events were found (P= 0.4)
Toma 2004	Compliance to intended 1 yr intervention treatment was 88.6%. 66.7% completed the intended 1 yr treatment with 12.2% requiring a dose reduction due to toxicity	84/121 (69.4%) adverse events occurred in 13cRA gp of a grade 1 toxicity
Pinto 2001	NR	More adverse events in the 13cRA gp than placebo: Skin dryness (P=0.01), chelitis (p<0.001), stomatitis (p=0.014), nausea (P=0.017)
Jyothirmayi 1996	89% on retinyl palmitate and 86% placebo completed supplementation for 1 yr	No clinically observed side effects were observed during and after supplementation, except dryness of tongue.
Bolla 1996	17% in intervention and 16% in placebo stopped treatment temporarily.25% in intervention and 17% in placebo stopped at 12 months and 33% versus 23% at 24 months	More adverse events were reported in the erteinate gp than placebo: toxic effect (P<0.001), chelitis (P<0.001), cutaneous (rash etc)(P<0.001) conjunctivitis (P<0.03), alopecia (P<0.05), onycholysis (P<0.001)
Benner 1994	33% in intervention did not complete 12 month course because of drug toxicity or non-compliance 6% in placebo gp discontinued due to toxicity	More adverse events were reported in the isotretinoin gp than placebo: Skin dryness (P<0.001), chelitis (P=0.001), Hypertriglyceridemia (P=0.019)
Lippman 1988	1 pp in each arm did not complete trial due to unacceptable levels of toxicity. Adherence was not reported	Side effects with isotretinoin were moderate, consisting of mucocutanous toxicity. The methotrexate group experienced GI toxicity and myelosuppression
	Rates of compliance across potentially malignant disorder trials	**Adverse events reported in potentially malignant disorder trials**
Papadimitrakopoulou, 2009	Taking ≥ 85% of meds were similar in the 3 arms: 74.1% in 13cRA, 72.7% in BC + RC and 77.8% in RP (P=0.87 Chi^2)	More adverse events were reported in 13cRA gp than 13cRA +RP or RP alone: cheltitis (P<0.0001), conjunctivitis (P=0.0003), skin reaction (P<0.0001). Grade 2+ toxicity was significantly higher in 13cRA gp

		(P<0.0001) and 6 pps in 13cRA gp discontinued treatment due to toxicity, 0 pp in other gps)
Chiesa 2005	Compliance to 4HPR was good: 92% of pps who completed treatment had a compliance between 90% and 100%	Total number of patients with complaints were higher in control (41.7%) versus 4HPR (19.2%) regarding skin dryness, dyspeptic syndrome, dermatitis and abnormal lab values
Gaeta 2000	pp compliance was very high compared with oral gel or cream	NR
Sankaranarayanan 1997	NR	No significant side effects were observed. 6 pps (vit A) v 3 pp (BC) headaches; 5 pps (vit A) v 2 pp (BC) muscular pains; 2pp (vit A) v 1 pp (BC) dry mouth
Piattelli 1999	NR	No side effects of using the gel were observed
Lippman 1993	11/70 were withdrawn during induction phase (3 for non-compliance) Compliance during the maintenance phase was excellent all evaluated pps took 80%+ of planned doses and 62% took at least 90%	Maintenance –phase toxicity was relatively mild: no between-gp differences in high grade reactions (3,4) in mucocutaneous toxicity but more low grade reactions (1,2) in isotretinoin gp than betacarotene. Hypertiglyceridermia (grade 3,4) was higher in isotretinoin gp (P=0.05).
Hong 1986	Compliance was assessed by pill count and daily calendar – no pill count data reported	Adverse events were higher in retinoic acid group but significance wasn't tested. Lower doses reduced the occurrence.

pp= participants; gp = group; NR = not reported; BC= betacarotene, vit = vitamin

Appendix A: Search strategy for MEDLINE (on OVID)

1 exp "Head and Neck Neoplasms"/ (211422)

2 ((oral or mouth) adj5 (neoplas$ or cancer$ or precancer$ or preneoplas$ or carcinoma$ or tumo?r$ or pre-malignancy or premalignancy)).tw. (20581)

3 ((head or neck) adj5 (cancer$ or neoplas$ or precancer$ or preneoplas$ or carcinoma$ or tumo?r$ or pre-malignan$ or premalignan$)).tw. (29976)

4 ((oesophag$ or esophag$) adj5 (cancer$ or neoplas$ or precancer$ or preneoplas$ or carcinoma$ or tumo?r$ or pre-malignan$ or premalignan$)).tw. (26757)

5 leukoplakia$.tw. (2875)

6 (thyroid$ adj5 (cancer$ or neoplas$ or precancer$ or preneoplas$ or carcinoma$ or tumo?r$ or pre-malignan$ or premalignan$)).tw. (27402)

7 ((pharynx or pharyngeal) adj5 (cancer$ or neoplas$ or precancer$ or preneoplas$ or carcinoma$ or tumo?r$ or pre-malignan$ or premalignan$)).tw. (2295)

8 (aerodigestive$ adj5 (cancer$ or neoplas$ or precancer$ or preneoplas$ or carcinoma$ or tumo?r$ or pre-malignan$ or premalignan$)).tw. (1326)

9 ((larynx or laryngeal$) adj5 (cancer$ or neoplas$ or precancer$ or preneoplas$ or carcinoma$ or tumo?r$ or pre-malignan$ or premalignan$)).tw. (12964)

10 (salivary adj5 (cancer$ or neoplas$ or precancer$ or preneoplas$ or carcinoma$ or tumo?r$ or pre-malignan$ or premalignan$)).tw. (5545)

11 ((nasophar$ or nasal or paranasal) adj5 (cancer$ or neoplas$ or precancer$ or preneoplas$ or carcinoma$ or tumo?r$ or pre-malignan$ or premalignan$)).tw. (11728)

12 ((face or facial) adj5 (cancer$ or neoplas$ or precancer$ or preneoplas$ or carcinoma$ or tumo?r$ or pre-malignan$ or premalignan$)).tw. (2943)

13 or/1-12 (238321)

14 exp Retinoids/ (42149)

15 retinoid$.tw. (13960)

16 Tretinoin.tw. (960)

17 Fenretinide.tw. (393)

18 13cRA.tw. (1990)

19 Etretinate.tw. (1136)

20 Acitretin.tw. (735)

21 "vitamin A".tw. (16700)

22 trans-retinoic.tw. (6127)

23 retinoic.tw. (22365)

24 retin-a.tw. (61)

25 vesanoid.tw. (8)

26 retinol.tw. (9943)

27 "aquasol a".tw. (6)

28 tiga?on.tw. (144)

29 roaccutane.tw. (53)

30 accutane.tw. (161)

31 etretin.tw. (60)

32 or/14-31 (60724)

33 13 and 32 (1334)

34 randomized controlled trial.pt. (309463)

35 controlled clinical trial.pt. (82674)

36 randomized.ab. (215844)

37 placebo.ab. (125637)

38 drug therapy.fs. (1460922)

39 randomly.ab. (156203)

40 trial.ab. (222878)

41 groups.ab. (1037810)

42 or/34-41 (2703101)

43 exp animals/ not humans/ (3604529)

44 42 not 43 (2292158)

45 33 and 44 (572)

46 Neoplasms/ (232270)

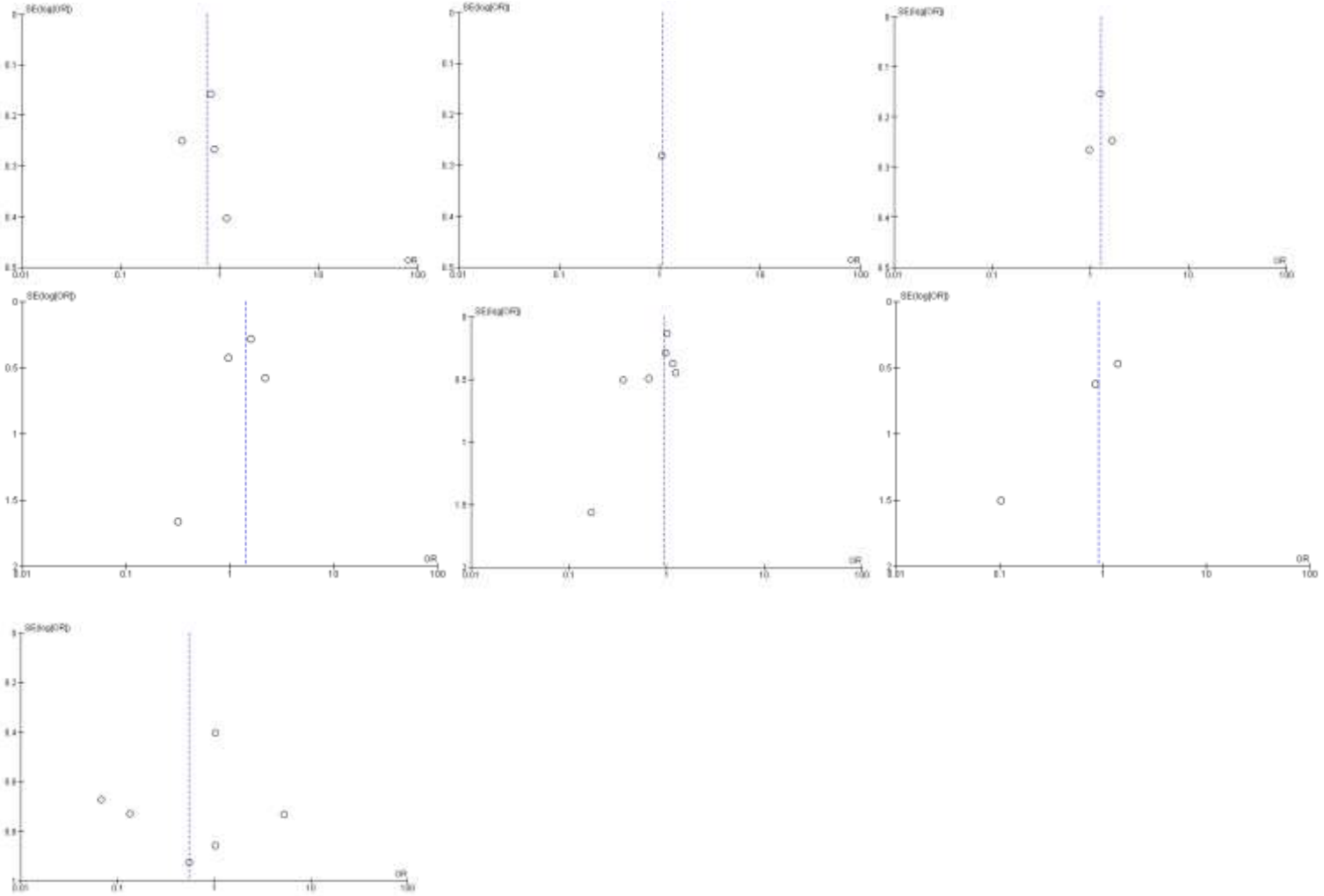
47 precancerous conditions/ (21853)

48 (cancer$ or neoplas$ or precancer$ or preneoplas$ or carcinoma$ or tumo?r$ or pre-malignan$ or premalignan$).ti. (1023555)

49 46 or 47 or 48 (1134656)

50 32 and 44 and 49 (2116)

Appendix B: Funnel Plots for each Outcome measure



Funnel plot of comparison (from top left to bottom right): Disease-free survival, cancer-related mortality, all-cause mortality, recurrence of cancer, second primary development, potentially malignant disorders.